

**The Groundbreaking Science of Healthy,
Permanent Weight Loss**

HOW



TO



MICHAEL GREGER, M.D., FACLM

***NEW YORK TIMES* BESTSELLING AUTHOR OF *HOW NOT TO DIE*
AND FOUNDER OF NUTRITIONFACTS.ORG**

**FEATURING DR. GREGER'S TWENTY-ONE TWEAKS
TO ACCELERATE WEIGHT LOSS**

HOW NOT TO DIET

THE GROUNDBREAKING SCIENCE
OF HEALTHY, PERMANENT WEIGHT LOSS

MICHAEL GREGER,
M.D., FACLM



FLATIRON
BOOKS
NEW YORK

[Begin Reading](#)

[Table of Contents](#)

[About the Author](#)

[Copyright Page](#)

**Thank you for buying this
Flatiron Books ebook.**

To receive special offers, bonus content,
and info on new releases and other great reads,
sign up for our newsletters.

[Sign Up](#)

Or visit us online at
us.macmillan.com/newslettersignup

For email updates on the author, click [here](#).

The author and publisher have provided this e-book to you for your personal use only. You may not make this e-book publicly available in any way. **Copyright infringement is against the law. If you believe the copy of this e-book you are reading infringes on the author's copyright, please notify the publisher at:** us.macmillanusa.com/piracy.

*To my mom,
the source of everything good in my life*

Preface

DOWN THE RABBIT HOLE

Surely, if there were a safe, simple, side effect-free solution to obesity, we would know about it by now, right?

I'm not so sure.

It takes an estimated average of seventeen years before evidence from scientific research is incorporated into day-to-day clinical practice.¹ One example that was particularly poignant for my family: heart disease. Decades ago, Dr. Dean Ornish and colleagues published evidence in one of the most prestigious medical journals in the world that our leading cause of death could be reversed with diet and lifestyle changes alone²—yet this monumental discovery was effectively ignored at the time.³ Even now, hundreds of thousands of Americans continue to perish every year from what we learned nearly thirty years ago is an arrestable, reversible condition. In fact, I had seen such a reversal with my own eyes.

My dear grandmother was cured of her end-stage heart disease by one of Ornish's contemporaries, Nathan Pritikin, using similar methods. She was sixty-five when she was given her medical death sentence, but—thanks to a healthy diet—was able to live another thirty-one years to age

ninety-six, to continue enjoying her six grandkids, including me.

If effectively the cure to the number-one killer of men and women could be ignored and get lost down some rabbit hole, what else might be buried in the medical literature? I've made it my life's mission to find out. That's why I went to medical school in the first place and why I started NutritionFacts.org.

So, like heart disease, might there already be a cure for obesity? That's what I intended to uncover.

Here's the problem: I hate diet books. Furthermore, I hate diet books that *purport* to hate diet books yet relish in all the same absurdities. This book is for those who want facts, not filler, fantasy, or fluff. If you want testimonials and before-and-after pictures, you've come to the wrong place. You don't need anecdotes when you have evidence. A Harvard sociologist of science calls those arguments by anecdotes in diet books "a deliberate attempt at credibility engineering."⁴ When you don't have the science to back you up, all you have are "success" stories.

I'm not interested in offering dueling anecdotes, nor am I interested in dietary dogma, beliefs, or opinions. What I am interested in is the science. When it comes to making life-and-death decisions that concern something as important as your own health and that of your family, as far as I'm concerned, there's only one question: *What does the best available balance of evidence say right now?* That's what I've tried to encapsulate in this book.

Often, diet books deal in pseudoscientific twaddle swaddled in the trappings of science. But how is the untrained reader supposed to know the difference between the two and decide among the competing claims? It's no wonder people tend to flock to their respective gurus to have their minds made up for them. However, no one is

born with this knowledge—and you have a right to demand to know where diet book authors got the information they're trying to sell you so you can check the credibility of the source and confirm its veracity. That's why I prefer presenting the science in video format on my website, where I can show the original data and link to downloads of all the primary sources. And here in this book, I've tried to cite each substantive statement of fact.

My goal was to create the oxymoron: an evidence-based diet book.

CAVEAT EATER

No other area of the national health probably is as abused by deception and misinformation as nutrition. Many travesties cheat the public of enormous sums of money, and of good health as well.

—WHITE HOUSE CONFERENCE ON FOOD, NUTRITION, AND HEALTH⁵

Frustrated by the current political climate of alternative facts and echo chambers? Welcome to my world. The entire diet industry is built upon a foundation of fake news. The nutrition field has been dealing with bald-faced lies since back in the pre-post-truth era, and diet books can be the worst offenders. “Often the loudest, most extreme voices drown out the well informed,” wrote two noted nutrition professors on the subject of diet books. “There is also money to be made.”⁶

Lots of money. Every month seems to bring us a trendy new diet or weight-loss fad, and they always sell because they always fail. The diet industry may rake in up to \$50 billion a year, and the business model is based on repeat customers.⁷ Racked with the guilt and self-hatred of failure, people often line right back up to be fooled again. I hope this book can help break that cycle by cutting through the BS.

Beyond the corrupting influence of commercial interests are the ideological biases. Too often in diet books, the rule is to obfuscate rather than illuminate, cherry-pick facts to push some pet theory, and ignore the rest to promote your own agenda. It’s the opposite of science. In true scholarship,

your conclusions follow from the evidence, not the other way around.

Unfortunately, even just sticking to the peer-reviewed scientific literature is not enough. An article in *The New England Journal of Medicine* on obesity myths concluded that “false and scientifically unsupported beliefs about obesity are pervasive” in medical journals as well.⁸ In that case, the only way to get at the truth is to dive deep into the primary literature and read all the original studies yourself rather than taking some contemporary reviewer’s word for it. But who’s got time for that? There are more than half a million scientific papers on the subject of obesity, with a hundred new ones published every day. Even researchers in the field might only be able to keep track of what’s going on in their narrow, subspecialized domains. But that’s precisely what we do at NutritionFacts.org. We comb through tens of thousands of studies a year so you don’t have to.

This is the kind of book I was made for. My research team and I were allowed to really flex our muscles, and the sorer those muscles got, the further we stretched ourselves, the more valuable we realized this contribution would be. Even “simple” questions on weight loss, like whether you should eat breakfast or skip it, or whether it’s better to exercise before or after meals, turned into major, thousand-article research projects. If our nose-to-the-grindstone research team had trouble sifting through the stacks, a practicing physician would have no chance and the public would be totally lost.

Whether you’re morbidly obese, just overweight like the average American, or at your ideal weight and wanting to keep it that way, our goal was to give you every possible tweak and technique we could find to build the optimal weight-control solution from the ground up.

I went into this project with the goal of creating a distillation of all the best science, but to my delight, I discovered all sorts of exciting new tools and tricks along the way. We did indeed uncover a treasure trove of buried data, like simple spices proven in randomized, double-blind, placebo-controlled studies to accelerate weight loss for pennies a day. With so little profit potential, it's no wonder those studies never saw the light of day.

And we were even able to traverse beyond the existing evidence base to propose a novel method to eliminate body fat. The proposed technique appears to have a strong theoretical basis but has never been put to the test because apparently no one has ever thought of it before. It can't be monetized either, but the only profit I care about is your health. That's why I donate to charity 100 percent of the proceeds I get from my DVDs, speaking engagements, and books, including the one you're holding right now. I just want to do for everyone's family what Pritikin did for mine.

Introduction

SOMETIMES BIGGER IS BETTER

My literary agent told me that no one wants a fat diet book. They want it to be as slim as they envision their future selves. Sorry to disappoint, but I couldn't help it. I wanted to document every evidence-based tip, trick, tweak, and hack to give people every possible advantage—whether you're obese, overweight, or just wanting to maintain your ideal weight.

In *How Not to Diet*, I cover everything from cultivating a healthy microbiome in your gut to manipulating your metabolism through chronobiology, matching meal timing to your circadian rhythms. Every section could have been a book in its own right. We certainly attempted book-length research on each subject and then tried to distill down the most compelling, actionable takeaways from each of the most promising strategies. To that end, this is really more like forty books packed into one. For those of you now wielding a physical copy of the book and thinking, *This is the compact version?*, take comfort in the fact that you can use it to curl for a little extra resistance exercise.

It was important to me to include all the details so you can make as informed a decision about your health as possible, but you can always skip down to the summaries at

the end of each section for my take-home suggestions. I wanted to be sure to clearly articulate how I arrived at each recommendation, because I don't want to be anyone's diet guru. I don't want you to take anything on faith but rather on evidence.

In the References section, I've included a website address and a QR code for the full list of the nearly five thousand citations referenced throughout this book. The advantage of presenting them online for you (beyond trimming five hundred pages and saving a few trees) is that it allowed me to hyperlink each and every citation to take you directly to the source, so you can download the PDFs and access the original research yourself. Here in the ebook you get the best of both worlds, with the full list of citations plus the code to access the primary sources.

Some of my conclusions are scientific slam dunks, but others are more uncertain, and I try to make the distinctions clear. That way, you can make up your own mind when trying to decide whether to incorporate any particular piece of my advice into your life. If you find yourself unconvinced by the data presented to support a particular recommendation, don't do it. The benefit of laying it all out is that you can decide for yourself. As famed scientist Carl Sagan (who also happened to be my next-door neighbor at Cornell!) put it: "Science by itself cannot advocate courses of human action, but it can certainly illuminate the possible consequences of alternative courses of action."⁹

WHAT ARE YOUR DIGITS?

Before we dive in, what does it really mean to be overweight? Obese? In simple terms, being overweight means you have too much body fat, whereas being obese means you have way too much body fat. In technical terms,

obesity is operationally defined as a body mass index (BMI) of 30 or more, while being overweight means you have a BMI of 25 to 29.9. A BMI between 18.5 and 24.9 is considered “ideal weight.”

Calculating your BMI is relatively easy: You can visit one of the scores of online BMI calculators, or you can grab a calculator and calculate it on your own. To do so, multiply your weight in pounds by 703. Then divide that twice by your height in inches. For example, if you weigh 200 pounds and are 71 inches tall (five foot eleven), that would be $(200 \times 703) \div 71 \div 71 = 27.9$, a BMI indicating that you would be, unfortunately, significantly overweight.

In the medical profession, we used to call a BMI under 25 “normal weight.” Sadly, that’s no longer normal. Being overweight became the norm by the late 1980s in the United States¹⁰ and appears to have steadily worsened ever since.¹¹

ISN'T A CALORIE A CALORIE?

Now that we see where the lines are drawn in the weight spectrum from optimal to obese, let’s review some basic assumptions. The notion that a calorie from one source is just as fattening as a calorie from any other source is a trope broadcast by the food industry as a way to absolve itself of culpability. Coca-Cola even put out an ad emphasizing this “one simple commonsense fact.”¹² As the chair of Harvard’s nutrition department put it, this “central argument” from industry is that the “overconsumption of calories from carrots would be no different from overconsumption of calories from soda.”¹³ If a calorie is just a calorie, why does it matter what kinds of foods we eat?

Let’s take the example of carrots versus Coca-Cola. While it’s true that in a tightly controlled laboratory setting, 240

calories of carrots—ten carrots—would have the same effect on calorie balance as the 240 calories in a bottle of Coke,¹⁴ this comparison falls flat on its face out in the real world. You could chug down those liquid calories in less than a minute, but eating 240 calories of carrots could take you more than two and a half hours of constant chewing. (It's been timed.¹⁵) Not only would your jaw get sore, but 240 calories of carrots is about five cups—you might not even be able to fit them all in your stomach. Like all whole plant foods, carrots have fiber, which adds bulk without adding net calories. What's more, you wouldn't even absorb all the carrot calories. As anyone who's eaten corn can tell you, some bits of vegetable matter can pass right through you, flushing out any calories they contain. A calorie may still be a calorie circling your toilet bowl, but it's not going to end up on your hips.

A more relatable comparison might be something like Cheerios versus Froot Loops. As Kellogg's is practically giddy to point out, its Froot Loops cereal has about the same number of calories as its rival's health-hallowed Cheerios. So why does Toucan Sam get singled out? (I was deposed as an expert witness in a case against sugary cereal manufacturers, so I heard these arguments firsthand.) Yes, the two cereals may have similar calories, but that doesn't take into account all the appetite-stimulating effects of concentrated sugar.¹⁶ In an experiment in which children were alternately offered high-versus lower-sugar cereals, had they eaten more Cheerios than Froot Loops, they could have gotten more calories, but the opposite happened. On average, the kids poured and ate 77 percent more of the sugary cereal. So even with comparable calorie counts, sugary cereals may end up nearly doubling caloric intake.¹⁷ In a lab, a calorie is a calorie, but in life, far from it.

Even if you eat and absorb the same number of calories, a calorie may *still* not be a calorie. As you'll learn, the same number of calories eaten at a different time of the day, in a different meal distribution, or after different amounts of sleep can translate into different amounts of body fat.

It's not only what we eat but how and when.

And the same number on the scale can mean different things on different diets or in different contexts. You could be losing weight but actually gaining body fat if your body sheds water and muscle mass. So it's not just about calories in versus calories out, eating less, and moving more. We'll see an illustration of this later, with a famous series of studies on prisoners in Vermont that showed that, depending on what the researchers fed them, it could take up to one hundred thousand more calories to create the same amount of weight gain. So you'll learn how they effectively made one hundred thousand calories disappear. But I'm getting ahead of myself.

A DETECTIVE STORY IN FOUR PARTS

In part I, the book starts with an outline of our growing problem with obesity—the causes, the consequences, and the solutions tried to date. It answers questions such as: *What led to the explosive increase in obesity starting in the late 1970s? Is being overweight really as bad for your health as “they” say? And what about the safety and efficacy of nonlifestyle approaches, such as stomach stapling, diet drugs, and weight-loss supplements?*

Then, in my attempt to build the optimal weight-loss strategy from scratch, I spend part II exploring all the key ingredients that might go into creating the ideal recipe for losing body fat. In part III, we see how all the diets out there stack up against this list of criteria, and we piece together

the foremost formula for healthy, sustainable weight control. You also get the tools to be able to assess all the newer-than-new diets that haven't even come out yet.

After that come the boosters. In part IV, I unveil all the tricks and tweaks for fast-tracking weight loss that I've found through my years of scouring the medical literature. These are ways in which any diet can be modified to maximize the dissolution of body fat. I arrange the boosters in a simple daily checklist so you can pick and choose a portfolio of techniques that works best for you. I have to warn against skipping to this section and going for the quick fixes while continuing to eat the same crappy foods. Though there are indeed different ways to eat the same foods to achieve better results, the boosters are strictly meant to be adjuncts to a healthy diet.

In the final section, I lay to rest all the burning questions on burning fat: *What are the best ways to exercise to achieve maximum weight loss? How can you safely boost your metabolism? What is the optimum amount of sleep? What does the science say about ketogenic diets, intermittent fasting, and high-intensity interval training?* I also introduce you to specific foods that double as fat blockers and fat burners, and starch blockers and appetite suppressants. And did you know that the different timing, frequencies, and combinations of foods can also matter? There's even a food that can prevent the metabolic slowing that your body uses to frustrate your weight-loss attempts.

Skeptical? You should be! I was too.

I went into this thinking I would just end up railing against all the gimmicky snake oil out there and put out much of the same standard advice on trimming calories and hitting the gym. I imagined what would set this work apart would be its comprehensiveness and strict grounding in science. I figured this book would distinguish itself—but more as a book of

reference than revolution. I certainly never thought I'd stumble across some novel weight-loss strategy. I just didn't realize how many new paths would be opened up by our newfound transformations in understanding of so many fields of human physiology. It's been thrilling to weave together all these cutting-edge threads to design a weight-loss protocol based on the best available evidence.

This has been a mammoth but joyful undertaking. People sometimes ask me why I don't go on vacations or even take a day off. I have to explain that I feel as though my entire life is a holiday. I feel so blessed to be able to dedicate my time to helping people while doing what I love: learning and sharing. I can't imagine doing anything else.

I. The Problem

THE CAUSES

The Weight of the World

Obesity isn't new, but the obesity *epidemic* is. We went from a few corpulent queens and kings, like Henry VIII and Louis VI (known as Louis le Gros, or "Louis the Fat"),¹⁸ to a pandemic of obesity, now considered to be perhaps the direst and most poorly contained public health threat of our time.¹⁹ Today, 71 percent of American adults are overweight and 40 percent of men and women appear to have so much body fat that they can be classified as obese, and there's no end in sight.²⁰ Earlier reports had suggested the rise in obesity was at least slowing down, but that doesn't actually appear to be the case.²¹ Similarly, we had thought we were turning the corner on childhood obesity after thirty-five years of unrelenting bad news, but the bad news marches on.²² Child and adolescent obesity rates have continued to rise, now into the fourth decade.²³

Over the last century, obesity appears to have jumped tenfold, from as few as one in thirty people²⁴ to now one in three, but it wasn't a steady rise. Something seems to have happened around the late 1970s, and not just in the United States.²⁵ The obesity pandemic took off at about the same time in most high-income countries around the globe in the 1970s and 1980s. The fact that the rapid rise appeared almost concurrently across the industrialized world suggests a common cause.²⁶

What might that trigger have been?

Any potential driver would have had to be global in nature and coincide with the upswing of the epidemic, so the change would have had to have started about forty years ago and been able to spread rapidly around the world.²⁷ So how do the various theories stack up? Some have blamed changes in our "built environment," for instance, pointing to shifts in city planning that have made our communities less conducive to walking, biking, and grocery shopping.²⁸ But that doesn't meet our criteria for a credible cause because there was no universal, simultaneous change in global neighborhoods within that time frame.²⁹

If you do a survey of hundreds of policy-makers, most blame the obesity epidemic on "lack of personal motivation,"³⁰ but that makes little sense. Here in the United States, for example, obesity shot up across the entire population in the late 1970s. Are you telling me that every sector of the U.S. population experienced some sort of simultaneous decline in willpower?³¹ Each age, sex, and ethnic group, with all their different attitudes and experiences, coincidentally lost their collective capacity for self-control at the same time?

More plausible than a global change in the nature of our characters would be some global change in the nature of our lives.³²

Fast Food vs. Slow Motion

The food industry blames inactivity. "If all consumers exercised," said the CEO of PepsiCo, "obesity wouldn't exist."³³ Coca-Cola went a step further and spent \$1.5 million to create the Global Energy Balance Network to downplay the role of diet in the obesity epidemic.

Leaked internal documents show the company planned on using the front group to serve as a “weapon” to “change the conversation” about obesity in its “war” with the public health community.³⁴

This tactic is so common among food and beverage companies it even has a name: *leanwashing*. You’ve likely heard of greenwashing, where companies deceptively pretend to be environmentally friendly. *Leanwashing* is the term used to describe companies that try to position themselves as helping to solve the obesity crisis when, instead, they’re directly contributing to it.³⁵ For example, Nestlé, the largest food company in the world, has rebranded itself the “world’s leading nutrition, health and wellness company.”³⁶ Yes, that Nestlé, of Nestlé Nesquik fame, makers of Cookie Crisp cereal and more than one hundred different brands of candy, including Butterfinger, Kit Kat, Goobers, Gobstoppers, Runts, and Nerds. Another of its slogans is “Good Food, Good Life.” Its Raisinets may have some fruit, but the company seems to me more Willy Wonka than wellness. Let’s just say that on its “What is Nestlé doing about obesity?” web page, the “Read about our Nestlé Healthy Kids programme” link gave me a Page Not Found error.³⁷

The constant corporate drumbeat of overemphasis on physical inactivity appears to be working. In response to a Harris poll question (“Which of these do you think are the major reasons why obesity has increased?”), a large majority (83 percent) chose lack of exercise, while only 34 percent chose excessive calorie consumption.³⁸ But blaming couch-potato-ness has actually been identified as one of the most common misconceptions about obesity.³⁹ The scientific community has come to a fairly decisive conclusion⁴⁰ that the factors governing caloric intake far more powerfully affect overall calorie balance.⁴¹

There’s even debate in the scientific literature as to whether changes in physical activity had “any role whatsoever” in the obesity epidemic.⁴² The increase in caloric intake per person is more than enough to explain the U.S.⁴³ and global⁴⁴ epidemics of obesity. In fact, if anything, the level of physical activity over the last few decades has gone up slightly in both Europe and North America, rather than declined.⁴⁵ Ironically, this bump may be a result of the extra energy it takes to haul around our heavier bodies, making changes in energy expenditure a consequence of the obesity problem rather than the cause.

Formal exercise is only a small part of our total daily activity, though. Think how much more physical work people used to do on the job, on the farm, or even in the home.⁴⁶ It’s not just the shift in collar color from blue to white. Increasing automation, computerization, mechanization, motorization, and urbanization have all contributed to increasingly more sedentary lifestyles over the last century—and therein lies the problem with the theory: The occupational shifts and advent of labor-saving devices have been gradual and largely predate the dramatic, recent rise in weight gain the world over.⁴⁷ Washing machines, vacuum cleaners, and the Model T were all invented before 1910. And indeed, when put to the test using state-of-the-art methods to measure energy in and energy out, it was caloric intake, not physical activity, that predicted weight gain over time.⁴⁸

The common misconception that obesity is due mostly to lack of exercise may not just be a benign fallacy, as personal theories of causation appear to impact people’s weight. Those who blame insufficient exercise are significantly more likely to be overweight themselves. Put them in a room with chocolate, for instance, and they can be covertly observed consuming more candy compared to those who put the onus of obesity on poor diet.⁴⁹ But you can’t know if such attitudes are playing a role in their weight problem until you put it to the test. So researchers randomized people to read a fictitious article implicating inactivity in the rise of obesity and found they indeed went on to eat significantly more sweets than those who instead were given an article that indicted diet.⁵⁰ A similar study evidently found that those presented with research blaming genetics subsequently ate significantly more cookies. The paper was entitled “An Unintended Way in Which the Fat Gene Might Make You Fat.”⁵¹

Do These Genes Make Me Look Fat?

To date, about one hundred genetic markers have been linked to obesity, but when you put all of them together, they account for less than 3 percent of the difference in body mass index between people.⁵² The “fat gene” you may have heard about (called FTO, short for “FaT mass and Obesity associated”) is the gene most strongly linked to obesity,⁵³ but it explains less than 1 percent of the difference between people (a mere 0.34 percent).⁵⁴

FTO codes for a brain protein that appears to affect your appetite.⁵⁵ Are you one of the billion people on Earth who carry a full complement of FTO susceptibility genes?⁵⁶ It doesn't really matter, because this only appears to result in a difference in intake of a few hundred extra calories *a year*,⁵⁷ while what it took to lead to the obesity epidemic is more like a few hundred calories *a day*.⁵⁸ FTO is the gene so far known to have the most effect on excessive weight gain,⁵⁹ but the chances of accurately predicting obesity risk based on FTO status are only slightly better than flipping a coin.⁶⁰

When it comes to obesity, the power of your genes is nothing compared to the power of your fork. Even the small influence the FTO gene does have appears to be weaker among those who are physically active⁶¹ and may be abolished completely in those eating healthier diets. FTO only appears to affect those eating diets higher in saturated fat (predominantly found in dairy, meat, and junk food). Those eating more healthfully appear to be at no greater risk of weight gain even if they inherited the “fat gene” from both their parents.⁶²

Physiologically, FTO gene status doesn't appear to affect your ability to lose weight.⁶³ Psychologically, knowing you're at increased genetic risk for obesity may motivate some people to eat and live more healthfully,⁶⁴ but it may cause others to fatalistically throw their hands up in the air and resign themselves to thinking it just runs in their families.⁶⁵ Obesity does tend to run in families, but so do lousy diets.

Comparing the weight of biological versus adopted children can help tease out the contributions of lifestyles versus genetics. Children growing up with two overweight biological parents were found to be 27 percent more likely to be overweight themselves, whereas adopted children placed in a home with two overweight parents were only 21 percent more likely to be overweight.⁶⁶ So genetics certainly play a role, but this suggests that it's more the children's environment than their DNA.

Diet Trumps Genes

One of the most dramatic examples of the power of diet over DNA comes from the Pima Indians of Arizona, who have among the highest rates of obesity⁶⁷ and diabetes⁶⁸ in the world. This has been ascribed to their relatively fuel-efficient genetic makeup.⁶⁹ Their propensity to store calories may have served them well in times of periodic scarcity when they were living off the land, but when the area became “settled,” their source of water, the Gila River, was diverted upstream. Those who survived the ensuing famine⁷⁰ had to abandon their traditional diet to live off government food programs, and chronic disease rates skyrocketed.⁷¹ Same genes, but a different diet, leading to a different result.

In fact, a natural experiment was set up. The Pima living across the border in Mexico come from the same genetic pool but were able to maintain more of their traditional lifestyle, centered around the food staples known as *the three sisters*: corn, beans, and squash.⁷² Same genes, but about five times less diabetes and obesity.⁷³

Genes may load the gun, but diet pulls the trigger.

Survival of the Fattest

It's been said: “Nothing in biology makes sense except in the light of evolution.”⁷⁴ The known genetic contribution to obesity may be small, but in a certain sense, you could argue it's actually all in our genes. That's because the excess consumption of available calories may be hardwired into our DNA.

We were born to eat. Throughout most of human history and beyond, we existed in survival mode, in a context of unpredictable scarcity, so we've been programmed with a powerful drive to eat as much as we can, while we can, and just store the calories we don't need right away on our bodies for later. Food availability could never be taken for granted, so those who ate more in the moment and were best able to store more fat for the future might better survive subsequent shortages to pass along their genes. Generation after generation, millennia after millennia, those with lesser appetites may have died out, while those who gorged themselves could have selectively lived long enough to pass along a genetic predisposition to eat and store more calories. That may be how we evolved into such voracious, calorie-conserving machines. Now that we're no longer in such lean times, though, we're no longer so lean.

What I just described is the "thrifty gene" concept,⁷⁵ the proposal that obesity is the result of a mismatch between the modern environment and the environment in which we evolved.⁷⁶ It's as if we're now polar bears in a jungle; fur and fat may provide an edge up in the Arctic but would be decidedly disadvantageous in the Amazon.⁷⁷ Similarly, a propensity to pack on the pounds may have been a plus in prehistoric times but can turn into a liability when our scarcity-sculpted biology is plopped down into the land of plenty.

So the prime cause for the obesity epidemic is neither gluttony nor sloth. Obesity may simply be a normal response to an abnormal environment.⁷⁸

Much of our physiology is finely tuned to stay within a narrow range of upper and lower limits. If we get too hot, we sweat; if we get too cold, we shiver. Our bodies have mechanisms to keep us in balance. In contrast, our bodies have had little reason to develop an upper limit to the accumulation of body fat.⁷⁹ In the beginning, there may have been evolutionary pressures to keep lithe and nimble in the face of predation, but thanks in part to weapons and fire, we haven't had to outrun as many saber-toothed tigers over the last two million years or so.⁸⁰ This may have left our genes with the one-sided selection pressures to binge on every morsel in sight and stockpile as many calories onto our bodies as possible.⁸¹

What was once adaptive is now a problem, or at least so says the thrifty gene hypothesis that originated more than a half century ago.⁸² The theory has since been refined and updated, but the basic premise remains largely accepted by the scientific community,⁸³ and the implications are profound.

In 2013, the American Medical Association voted to classify obesity as a disease⁸⁴ against the advice of its own Council on Science and Public Health.⁸⁵ Not that it necessarily matters what we call it—a rose by any other name would cause just as much diabetes—but disease implies dysfunction. Bariatric drugs and surgery are not fixing some physiological malfunction. Our bodies are just doing what they were designed to do in the face of excess calories.⁸⁶ Rather than some sort of disorder, weight gain may be largely a normal response, by normal people, to an abnormal situation.⁸⁷ And with more than 70 percent of Americans now overweight,⁸⁸ it's *literally* normal.

Won't Work for Food

The traditional medical view on obesity, as summed up nearly a century ago: "All obese persons are alike in one fundamental respect—they literally overeat."⁸⁹ While this may be true in a technical sense, it is in reference to overeating calories, not food. Our primitive urge to overindulge is selective. People don't tend to lust for lettuce. We have a natural, inborn preference for sweet, starchy, fatty foods, because that's where the calories are concentrated.

Think about hunting and gathering efficiency. We used to have to work hard for our food. Prehistorically, it wouldn't have made sense to spend all day collecting types of food that, on average, don't provide at least a day's worth of calories. You would have been better off

staying back at the cave. So we evolved to crave foods with the biggest caloric bang for their buck.⁹⁰

If you were able to steadily forage a pound of food an hour and it had 250 calories per pound, it might take you ten hours just to break even on your calories for the day. But if you were gathering something with 500 calories a pound, you could be done foraging in five hours and spend the next five focusing on your wall paintings. So the greater the energy density, the more calories per pound, the more efficient the foraging. We developed an acute ability to discriminate foods based on calorie density and instinctively desire the densest.⁹¹

If you study the fruit and vegetable preferences of four- and five-year-old children, what they like correlates with calorie density. They prefer bananas over berries and carrots over cucumbers. Isn't that just a preference for sweetness? No, they also prefer potatoes over peaches and green beans over melon,⁹² just like monkeys prefer avocados over bananas.⁹³ We appear to have an inborn drive to maximize calories per mouthful.

The researchers in the studies of children only tested whole fruits and vegetables, so all the foods naturally had fewer than five hundred calories per pound, with bananas topping the chart at about four hundred. Something funny happens when you start going much above that: We lose our ability to differentiate between which foods have the highest caloric density. Over a natural range of calorie densities, we have an uncanny aptitude to pick out the subtle distinctions. However, once you start heading toward chocolate, cheese, and bacon territory, which can reach thousands of calories per pound, our perceptions become relatively numb to the differences. No wonder, since these foods were unknown to our prehistoric brains. Aberrant behavior explained by an evolutionary mismatch,⁹⁴ like sea turtle hatchlings crawling in the wrong direction toward artificial light rather than the moon and never reaching the ocean, or dodo birds failing to evolve a fear response because they had no natural predators—and we all know how that turned out.

Full of CRAP

The food industry exploits our innate biological vulnerabilities by stripping down crops into almost pure calories—straight sugar, oil (which is pretty much pure fat), and white flour (which is mostly refined starch). First, they remove the fiber, because it effectively has zero calories. Run brown rice through a mill to make it white, and you lose about two-thirds of the fiber. Turn whole-wheat flour into white flour and lose 75 percent of the fiber. Or you can run crops through animals (to make meat, dairy, and eggs) and remove 100 percent of the fiber.⁹⁵ What you're left with is CRAP, an acronym conceived by one of my favorite dietitians, Jeff Novick, for *calorie-rich and processed* foods.⁹⁶

Calories are condensed in the same way plants are turned into addictive drugs like opioids and cocaine: concentration, crystallization, distillation, and extraction.⁹⁷ They even appear to activate the same reward pathways in the brain.⁹⁸ Put people with "food addiction" in an MRI scanner and show them a picture of a chocolate milkshake, and the areas that light up in their brains are the same⁹⁹ as when cocaine addicts are shown a video of smoking crack¹⁰⁰ or when alcoholics are given a whiff of whiskey.¹⁰¹

Food addiction is a misnomer. People don't suffer out-of-control eating behaviors to food in general. We don't tend to compulsively crave cabbage. But milkshakes are packed with sugar and fat, two of the signals to our brains for calorie density. When people are asked to rate different foods in terms of cravings and loss of control, most incriminated was a load of CRAP—highly processed foods like donuts, along with cheese and meat.¹⁰² Those foods least related to problematic eating behaviors? Fruits and vegetables. Calorie density may be the reason people don't get up in the middle of the night and binge on broccoli.

Animals don't tend to get fat eating the foods they were designed to eat. There is a confirmed report of free-living primates becoming obese, but that was a troop of baboons

who evidently stumbled across some dumpsters at a tourist lodge. The “garbage-feeding animals” weighed 50 percent more than their wild-feeding counterparts.¹⁰³ Sadly, we, too, can suffer the same mismatched fate and become obese by eating garbage. For millions of years before we learned how to hunt, our biology evolved largely on leaves, roots, shoots, fruits, and nuts.¹⁰⁴ Ironically, even the creationists agree that we started out plant-based in Eden’s garden.¹⁰⁵ Maybe it would help if we went back to the basics and cut the CRAP.

Toxic Food Environment

It is hard to eat healthfully against the headwind of such strong evolutionary forces. No matter our level of nutrition knowledge, in the face of pepperoni pizza, the ancestral heritage baked into our genes screams, *Eat it now!*¹⁰⁶ Anyone who doubts the power of basic biological drives should see how long they can go without blinking or breathing. Any conscious decision to hold your breath is soon overcome by the compulsion to breathe. In medicine, shortness of breath is sometimes even referred to as *air hunger*.

The battle of the bulge is a battle against biology, so obesity is not some moral failing. I can’t stress enough that becoming overweight is a normal, natural response to the abnormal, unnatural ubiquity of calorie-dense, sugary, and fatty foods.

The sea of excess calories in which we are now floating (and in which many of us are now drowning) has been referred to as a “toxic food environment.”¹⁰⁷ This helps direct focus away from the individual and toward societal forces at work, such as the fact that the average child may be blasted with ten thousand food commercials a year. Or maybe I should say *pseudo*-food commercials, as 95 percent of the ads were found to be for candy, liquid candy (soft drinks), breakfast candy (sugary cereals), and fast food.¹⁰⁸

Wait a second. If weight gain is just a natural reaction to the easy availability of mountains of cheap, tasty calories, then why isn’t everyone fat? Well, in a certain sense, most everyone is. It’s been estimated that more than 90 percent of American adults are “overfat,” defined as having excess body fat sufficient to impair health.¹⁰⁹ This can occur even in normal-weight individuals (often due to excess abdominal fat), but even if you just look at the numbers on the scale, being overweight has become the norm. If you look at the bell curve, more than 70 percent of us are overweight. A little less than a third are on one side at normal weight and more than a third are on the other side, so overweight they’re obese.¹¹⁰

But if it really is the food, why doesn’t *everyone* get fat? That’s like asking, “If cigarettes really are to blame, why don’t *all* smokers get lung cancer?” This is where genetic dispositions and other exposures can weigh in to tip the scales.¹¹¹ Different people are born with a different susceptibility to cancer, but that doesn’t mean smoking doesn’t play a critical role in exploding whatever inherent risk we have—and the same goes for obesity and our toxic food environment. We can try to tip the scales with smoking cessation and a more healthful diet.

If you lock up two dozen folks in a research study and feed each the exact same number of excess calories, they all gain weight, but some gain more than others. In one study, overfeeding the same thousand calories a day, six days a week for one hundred days caused weight gains ranging from about nine pounds to twenty-nine pounds. Some people are just more genetically susceptible. The twenty-four people in the study were twelve sets of identical twins, and the variation in weight gain between each of them was about a third less than between the unrelated subjects.¹¹² A similar study with weight loss from exercise found a similar result.¹¹³ So, yes, genetics play a role, but that just means some people have to work harder than others. Ideally, inheriting a predisposition for extra weight gain shouldn’t give reason for resignation but rather motivation to put in the extra effort to unseal your fate.

Fattening Grandchildren from the Womb

Identical twins don't just share DNA; they shared a uterus too. Might that also help account for some of their metabolic similarities? Fetal overnutrition, evidenced by an abnormally large birth weight, seems to be a strong predictor of obesity in childhood and later in life.¹¹⁴ Could it be that you are what your mom ate?

Who do you think most determines the birth weight of a test-tube baby—the donor mom who provided all the DNA, or the surrogate mom who provided the intrauterine environment? When it was put to the test, the womb won. Incredibly, a baby born to an obese surrogate mother with a skinny biological mom may harbor a greater risk of becoming obese than a baby from a big biological mom born to a slim surrogate. The researchers concluded that “the environment provided by the human mother is more important than her genetic contribution to birth weight.”¹¹⁵

The most compelling data come from comparing obesity rates in siblings born to the same mother before and after she had bariatric (weight loss) surgery.¹¹⁶ Compared to their brothers and sisters born after the surgery, those born when the mom weighed about one hundred pounds more had higher rates of inflammation and metabolic derangements, and, most critically, three times the risk of severe obesity (affecting 35 percent of those born before the weight loss, compared to 11 percent born after). The researchers concluded that “these data emphasize how critical it is to prevent obesity and treat it effectively to prevent further transmission to future generations.”¹¹⁷

But wait. Mom had the same DNA before and after the surgery. She passed down the same genes. How could her weight during pregnancy affect the weight destiny of her children any differently? We finally figured out the mechanism by which this can happen: epigenetics.

Epigenetics, which literally means *above genetics*, layers an extra level of information on top of the DNA sequence that can both be affected by our surroundings and potentially passed on to our children.¹¹⁸ This is thought to account for the “developmental programming”¹¹⁹ (also known as *metabolic imprinting*¹²⁰) that can occur in the womb depending on the weight of the mother, or even the grandmother. Since all the eggs in an infant daughter's ovaries are already preformed before birth,¹²¹ a mother's weight status during pregnancy could potentially affect the obesity risk of her grandchildren too.¹²² Either way, you can imagine how this could result in a vicious intergenerational cycle where obesity begets obesity.

Is there anything we can do about it? Well, prevention may be the key. Given the epigenetic influence of maternal weight during pregnancy, a symposium of experts on pediatrics concluded that “planning of pregnancy, including prior optimization of maternal weight and metabolic condition, offers a safe means to initiate the prevention rather than treatment of pediatric obesity.”¹²³ Easier said than done, but overweight moms-to-be may take comfort in the fact that even the moms in the study who had given birth to kids with three times lower risk of obesity were still, on average, obese themselves,¹²⁴ suggesting that significant weight loss can help even if you're not able to get down to a normal weight.

What Happened in the 1970s?

The rise in the number of calories provided by the U.S. food supply since the 1970s is more than sufficient to explain the entire obesity epidemic.¹²⁵ Similar spikes in calorie surplus were noted in developed countries around the world in parallel with,¹²⁶ and presumed primarily responsible for,¹²⁷ the expanding waistlines of their populations. By the year 2000, after taking exports into account, the United States was producing 3,900 calories a day for every man, woman, and child, nearly twice as much as many people need.¹²⁸

The number of calories in the food supply actually declined over the first half of the twentieth century, only starting its upward climb to unprecedented heights in the 1970s.¹²⁹ The drop in the first half of the century was attributed to the reduction in hard manual labor. The population had decreased energy needs, so they ate decreased energy diets. They didn't need all the extra calories. But then, the so-called energy balance flipping point occurred. (*Energy balance* is the concept of calories in versus calories out.) Why did the “move less, stay lean” phase that had existed throughout most of the century turn into the “eat more, gain weight” phase that plagues us to this day?¹³⁰ What changed to bring about this flipping point?

What happened in the 1970s was a revolution in the food industry. In the 1960s, most food was prepared and cooked in the home. The average housewife spent hours a day cooking and cleaning up after meals (the husband averaged nine minutes).¹³¹ But then a profound transformation took place. Technological advances in food preservation and packaging enabled manufacturers to mass prepare and distribute food for ready consumption. The metamorphosis has been compared to what had happened a century before in the Industrial Revolution with the mass production and supply of manufactured

goods. This time, though, it was the mass production and supply of food. Using new preservatives, artificial flavors, and techniques such as deep freezing and vacuum packing, food companies could take advantage of economies of scale¹³² to mass-produce ready-made, durable, palatable edibles that offer an enormous commercial advantage over fresh and perishable foods.¹³³ And the packaged food sector is now a multitrillion-dollar industry.¹³⁴

Think ye of the Twinkie. With enough time and effort, any ambitious cook could create cream-filled cakes in their own kitchen, but today they are available at every turn for less than a dollar.¹³⁵ If every time we wanted a Twinkie we had to bake it ourselves, we'd probably eat far fewer of them.¹³⁶

Consider the humble potato. We've long been a nation of potato eaters, but they were largely baked or boiled. Anyone who has made fries from scratch knows what a pain it is, with all the peeling, cutting, and splattering. But with sophisticated machinations of mechanization, french fry production became centralized so fries could be shipped at -40°F to any fast-food deep-fat fryer or supermarket frozen food section in the country to become America's favorite vegetable. Nearly all the increase in potato consumption in recent decades has been in the forms of french fries and potato chips.¹³⁷

Cigarette production offers a compelling parallel. Before the automated rolling machine was invented, cigarettes had to be rolled by hand. It took fifty workers to produce the same number of cigarettes a machine could make in a single minute. After automation, cigarette prices plunged and production leaped into the billions.¹³⁸ Cigarette smoking went from being relatively uncommon to almost everywhere. In the twentieth century, the average per capita cigarette consumption rose from 54 cigarettes a year to 4,345 by the time of the 1964 Surgeon General's report.¹³⁹ The average American went from smoking about 1 cigarette a week to 70. That's a half pack a day.

Tobacco itself was just as addictive before and after mass marketing. What changed was the much greater opportunity for cheap, easy access. French fries have always been tasty, but they went from being rare even in restaurants to omnipresent around every corner. You can probably even find them next to the gas station where you can get your Twinkies and cigarettes.

The first Twinkie dates back to 1930, though, and Ore-Ida started selling frozen french fries in the 1950s.¹⁴⁰ So there has to be more to the story than just technological innovation.

Aiding and Abetting

The rise in calorie surplus sufficient to explain the obesity epidemic was less a change in food *quantity* than in food *quality*, with an explosion in cheap, high-calorie, low-quality convenience foods. The federal government very much played a role in making this happen. U.S. taxpayers unwittingly give billions in subsidies to prop up the likes of the sugar industry, the corn industry and its high-fructose syrup, and the soybean industry, which processes about half of its crop into vegetable oil and the other half into cheap animal feed to help make Dollar Menu meat.¹⁴¹ When was the last time you sat down to some sorghum? Exactly. Why then do taxpayers give nearly a quarter billion dollars a year to the sorghum industry?¹⁴² It's almost all fed to livestock.¹⁴³ We've created a pricing structure that favors the production of sugars, oils, and animal products.¹⁴⁴

The first farm bill started out as an emergency measure during the Great Depression of the 1930s to protect small farmers, but subsequent ones were weaponized by Big Ag into cash cows with pork barrel politics.¹⁴⁵ Agricultural policies in the United States and Europe have been deliberately designed to lower the costs of basic cash crops like sugar and staples like meat, wheat, dairy, and eggs.¹⁴⁶ There is a lot of money at stake—and in steak. From 1970 to 1994, for example, global beef prices dropped by more than 60 percent.¹⁴⁷ If

it weren't for taxpayers sweetening the pot with billions of dollars a year,¹⁴⁸ high-fructose corn syrup would cost the soda industry about 10 percent more.¹⁴⁹

Subsidies are one of the reasons chicken is so cheap. After one of the farm bills, corn and soy were subsidized below the cost of production for cheap animal fodder, effectively handing the poultry and pork industries around \$10 billion each.¹⁵⁰ That's not chicken feed. Or rather, it is!

This is changing what we eat. Thanks in part to subsidies, meats, sweets, eggs, oils, dairy, and soda were all getting relatively cheaper as the obesity epidemic took off (compared to the overall consumer food price index), whereas the relative cost of fresh fruits and vegetables *doubled*.¹⁵¹ This may help explain why, during about the same period, the percentage of Americans getting five servings of fruits and vegetables a day dropped from 42 percent to 26 percent.¹⁵² Why not subsidize produce instead? Because that's not where the money is.

Whole foods, or minimally processed foods such as canned beans or tomato paste, are what's referred to in the food business as *commodities*. They have such slim profit margins that they're sometimes even sold at or below cost as "loss leaders" to attract customers in the hopes they'll also buy the "value-added" products,¹⁵³ the most profitable of which (for producers and vendors alike) are the ultraprocessed, fatty, sugary, and salty concoctions of artificially flavored, artificially colored, and artificially cheap ingredients, thanks to taxpayer subsidies.

Different foods reap different returns. Measured in profit per square foot of supermarket selling space, confectionaries like candy bars consistently rank among the most lucrative. Fried snacks like potato chips and corn chips are also highly profitable. PepsiCo's subsidiary Frito-Lay brags that while its products represent only about 1 percent of total supermarket sales, they may account for more than 10 percent of the operating profits for supermarkets and 40 percent of profit growth.¹⁵⁴

It's no surprise then that the entire system is geared toward garbage. The rise in the calorie supply wasn't just *more* food but more of a different *kind* of food. More than half of all calories consumed by most adults in the United States these days were found to originate from these subsidized foods, and we appear to be worse off for it. Those eating the most have significantly higher levels of chronic disease risk factors, including elevated cholesterol, inflammation, and body weight.¹⁵⁵

There's a dumb dichotomy about the drivers of the obesity epidemic: Is it the sugar or the fat? Both are highly subsidized, and both took off during the unfolding epidemic. Along with a significant rise in refined grain products, the rise in obesity was accompanied by about a 20 percent increase in per capita pounds of added sugars and a 36 percent increase in added fats¹⁵⁶ (mostly in the form of oil,¹⁵⁷ presumably from fried fast food and processed junk).¹⁵⁸ Both added sugars and added fats now represent major sources of calories in the American diet.¹⁵⁹

Quarter Pounder

In the 1970s, the U.S. government went from just subsidizing some of the worst foods to actually paying companies to make more of them. During that decade, the farm bills reversed long-standing policies aimed at limiting production to protect prices and instead started giving payouts in proportion to output.¹⁶⁰ Extra calories began pouring into the food supply.

Then, in 1981, the CEO of General Electric gave a speech that effectively launched the "shareholder-value movement," reorienting the primary goal of corporations toward maximizing short-term returns for investors.¹⁶¹ This placed extraordinary pressures on food companies from Wall Street to post increasing profit growth every quarter to boost their

share prices. There was already a glut of calories on the market, and now they had to sell even more.

This puts food and beverage CEOs into a near impossible bind. It's not like they're rubbing their sticky hands together at the thought of luring more Hansels and Gretels to their doom in their houses of candy. Food giants cannot necessarily do the right thing if they wanted; they are beholden to investors. If they stopped marketing to kids or tried to sell healthier food or attempted anything that could jeopardize their quarterly profit growth, Wall Street could demand a change in management.¹⁶² Healthy eating is bad for business. It's not some grand conspiracy—it's not even anyone's fault. It's just how the system works.

Marketing Excesses

Given the constant demands for corporate growth and rapid returns in an already oversaturated marketplace, the food industry needed to get people to eat more. Like the tobacco industry before it, the food industry turned to the ad men—and in a big way.¹⁶³ Tens of millions of dollars are now spent annually advertising a single brand of candy bar.¹⁶⁴ McDonald's alone spends billions a year.¹⁶⁵ Thus far, the food industry has spent more money on advertising than any other sector of the economy.¹⁶⁶

Reagan-era deregulation removed the limits placed on marketing food products on television to children.¹⁶⁷ In addition to the ten thousand food ads children may see on TV a year,¹⁶⁸ there is marketing content online, in print, at school, on their phones, at the movies, and everywhere in between.¹⁶⁹ Nearly all of it is for products detrimental to their health.¹⁷⁰

Besides its massive early exposure¹⁷¹ and ubiquity, food marketing has become highly sophisticated. With the help of child psychologists, companies learn how best to influence children to manipulate their parents. Packaging is designed to most effectively attract a child's attention and then placed at their eye level in the store.¹⁷² You know those mirrored bubbles in the ceilings of supermarkets? They're not just for shoplifters. Closed-circuit cameras and GPS-like devices on shopping carts are used to strategize how best to guide shoppers toward the most profitable products.¹⁷³ Behavioral psychology is widely applied to increase impulse buying, and even eye-movement tracking technologies are utilized.¹⁷⁴

The unprecedented rise in the power, scope, and sophistication of food marketing starting around 1980 aligns well with the blastoff slope of the obesity epidemic. Since then, some of the techniques, such as product placement, in-school advertising, and event sponsorships, skyrocketed from essentially nothing to multibillion-dollar industries. This led at least one noted economist to conclude that “the most compelling single interpretation of the admittedly incomplete data we have is that the large increase in obesity is due to marketing.”¹⁷⁵ Innovations in manufacturing and political maneuvering led to a food supply bursting at the seams with nearly four thousand calories a day for each one of us, but the critical piece may have been the advancements in marketing manipulations used to try to peddle that surplus into our mouths.¹⁷⁶

Wining and Dining

The opening words of the National Academy of Medicine's report on the threat posed by food ads: “Marketing works.”¹⁷⁷ Yes, there's a large number of well-conducted randomized studies I could share with you to show how advertising exposure and other marketing methods can change your eating behavior and get you to eat more,¹⁷⁸ but what do you need to know beyond the fact that the industry spends tens of billions of dollars on it?¹⁷⁹ To get people to drink its brown sugar water, do you think Coca-Cola would spend a penny more than it thought it had to? It's like when my medical colleagues accept invitations to “drug lunches” from pharmaceutical representatives and take offense that I would suggest

it might affect their prescribing practices. Do they really think drug companies are in the business of giving away free money for nothing? They wouldn't do it if it didn't work. There is no free lunch.

Just to give you a sense of marketing's insidious nature, let me share an interesting piece of research published in *Nature*, the world's leading¹⁸⁰ scientific journal. The article titled "In-Store Music Affects Product Choice" documented an experiment in which either French accordion or German Bierkeller music was played on alternate days in the wine section of a grocery store.¹⁸¹ On the days the French music played in the background, people were three times more likely to buy French wine, and on German music day, shoppers were about three times more likely to buy German wine. Despite the dramatic effect—not just a few percent difference but a complete threefold reversal—when approached afterward, the vast majority of shoppers denied the music had influenced their choices.¹⁸²

Like a Kid in a Candy Store

In addition to the \$10 billion or so spent on advertising each year, the food industry spends around another \$20 billion on other forms of marketing, such as trade shows, incentives, consumer promotions, and supermarket "slotting fees,"¹⁸³ which are the purchasing of shelf space from grocery stores by food and beverage companies to prominently display their most profitable products. The practice is evidently known as *cliffing*, because companies are forced to bid against each other for eye-level shelf placement, with the loser being pushed "over the cliff."¹⁸⁴ With slotting fees up to \$20,000 per item, per retailer, and per city,¹⁸⁵ you can imagine what kinds of products get the special treatment. Hint: It ain't broccoli.

To get a sense as to what types of products merit prime-shelf real estate, look no further than the checkout aisle. "Merchandising the power categories on every lane is critical," reads a trade publication on the "best practices for superior checkout merchandising." And what are the "power categories"? Candy bars and beverages. Evidently, even a 1 percent power category boost in sales could earn a store an extra \$15,250 a year.¹⁸⁶ It's not that supermarkets don't care about their customers' health. It's more that publicly traded companies (like most of the leading grocery store chains) are impelled to increase profits above other considerations.¹⁸⁷

Driven by Distraction

We all like to think we make important life decisions, such as what to eat, consciously and rationally. If that were the case, though, we wouldn't be in the midst of an obesity epidemic.¹⁸⁸ As I explore in the Habit Formation section, most of our day-to-day behavior does not appear to be dictated by careful, considered deliberations. Rather, we tend to make more automatic, impulsive decisions triggered by unconscious cues or habitual patterns, especially when we're tired, stressed, or preoccupied. The unconscious parts of our brains are thought to guide human behaviors as much as 95 percent of the time,¹⁸⁹ and this is the arena where marketing manipulations do most of their dirty work.

The parts of our brains that govern conscious awareness may only be able to process about fifty bits of information per second, which is roughly equivalent to a short tweet. Our entire cognitive capacity, on the other hand, is estimated to process in excess of ten million bits per second. Because we're only able to purposefully process a limited amount of information at a time, our decisions can become even more impulsive if we're distracted or otherwise unable to concentrate.¹⁹⁰ An elegant illustration of this "cognitive overload" effect was provided by an experiment involving fruit salad and chocolate cake.

Before calls could be made at a touch of a button or the sound of our voice, the seven-digit span of a phone number was based in part on the longest sequence most people can recall on the fly. We only seem able to hold about seven chunks of information (plus or minus two) in our immediate, short-term memory.¹⁹¹ So this was the setup: Randomize people to memorize either a seven-digit number or a two-digit number to be recalled in another room down the hall. As they walk from one room to the other, offer each of them the choice of a fruit salad or a piece of chocolate cake. Memorizing a two-digit number is

easy and presumably takes few cognitive resources. Under the two-digit condition, most chose the fruit salad. Faced with the same decision, most of those trying to keep seven digits in their heads just went for the cake.¹⁹²

This can play out in the real world by potentiating the effect of advertising. Have people watch a TV show with commercials for unhealthy snacks, and, no surprise, they eat more unhealthy snacks compared to those exposed to nonfood ads. Or maybe that is a surprise. We all like to feel as if we're in control and not so easily manipulated. The kicker is we may be even more susceptible the less we're paying attention. Randomize people to the same two- or seven-digit memorization task while watching a TV show, and the snack-attack effect was magnified among those who were more preoccupied.¹⁹³ How many of us have the TV playing in the background or multitask during commercial breaks? This research suggests that doing so may make us even more impressionable to the subversion of our better judgment.

There's an irony in all of this. Calls for restrictions on marketing are often resisted by invoking the banner of freedom. What does that even mean in this context, when research shows how easily our free choices can be influenced without our conscious awareness?¹⁹⁴ A senior policy researcher at the RAND Corporation even went as far as to suggest that given the dire health consequences of our unhealthy eating habits, insidious marketing manipulations "should be considered in the same light as the invisible carcinogens and toxins in the air and water that can poison us without our awareness."¹⁹⁵

Passive Overconsumption

Food and beverage companies frame body weight as a matter of personal choice. But even when we're not distracted, the power of the "eat more" food environment may sometimes overcome our conscious controls over eating.¹⁹⁶ One look around the room at a dietitians' convention can tell you that even nutrition professionals are vulnerable to the aggressively marketed ubiquity of tasty, cheap, convenient calories. This suggests there are aspects of our eating behaviors that defy personal insight by flying below the radar of conscious awareness.¹⁹⁷ Appetite physiologists call the result of these subconscious actions *passive overconsumption*.¹⁹⁸

Remember that brain scan study where the thought of a milkshake lit up the same reward pathways in the brain as when cocaine addicts saw videos of smoking crack or alcoholics got a whiff of whiskey? That was triggered with just a *picture* of a milkshake. Intellectually, we know it's only an image, but our lizard brains just see survival. Dopamine gets released, cravings get activated, and we're motivated to eat. It's simply a reflexive response over which we have seemingly little control, which is why marketers ensure there are pictures everywhere of milkshakes and the like.¹⁹⁹

Maintaining a balance between calories in and calories out feels like a series of voluntary acts under conscious control, but it may be more akin to bodily functions, such as blinking, breathing, coughing, swallowing, or sleeping. You can try to will yourself power over any of these, but, by and large, they just happen automatically, driven by ancient scripts.²⁰⁰

Portions Out of Proportions

During any given two-day period, it seems half of U.S. children consume fast food.²⁰¹ Though attempts have been made to tie fast-food consumption with burgeoning obesity,²⁰² it may just be a marker for a lousier diet in general.²⁰³ Value-meal bundling and supersizing portions are not unique to the fast-food industry. Portion sizes have increased throughout the restaurant sector.

Compared to McDonald's original sizes in 1955, its burger, fries, and soda offerings have increased 250–500 percent.²⁰⁴ But huge food is everywhere—half-pound muffins,²⁰⁵ steak house steaks weighing a pound and a half,²⁰⁶ and pasta bowls capable of harboring two pounds of Alfredo.²⁰⁷ Have you seen some of the giant chocolate bars these days? At the movie theater, a "medium" popcorn today may hold sixteen cups of greased kernels and top off at a thousand calories.²⁰⁸

What role has expanding sizes played in expanding our sizes? To be a plausible driver of the obesity crisis, candidate factors would not only match the epidemic curve but also be shown demonstrably to cause weight gain. The increases in portion size do seem to parallel obesity trends, but the experimental data are limited.²⁰⁹

Manipulating portion sizes at a meal or over the course of a day can reliably affect intake,²¹⁰ perhaps due to the tendency for people to take larger and faster bites when provided with bigger portions.²¹¹ The longest big-portion-size study I could find only lasted eleven days. In that time, however, a 50 percent increase in portion sizes increased intake by more than four hundred calories a day. Critically, this effect was sustained throughout the duration of the study and did not appear to decline over time, suggesting that bigger servings may indeed lead to bigger curvings.²¹²

Of course, it matters *what* you're overeating. Some foods, like many vegetables, have such a low calorie density that you would tire from chewing before you could overdo it. You'd have to eat a wheelbarrow full of cabbage before you'd ever need to begin worrying about overindulging. The portion-size effect has even been used to encourage healthier habits by dishing out extra veggies.²¹³ So "simply telling people to eat less of everything may not be the most effective message," wrote one of the principal investigators in the obesity field.²¹⁴ Thus, this is not a call to buy baby carrots and cherry tomatoes. Size may matter, but substance is more salient.

Every Day We Run the Gauntlet

Not only are food ads ubiquitous, but so, too, is the food being advertised. The types of establishments selling food products expanded dramatically in the 1970s and 1980s,²¹⁵ and now that jolt of dopamine and the artificially stimulated feelings of hunger are around every turn.²¹⁶ Candy and snacks can be found at the checkout counters of gas stations, drugstores, bookstores, and places that used to just sell clothes, hardware, building supplies, or home furnishings. The largest food retailer in the United States is Walmart.²¹⁷

It has become socially acceptable to eat anywhere—in your car, on the street, at your desk, or even on a crowded bus. We've become a snacking society.²¹⁸ Vending machines are pervasive. Daily eating episodes seem to have gone up by about a quarter from the late 1970s, from about four occasions a day to five, which potentially accounts for twice the calorie increase attributed to increasing meal sizes.²¹⁹ Snacks and beverages alone could account for the bulk of the calorie surplus implicated in the epidemic.²²⁰

And think of the children. Here we are trying to do the best for our kids, role modeling healthy habits and feeding them healthy foods, but then they venture out into a veritable tornado of junk foods and manipulative messages. As a commentary in *The New England Journal of Medicine* asked, why should our efforts to protect our "children from life-threatening illness be undermined by massive marketing campaigns from the manufacturers of junk food?"²²¹ Pediatricians are now encouraged to have the "French Fry Discussion" with parents at the twelve-month "well-child visit" and no longer wait until kids are two years old.²²² And even that may be too late. Two-thirds of infants are fed junk food before their first birthday.²²³

Dr. David L. Katz may have said it best in *Harvard Health Policy Review*:

*Those who contend that parental or personal responsibility should carry the day despite these environmental temptations might consider the implications of generalizing the principle. Perhaps children should be encouraged, but not required, to attend school and tempted each morning by alternatives, such as buses to the circus, zoo, or beach.*²²⁴

Is Big Food Making Us Big Too?

The plague of tobacco-related deaths wasn't just due to the mass manufacture and marketing of cheap cigarettes. Tobacco companies actively sought to make their products even more craveable by spraying the sheets of tobacco with nicotine and additives like ammonia to provide a bigger nicotine kick.²²⁵ The food industry employs taste engineers to accomplish a similar goal: maximize the irresistibility of their products.

Taste is the leading factor in food choice.²²⁶ Salt, sugar, and fat are used as the three points of the compass to create “superstimulating” “hyperpalatability” to tempt people into impulsive buys and compulsive consumption.²²⁷ Foods are designed intentionally to hook into our evolutionary triggers and breach whatever biological barriers help keep consumption within reasonable limits.²²⁸

Big Food is big business. The processed food industry alone brings in more than \$2 trillion a year.²²⁹ That affords it the economic might to manipulate more than just taste profiles; it influences public policy and scientific inquiry as well. The food, alcohol, and tobacco industries have all used similar unsavory tactics: blocking health regulations, co-opting professional organizations, creating front groups, and distorting the science.²³⁰ The common playbook shouldn’t be surprising given the many common corporate threads—at one time, for example, cigarette giant Philip Morris owned both Kraft and Miller Brewing.²³¹

In 2009, the food industry spent more than \$50 million to hire 350 lobbyists to influence legislation, most of whom were “revolvers,” former federal employees in the revolving door between industry and its regulators. They could push corporate interests from the inside and then turn around and be rewarded with cushy lobbying jobs after their “public service.”²³²

In the following year, the food industry acquired a new weapon, a stick to go along with all those carrots. On January 21, 2010, the Supreme Court’s 5–4 *Citizens United* ruling permitted corporations to spend unlimited amounts of money on campaign ads to trash anyone who dared stand against them.²³³ No wonder our elected officials have so thoroughly shrunk from the fight,²³⁴ leaving us largely with a government of Big Food, by Big Food, and for Big Food.²³⁵

Globally, a similar dynamic exists. Weak tea calls from the public health community for voluntary standards are met not only with vicious fights against meaningful change²³⁶ but also massive transnational trade and foreign investment deals that cement protection of food industry profits into the laws of the lands.²³⁷

The corrupting commercial influence even extends to medical associations. Reminiscent of the “Just what the doctor ordered” cigarette ads of yesteryear,²³⁸ the American Academy of Family Physicians has accepted millions from the Coca-Cola Company, in part to explicitly “develop consumer education content on beverages and sweeteners.”²³⁹ When the American Academy of Pediatrics was called out for its proud new corporate relationship with Coke and the company’s “invaluable commitment to children’s health,”²⁴⁰ an executive vice president of the academy tried to quell protest by explaining that this alliance was not without precedent: The American Academy of Pediatrics had had relationships with Pepsi and McDonald’s for some time.²⁴¹

On the front line, fake grassroots “AstroTurf” groups are used to mask the corporate message. In the footsteps of Get Government Off Our Back, memorably acronymed GGOOB and created by R. J. Reynolds to fight tobacco regulation, the front group Americans Against Food Taxes may just as well be called Food Industry Against Food Taxes.²⁴² The power of front-group formation was enough to bind two bitter corporate rivals, the Sugar Association and the Corn Refiners Association, and have them link arms with the American Beverage Association and the National Confectioners Association to partner together as Americans for Food and Beverage Choice.²⁴³

Another tried-and-true tobacco industry tactic:²⁴⁴ Research front groups like Coca-Cola’s Global Energy Balance Network can be used to subvert the scientific process by shaping²⁴⁵ or suppressing²⁴⁶ science that deviates from the corporate agenda. The trans fat story is one of many examples. Food manufacturers have not only long denied that trans fat was associated with disease,²⁴⁷ they actively worked to limit inquiry²⁴⁸ and discredit research findings.²⁴⁹

One estimate places the global death toll from foods high in trans fat, saturated fat, salt, and sugar at fourteen million lost lives. Every year.²⁵⁰ The inability of countries around the world to turn the tide on obesity “is not a failure of individual will-power,” said the director-general of the World Health Organization.²⁵¹ “It is a failure of political will to take on the powerful food and soda industries.”²⁵² She ended her keynote address entitled “Obesity and Diabetes: The Slow-Motion Disaster” before the National Academy of Medicine with these words: “The interests of the public must be prioritized over those of corporations.”²⁵³

We Have to Stop Eating Like This

When it comes to uncovering the root causes of the obesity epidemic, there appears to be a sort of manufactured confusion. Major studies assert the causes are “extremely complex” and “fiendishly hard to untangle.”²⁵⁴ Having just reviewed the literature, it doesn’t seem like much of a mystery to me.

It’s the food.

Attempts at obfuscation—rolling out hosts of implausible explanations like sedentary lifestyles or lack of self-discipline—serve the needs of the manufacturers and marketers more than the public’s health and the interest of truth.²⁵⁵ When asked about the role of restaurants in the obesity epidemic, the president of the National Restaurant Association replied, “Just because we have electricity doesn’t mean you have to electrocute yourself.”²⁵⁶ Yes, but much of the food industry is effectively attaching electrodes to shock and awe the reward centers in our brains to undermine our self-control.

Advances in processing and packaging, combined with government policies and handouts that fostered cheap commodities for the “food industrial complex,”²⁵⁷ led to a glut of ready-to-eat, ready-to-heat, or ready-to-drink products. To help assuage impatient investors, marketing became ever-more pervasive and persuasive. All these factors conspired to create unfettered access to copious, convenient, low-cost, high-calorie foods often willfully engineered with chemical additives to be hyperstimulatingly sweet or savory, yet only weakly satiating.

As we each sink deeper into a quicksand of calories, more and more mental energy is required to swim upstream against the constant bombardment of advertising and 24-7 panopticon of arm’s-length tempting treats.²⁵⁸ There’s so much food flooding the market now that much of it ends up in the trash. Food waste has progressively increased by about 50 percent since the 1970s.²⁵⁹ Perhaps better in the landfill, though, than filling up our stomachs. And too many of these cheap, fattening foods prioritize shelf life over human life.

But dead people don’t eat. Don’t food companies have a vested interest in keeping their consumers healthy? A question such as this reveals a fundamental misunderstanding of the system. A public company’s primary responsibility is to reap returns for investors. Consider the fact that the tobacco industry produces products that *kill* one in two of its most loyal customers.²⁶⁰ It’s not about customer satisfaction but shareholder satisfaction. The customer always comes second.

Just as weight gain may be a perfectly natural reaction to a fattening food environment, governments and businesses are just responding normally to the political and economic realities of our system.²⁶¹ Can you think of a single major industry that would benefit from people eating less junk? “Certainly not the agriculture, food product, grocery, restaurant, diet, or drug industries,” emeritus professor Marion Nestle wrote in a *Science* editorial when she was chair of nutrition at New York University. “All flourish when people eat more, and all employ armies of lobbyists to discourage governments from doing anything” about it.²⁶²

If part of the problem is cheap, tasty convenience, is the solution hard-to-find food that’s unappealing and expensive? Or might there be a way to get the best of all worlds—easy,

healthy, delicious, satisfying meals that help you lose weight?
I wrote this book to find out.

THE CONSEQUENCES

As Queasy as ABC

The largest study in history on the health effects of being overweight analyzed data from more than fifty million people in nearly two hundred countries and found that too much excess body weight accounts for the premature deaths of about four million people every year. Most of these deaths are from heart disease, but the researchers found “convincing” or “probable” evidence linking obesity to twenty different disorders²⁶³—a veritable alphabet soup of potential health concerns.

A Is for Arthritis

In the ABCs of health consequences, *A* is for *arthritis*. Obesity can worsen rheumatoid arthritis²⁶⁴ and increase the risk of another inflammatory joint disease,²⁶⁵ gout, known as *the disease of kings* thanks to their overly rich diets. The most common joint disease in the world, though, is osteoarthritis,²⁶⁶ and obesity may be its main modifiable risk factor.²⁶⁷

Osteoarthritis develops when the cushioning cartilage lining of joints breaks down faster than the body can build it back up.²⁶⁸ The knees are the most commonly affected, leading to the assumption that the disease’s relationship to obesity was simply the excess wear and tear from added load on the joints. Non-weight-bearing joints, like the hands and wrists, can also be affected, however, which suggests the link isn’t purely mechanical. Obesity-related *dyslipidemia* may be playing a role,²⁶⁹ with elevations in the amount of fat, cholesterol, and triglycerides in the blood aggravating inflammation in the joints.²⁷⁰

Losing just around a pound a year over a span of a decade may decrease the odds of developing osteoarthritis by more than 50 percent.²⁷¹ Weight reduction may even obviate the need for knee replacement surgery. Within just eight weeks, obese osteoarthritis sufferers who had been randomized to lose weight improved their knee function as much as those going through surgery. Researchers concluded that losing around twenty pounds of fat “might be regarded as an alternative to knee replacement.”²⁷²

But isn’t it easier to just get your knee replaced than lose twenty pounds? Rarely discussed is the fact that nearly one in two hundred knee replacement patients dies within ninety days of surgery. Given the extreme popularity of the operation—about seven hundred thousand are performed each year in the United States—an orthopedics journal editor suggested that “people considering this operation are inadequately attuned to the possibility that it may kill them.”²⁷³ A surgeon responded by questioning whether patients should be told about what is arguably the “single most-salient fact”:²⁷⁴

*To me, the real question is whether this knowledge will help the patient. Will it add to the anxiety of the already-anxious patient, perhaps to the point of denying that patient a helpful operation? Or will this knowledge motivate a less-handicapped patient to stick to a diet and physical activity regime? Ultimately, then, the question boils down to the surgeon’s judgment.*²⁷⁵

Even among the vast majority who survive the surgery, approximately one in five knee replacement patients describes being unsatisfied with the outcome.²⁷⁶ Weight loss, on the other hand, may offer a nonsurgical alternative that instead treats the *cause* and offers only beneficial side effects.

B Is for Back Pain and Blood Pressure

Being overweight is also a risk factor for low back pain,²⁷⁷ sciatica,²⁷⁸ lumbar disc degeneration,²⁷⁹ and herniation.²⁸⁰ As with arthritis, this may be due to the combination of the hefty joint load plus the inflammation and cholesterol associated with being heavier.²⁸¹ Autopsy studies show that the lumbar arteries that feed the spine can get clogged with atherosclerosis and starve the discs in the lower back of oxygen and nutrients.²⁸²

B is also for *blood pressure*. Excess visceral fat can physically compress our kidneys,²⁸³ and the increased pressure can effectively squeeze sodium back into our bloodstreams, increasing our blood pressures. Together, the combination of obesity and hypertension can have “disastrous health implications.”²⁸⁴ Ready for some good news? Even just a few pounds of weight loss can help take off the pressure. Losing weight has been described as a “vital strategy for controlling hypertension.”²⁸⁵ In fact, losing around nine pounds was shown to lower blood pressures²⁸⁶ about as much as cutting salt intake²⁸⁷ approximately in half.²⁸⁸

C Is for Cancer

As many as three-quarters of people surveyed were evidently unaware of the link between obesity and cancer²⁸⁹ when in fact, based on a comprehensive review of a thousand studies, excess body fat raises the risk of most cancers, including esophageal, stomach, colorectal, liver, gallbladder, pancreatic, breast, uterine, ovarian, kidney, brain, thyroid, and bone marrow (multiple myeloma) cancers.²⁹⁰ Why? It could be due to the chronic inflammation that comes with obesity²⁹¹ or the high insulin levels due to insulin resistance.²⁹² (Besides controlling blood sugars, insulin is a potent growth factor that can promote tumor growth.²⁹³) In women, it could also be the excess estrogen.²⁹⁴

After the ovaries shut down at menopause, fat takes over as the principal site of estrogen production. This is why obese women have up to nearly twice the estrogen levels circulating in their bloodstreams,²⁹⁵ which is associated with increased risk of developing—and dying from—breast cancer.²⁹⁶ A twenty-pound weight loss can reduce estrogen levels within the breast by 24 percent.²⁹⁷ The data on prostate cancer aren’t as strong,²⁹⁸ though obesity is associated with increased risk of invasive penile cancer.²⁹⁹

One reason we’re confident the link between obesity and cancer is cause and effect, and not just an indirect consequence of eating poorly, is because when people lose weight—even just through bariatric surgery—their overall risk of cancer goes down. Those experiencing a sustained loss of about forty pounds after surgery went on to develop around one-third fewer cancers over the subsequent decade or so, compared with a nonsurgical control group of matched individuals who continued to slowly gain weight over time.³⁰⁰ The exception is colorectal cancer.³⁰¹

Colorectal cancer appears to be the only malignancy for which the risk goes *up* after obesity surgery. After bariatric surgery, the rate of rectal cancer death may triple.³⁰² The rearrangement of anatomy involved in one of the most common surgeries—gastric bypass—is thought to increase bile acid exposure along the intestinal lining. This causes sustained pro-inflammatory changes even years after the procedure, which are thought to be responsible for the increased cancer risk.³⁰³ In contrast, losing weight by dietary means has the potential to decrease obesity-related cancer risk across the board.

D Is for Diabetes

As laid out in a consensus statement from the International Diabetes Federation, obesity is considered the single most important risk factor for the development of type 2 diabetes,³⁰⁴ which is now the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness.³⁰⁵ Ironically, many of the leading drugs used to treat diabetes, including insulin itself, actually cause further weight gain, creating a vicious cycle.³⁰⁶ So, again, using lifestyle medicine to treat the underlying cause is not only the safest, simplest, and cheapest route but also can be the most effective.

E Is for Encephalopathy

Encephalopathy means *brain disease*, and there are consistent data linking obesity in middle age to higher risk of dementia later in life.³⁰⁷ Overweight individuals have about one-third higher risk, and those who are obese in midlife seem to have about 90 percent greater risk of becoming demented.³⁰⁸ The risk isn't just limited to future dysfunction, though. People with excess body weight don't appear to think as clearly at any age.

Obese individuals show broad impairments in what are called *executive functions of the brain*, such as working memory, decision-making, planning, cognitive flexibility, and verbal fluency.³⁰⁹ These play a critical role in everyday life. People may think about their obesity and the resulting stigma they experience as much as five times every hour,³¹⁰ but the cognitive deficits do not appear to arise just from being distracted by these thoughts. There are actually structural brain differences between normal-weight and overweight individuals.

A review entitled "Does the Brain Shrink as the Waist Expands?" noted gray matter atrophy across all ages among those carrying excess body fat.³¹¹ This reduced brain volume correlates with the lower executive function.³¹² Compromised integrity of the rest of the brain, the white matter, has also been shown, which suggests accelerated brain aging even in young adults and children with obesity.³¹³ This implies that there's something about the obesity itself that is affecting brain function, rather than a later clinical consequence of corresponding conditions such as high blood pressure.³¹⁴ Purported mechanisms for such executive dysfunction include inflammation and oxidative stress, both related to obesity.³¹⁵

Does weight loss improve cognitive function? Based on a meta-analysis of twenty studies, mental performance across a variety of domains can be significantly improved with even modest weight loss, though no studies have yet been done to determine if this then translates into a normalization of Alzheimer's disease risk.³¹⁶

F Is for Fertility

F is for *fertility*, or rather *failed fertility*. Overweight couples struggling to have children "should be educated on the detrimental effects of fatness," one meta-analysis concluded, as weight loss is associated with an improvement in pregnancy rates among infertile women.³¹⁷ Men may also suffer impaired fertility. The heavier a man is, the greater his risk of having a low sperm count or being completely sterile.³¹⁸ This in part may be because of the effects of excess body fat on testosterone levels.

Fat isn't the primary site of estrogen production only in postmenopausal women but in men as well. There's an enzyme in body fat that actually converts testosterone into estrogen.³¹⁹ Even going from obese to just overweight could potentially raise testosterone levels in the blood of men by 13 percent.³²⁰

A more dramatic cause of infertility in obese men is called *hidden penis*. Also referred to in the medical literature as *buried penis*, *concealed penis*, or *inconspicuous penis*, it occurs when excess fat in the pubic area subsumes the male member. It's also called *trapped penis* because the moist enfolding skin can result in a chronic inflammatory dermatitis leading to scarring and requiring surgical intervention.³²¹ So *F* may also stand for *Free Willy*.

G Is for Gallstones and GERD

What is the number-one digestive reason people are hospitalized? Gallbladder attack. Every year, more than a million Americans are diagnosed with gallstones, and about seven hundred thousand have to get their gallbladders surgically removed.³²² It's a relatively safe procedure.³²³ Immediate complication rates tend to be under 5 percent, and the mortality rate is only about one in a thousand.³²⁴ However, 10 percent of patients may develop "post-cholecystectomy syndrome" with persistent gastrointestinal symptoms weeks or months after their gallbladders are removed.³²⁵

What are gallstones made of? In 80 to 90 percent of cases, gallstones are mostly just crystallized cholesterol, forming like rock candy in the gallbladder.³²⁶ This was used to

explain why some small, earlier studies found that nonvegetarians had a higher incidence of gallstones given their higher cholesterol levels,³²⁷ but the results from larger, more recent studies are more equivocal.^{328,329} The biggest purported cause-and-effect risk factor³³⁰ may be obesity,³³¹ which increases risk as much as sevenfold.³³²

Ironically, rapid weight loss may also be a trigger of gallbladder attacks. A half pound a day has been deemed the “upper limit for medically safe weight loss” based on gallstone formation. Ultrasound studies found that above that limit, the incidence of new stones can go from less than one in two hundred a week up to one in thirty.³³³ To help prevent a gallstone attack, you can increase your fiber intake. Not only is dietary fiber intake associated with less gallbladder disease,³³⁴ but those placed on high-fiber foods during a weight-loss regimen suffered significantly less gallbladder sludging than those losing the same weight without the extra fiber.³³⁵

Fiber-rich food consumption can also decrease the risk of acid reflux (Gastroesophageal Reflux Disease, or GERD). The excess abdominal pressure due to obesity may push up acid into the throat, causing heartburn and inflammation.³³⁶ The increased pressure on the abdominal organs associated with obesity may also explain why overweight women suffer from more vaginal prolapse,³³⁷ where organs such as the rectum push out into the vaginal cavity.

H Is for Heart Disease

Of the four million deaths attributed to excess body weight every year around the world, nearly 70 percent are due to cardiovascular disease.³³⁸ Is it just because those people had been eating poorly? Genetic studies suggest that people effectively randomized from conception to be heavier—just based on their genes—do indeed have higher rates of heart disease and stroke regardless of what they eat.³³⁹ So, if we lose weight, does our risk drop?

The SOS trial, which stands for *Swedish Obese Subjects*, was the first long-term controlled trial to compare the outcomes of thousands of bariatric surgery patients to matched control subjects who started out at the same weight but went the nonsurgical route. The control group maintained their weights, whereas the surgical group maintained about a 20 percent weight loss over the next ten to twenty years. Over that time, the surgical weight-loss group not only developed 80 percent less diabetes but suffered significantly fewer heart attacks and strokes, so, not surprisingly, they significantly reduced their total mortality overall.³⁴⁰

I Is for Immunity

The SOS trial also found that those who lost weight got less cancer.³⁴¹ This may be because antitumor immunity appears to be affected by weight. Natural killer cells are our immune systems’ first line of defense against cancer cells (as well as many viral infections), and their function is severely impaired by obesity. When obese individuals were randomized to a weight-loss program, there was a significant reactivation of natural killer cell function within just three months.³⁴² However, the program involved an exercise component, so it’s hard to tease out the impact of the weight loss itself since physical activity alone can boost natural killer cell activity.³⁴³

On the other end of the spectrum, obesity is suspected to be a causal risk factor for the development of multiple sclerosis, an autoimmune disease.³⁴⁴ This suggests obesity is associated with the worst of both worlds when it comes to immune function: underactivity when it comes to protecting against cancer and infection, but overactivity when it comes to certain inflammatory autoimmune conditions.³⁴⁵

J Is for Jaundice

Thanks to the obesity epidemic, nonalcoholic fatty liver disease (NAFLD) is now the most common liver disorder in the industrialized world.³⁴⁶ Fat doesn’t just end up in our bellies and thighs but inside some of our internal organs. More than 80 percent of individuals with

abdominal obesity may have fatty infiltration into their livers,³⁴⁷ and in those with severe obesity, the prevalence can exceed 90 percent.³⁴⁸ This can lead to inflammation, scarring, jaundice, and, ultimately, cirrhosis and liver cancer.³⁴⁹ Currently, the advanced form of NAFLD, nonalcoholic fatty hepatitis, is the leading cause of liver transplants in American women, and men are expected to catch up by 2020.³⁵⁰

K Is for Kidneys

Obesity is also one of the strongest risk factors for chronic kidney disease. Our kidneys compensate for the metabolic demands of excess weight by red-lining into what's called *hyperfiltration* to deal with the extra workload. The resulting increased pressure within the kidneys can damage the sensitive organs and increase the risk of kidney failure over the long term.³⁵¹

... and L, M, N, O, P Through Z

If we wanted to keep singing the alphabet of obesity-related health concerns, *L* could be for *diminished lung function*,³⁵² *M* for a cluster of risk factors known as *metabolic syndrome*,³⁵³ and so on. There's even an *X*—for *xiphodynia*, pain at the tip of the bottom of the breastbone from being bent outward by an expanding abdomen.³⁵⁴

Counting the Costs

Given the myriad health conditions associated with excess weight, medical spending attributable to obesity is nearly \$2,000 per person per year,³⁵⁵ with obese workers with multiple complications costing companies up to \$10,000 more in health-care coverage compared to lean counterparts.³⁵⁶ Beyond just brazen discrimination, this actually may account for some of the wage gap obese employees experience as companies try to make up for these costs.³⁵⁷ Between health-care costs and diminished productivity in terms of lost workdays, the total per capita lifetime costs of long-term obesity have been estimated to exceed \$200,000.³⁵⁸

Some estimates peg the current national cost of obesity at about \$150 billion,³⁵⁹ with another \$50 billion per year added by 2030 as our increasingly heavy baby boomers continue to age.³⁶⁰ The Milken Institute appraised the cost of obesity as a *trillion-dollar* drag on the economy,³⁶¹ more than twice what we spend on national defense.³⁶² Others diametrically disagree, based on the morbid fact that obese individuals may not live as long. Just as the medical costs of tobacco-related diseases may be more than offset by the shortened survival of smokers, the lifetime health-care costs of obese individuals may turn out to be lower because they are expected to die so much sooner.³⁶³ So the true cost may be calculated in lives rather than dollars.

Larger Than Life

Martin Luther King Jr. warned that “human progress is neither automatic nor inevitable,”³⁶⁴ and the same may be true of the human life span.³⁶⁵ In 1850, life expectancy in the United States was less than forty years,³⁶⁶ but it has steadily increased over the last two centuries,³⁶⁷ gaining about two years per decade—until recently, that is. Longevity gains have faltered or even reversed, and the greatest victims will be our children. Thanks to the obesity epidemic, we may now be raising the first American generation to live shorter lives than their parents.³⁶⁸

The downward trend in longevity is expected to accelerate as the current, younger generation—who started out heavier from a younger age than ever before—matures into adulthood. If the obesity epidemic continues unchecked, current trends signal a potential “looming social and economic catastrophe.”³⁶⁹ In the coming decades, some predict we may lose two to five years—or more—of life expectancy in the United States. To put that into perspective, a miracle cure for *all* forms of cancer would only add three and a half

years to the average American life span.³⁷⁰ In other words, reversing the obesity epidemic might save more lives than curing cancer.

The Obesity Paradox

The evidence that being overweight increases our risk for debilitating diseases like diabetes is considered indisputable, but, surprisingly, there is controversy surrounding body weight and overall mortality.³⁷¹ In 2013, scientists from the Centers for Disease Control and Prevention (CDC) published a meta-analysis in *The Journal of the American Medical Association* suggesting that being overweight was actually advantageous. Yes, grade 2 or grade 3 obesity, which is like being the average American's height, five foot six,³⁷² and weighing about 215 pounds or more, was associated with living a shorter life, but grade 1 obesity (about 185–215 pounds at the same height) was not. And, being overweight (155–185 pounds at average height) appeared to be protective compared to those who were normal weight (115–155 pounds at five foot six). The overweight individuals, with a BMI of 25–30, appeared to live the longest.³⁷³

Headline writers were giddy: “Being Overweight Can Extend Life,” “Dreading Your Diet? Don’t Worry ... Plump People Live LONGER,”³⁷⁴ and “Extra Pounds Mean Lower Chance of Death.”³⁷⁵ Not surprisingly, the study ignited a firestorm of controversy in the public health community and was called “ludicrous,”³⁷⁶ “flawed,” and “misleading.”³⁷⁷ The chair of nutrition at Harvard lost his cool, calling it “really a pile of rubbish,”³⁷⁸ fearing the food industry might exploit the study in the same way the petroleum industry misuses a manufactured controversy over climate change.³⁷⁹

Public health advocates can’t just dismiss data they find inconvenient, though. Science is science. But how could being overweight increase the risk of life-threatening diseases, yet, at the same time, make you live longer? This became known as the *obesity paradox*.³⁸⁰ The solution to the puzzle appears to lie with two major sources of bias, the first being confounding by smoking.³⁸¹

As I’ll explore in the Amping AMPK section, the nicotine in tobacco can lead to weight loss. So if you’re skinnier because you smoke, then it’s no wonder you’d live a shorter life with a slimmer waist. The failure to control for the effect of smoking in studies purporting to show an “obesity paradox” leads to the dangers of obesity being “grossly underestimated.”³⁸²

The second major source of bias is reverse causality. Instead of lower weight leading to life-threatening diseases, isn’t it more likely that life-threatening diseases lead to lower weight? Conditions such as hidden tumors, chronic heart or lung disease, alcoholism, and depression can all cause unintentional weight loss months or even years before a diagnosis is made.³⁸³ As we’ve discussed, it’s become normal to be overweight in this country.³⁸⁴ People who are “abnormally” thin—that is, at an ideal weight—could actually be taking care of themselves, but they also may be heavy smokers, elderly and frail, or seriously ill with weight loss from their disease.³⁸⁵

Deadweight

To put the obesity paradox issue to the test once and for all, the Global BMI Mortality Collaboration was formed, reviewing data from more than ten million people from hundreds of studies in dozens of countries—the largest evaluation of BMI and mortality in history.³⁸⁶ To help eliminate bias, the researchers omitted smokers and those with known chronic disease. They then excluded the first five years of follow-up to try to remove from the analysis those with undiagnosed conditions who had lost weight due to an impending death. The results were clear: Being overweight or any grade of obesity was associated with a significantly greater risk of dying prematurely.³⁸⁷ In fact, adjusting for those biases

leads to “eliminating the obesity paradox altogether.”³⁸⁸ In other words, the so-called obesity paradox appears to be just a myth.³⁸⁹

Indeed, when intentional weight loss is actually put to the test, people live longer. Bariatric surgery studies like the SOS trial show weight loss reduces long-term mortality,³⁹⁰ and randomizing people to lose weight through lifestyle changes shows the same.³⁹¹ Losing a dozen pounds through diet and exercise was found to be associated with a 15 percent drop in overall mortality risk. Exercise alone may extend life span even without weight loss,³⁹² but there also appears to be a similar longevity benefit of weight loss through dietary means alone.³⁹³

The Optimal BMI for Optimal Longevity

The largest studies in the United States³⁹⁴ and around the world³⁹⁵ found that having a normal body mass index, a BMI of 20–25, is associated with the longest life span. Putting together all the best available studies with the longest follow-up, that can be narrowed down even further to a BMI of 20–22.³⁹⁶ You can use this unisex chart to see what your optimal weight might be based on your height:

Height	Ideal Weight	Height	Ideal Weight	Height	Ideal Weight	Height	Ideal Weight
4'9"	92–102	5'2"	109–120	5'7"	128–140	6'	147–162
4'10"	96–105	5'3"	113–124	5'8"	132–145	6'1"	152–167
4'11"	99–109	5'4"	117–128	5'9"	135–149	6'2"	156–171
5'	102–113	5'5"	120–132	5'10"	139–153	6'3"	160–176
5'1"	106–116	5'6"	124–136	5'11"	143–158	6'4"	164–181

So even within a “normal” BMI, the risk of developing chronic diseases, such as type 2 diabetes, heart disease, and several types of cancer, starts to rise toward the upper end, starting as low as a BMI of 21. BMIs of 18.5 and 24.5 are both considered within the normal range, but a BMI of 24.5 may be associated with twice the heart disease risk compared to 18.5.³⁹⁷ The ideal BMI appears to be between 20 and 22, confirmed in a study of an “unusually slim cohort” from the Oxford Vegetarian Study.³⁹⁸

Just as there are gradations of risk within a normal BMI range, there is a spectrum within obesity. Grade 3 obesity, characterized as having a BMI greater than 40, can be associated with the loss of a decade of life or more. At a BMI greater than 45, such as a five-foot-six person at 280 pounds, life expectancy may shrink to that of a cigarette smoker.³⁹⁹

Health at Every Size™?

There are “obesity skeptics” who argue that the health consequences of obesity are unclear or even greatly exaggerated. They are a motley bunch of unlikely bedfellows, ranging from feminists, queer theorists, and new ageists to “far right wing, pro-gun, pro-America websites where the idea [is] that obesity alarmists are nanny-state communists who simply want to stop us from having fun.”⁴⁰⁰

There are also many “fat activists” who try to downplay the risks of obesity. The director of medical advocacy for the Council on Size and Weight Discrimination routinely takes part in obesity conferences and government panels on obesity. She is quoted as saying, “I’m not actually particularly that interested in [health]” and “God, I hate science.”⁴⁰¹ Unlike activists who, for example, organized to raise consciousness to stamp out the AIDS epidemic, the size-acceptance movement appears to have the opposite goal, rallying for *less* public awareness and treatment of the problem.⁴⁰² (They do have good slogans, though: “We’re here, we’re spheres, get used to it!”⁴⁰³) I’m all for fighting size stigma and discrimination, but the adverse health consequences of obesity are an established scientific fact. In a

study of more than six hundred centenarians, those one hundred years old and older, fewer than 2 percent of the women and not a single one of the men were obese.⁴⁰⁴

Can't you be fat but fit? There appears to be a rare subgroup of obese individuals who don't suffer the typical metabolic costs of obesity, such as high blood pressure and high cholesterol.⁴⁰⁵ This raised the possibility that there may be such a thing as "benign obesity."⁴⁰⁶ It may just be a matter of time before the risk factors develop.⁴⁰⁷ But even if they don't develop, followed long enough, even "metabolically healthy" obese individuals are at increased risk of diabetes,⁴⁰⁸ fatty liver disease,⁴⁰⁹ cardiovascular events such as heart attacks, and/or premature death.⁴¹⁰ Bottom line? There is strong evidence that "healthy obesity" is a myth.⁴¹¹

Hating Their Guts

The size-acceptance movement is definitely right about one thing, though: the extraordinary scourge of weight stigma. Described as the last "acceptable" form of bias,⁴¹² weight stigma is the rampant discrimination and stereotyping of overweight individuals. Fifty overweight women were asked to keep a diary of all the times they felt they were stigmatized for their weights. Over just one week, more than a thousand instances were recorded.⁴¹³ An overweight woman may expect to be harassed (such as called names or insulted), encounter physical barriers (like being unable to fit into public seats), or be discriminated against (such as receiving perceived poorer service at restaurants or stores) on average about three times a day. Obese men report three times less discrimination than women of the same size,⁴¹⁴ so it may be only a daily occurrence for them.

This weight stigma starts surprisingly early. Children as young as three years old label overweight peers as "mean," "stupid," "lazy," and "ugly."⁴¹⁵ One of the most poignant illustrations comes from a famous study published in 1961. Children in summer camps and schools across a swath of different social, cultural, and ethnic backgrounds in California, Montana, and New York were asked to rank the following images as to whom they liked best:

1. a child in crutches with one leg in a brace
2. a child in a wheelchair
3. a child with one hand missing
4. a facially disfigured child
5. an obese child

In every population of kids they tested, there was "remarkable uniformity."⁴¹⁶ The obese child always came in dead last.

But that was ages ago. What happened when the original study was repeated? Researchers published the forty-year follow-up in 2003, and guess what they found? The title of the study gives it away: "Getting Worse: The Stigmatization of Obese Children." The obese child was liked even less.⁴¹⁷ This parallels trends throughout society with a 70 percent jump in perceived weight discrimination recorded in national surveys since the mid-1990s.⁴¹⁸

Attitudes among educators may not be helping. More than a quarter of teachers and other school staff surveyed felt that becoming obese is "one of the worst things that could happen to a person."⁴¹⁹ Even parents can be biased, providing less support for college for their overweight daughters compared to thinner siblings.⁴²⁰ As two prominent obesity researchers commented, "It is strong prejudice indeed when parents discriminate against their own children."⁴²¹

What about doctors? One representative national survey found that more than half of physicians viewed obese patients as "awkward, unattractive, ugly, and noncompliant."⁴²²

About a quarter of nurses agreed or strongly agreed with the statement “Caring for an obese patient usually repulses me.”⁴²³ This antagonism can have serious health consequences for those who may need care the most. For example, obese women are at higher risk for developing cervical,⁴²⁴ endometrial, and ovarian cancers,⁴²⁵ yet they are less likely to be screened. Morbidly obese patients only have about half the odds of getting their recommended pelvic exams.⁴²⁶ Though some of this may be avoidance on the part of the patient, some doctors just turn away obese patients. *The Sun Sentinel* polled OB-GYN practices in Florida and found that as many as one in seven refused to see heavier women, for example, setting weight cutoffs for new patients starting at two hundred pounds.⁴²⁷

Even doctors who welcome obese patients have been found to give them short shrift. Physicians randomized to receive a medical chart of a migraine patient who either presented as average weight or obese said they would give the obese patient about 28 percent less of their time⁴²⁸—and it’s less quality time too. Recorded doctor visits found physicians tend to build less emotional rapport with overweight patients.⁴²⁹

At least the doctors appear able to hide their disdain. In a study entitled “Obese Patients Overestimate Physicians’ Attitudes of Respect,” despite the negative attitudes doctors harbored toward their obese patients, the same patients expressed their satisfaction with their providers. The researchers concluded, “While physicians may be successfully playing the part, the lack of true respect suggests ... the authenticity of the patient-physician relationship should be questioned.”⁴³⁰

For Shame

Weight stigma may perpetuate a cycle of stress leading to obesity, leading to even more stress. I discuss this concept further in the Stress Hormone Relief section. Across thousands of individuals followed for four years, those reporting discriminatory experiences had more than twice the odds of becoming obese. As well, those who started out obese had more than three times the odds of staying that way compared to people who started out at the same weight but didn’t experience discrimination.⁴³¹ This could be from stress-induced eating on one side of the calorie-balance equation or stigma-induced exercise avoidance on the other.

Obese individuals with more frequent experiences with weight stigma report greater avoidance of exercising in public, feeling judged and embarrassed.⁴³² These “too fat to exercise”⁴³³ fears may be well grounded. Strong anti-fat biases have been documented in both fitness professionals and regular gym-goers,⁴³⁴ which may present an unwelcoming environment in fitness centers and health clubs.⁴³⁵

Whichever side of the calorie equation gets tipped, those who experience weight stigma can end up suffering health consequences independent of any added weight. Those reporting more frequent fat prejudice exhibit higher levels of depression,⁴³⁶ inflammation,⁴³⁷ and oxidative stress,⁴³⁸ as well as shorter life spans. Two studies following a total of nearly twenty thousand people both found about a 50 percent increase in mortality risk among those reporting greater daily discrimination.⁴³⁹ Despite these hazards, some scholars advocate for even *more* fat shaming.

The president emeritus of the prestigious Hastings Center infamously advocated for “a kind of stigmatization lite,” using social pressures to compel people to lose weight without resorting to outright discrimination. After all, he argued, what else has the potential to counter the persuasive force of the billions spent in advertising every year by the food and beverage industry? It worked against tobacco. He recalls his own battle with addiction: “The force of being shamed and beat upon socially was as persuasive for me to stop smoking as the threats to my health.” The public health campaign to stigmatize cigarettes turned what had been considered “simply a bad habit into reprehensible behavior.”⁴⁴⁰

When such campaigns have been tried, they have been met with fierce resistance. Georgia's Strong4Life campaign featured billboards of morose-looking obese children with such captions as "Warning: Chubby kids may not outlive their parents" and "It's hard to be a little girl when you're not."⁴⁴¹ The campaign sponsors defended the ads as an attempt to break through the denial in a state with some of the highest recorded childhood obesity rates⁴⁴²—but it's only defensible if it works.

So does it? Being labeled "too fat" in childhood was associated with a higher risk of becoming obese compared to children who weighed the same but were never told that.⁴⁴³ Does this mean we should just ignore the elephant in the room? Many doctors apparently think so.

Just as veterinarians have been found to be reluctant to tell people their pets are obese,⁴⁴⁴ many pediatricians are similarly quiet when it comes to discussing weight concerns with parents. Less than a quarter of parents of overweight children report having been told that about their children's weight status by their pediatricians.⁴⁴⁵ One might think it would be obvious, but a Gallup survey found that parents appear to be "notoriously poor judges of their children's weight." Similarly, despite skyrocketing obesity, the percentage of adults who describe themselves as overweight has remained essentially unchanged over the past few decades. All this, Gallup concluded, helps "paint a picture of mass delusion in the United States about its rising weight."⁴⁴⁶

I think patients have the right to be informed. Those told by their doctors that they are overweight have nearly four times the odds of attempting weight loss⁴⁴⁷ and about twice the odds of succeeding.⁴⁴⁸ Just as physicians who smoke are less likely to challenge their patients who smoke, overweight physicians are less likely to bring up the subject of weight loss⁴⁴⁹ or even document obesity in patient charts.⁴⁵⁰ Ironically, overweight patients trust diet advice more from overweight doctors than those who are normal weight.⁴⁵¹

As obesity rates have gone up, the rate of weight counseling advice from primary care physicians has inexplicably gone down.⁴⁵² Even when they do manage to counsel patients, doctors appear to have little to offer in terms of specifics. Fewer than half who were surveyed said they provide specific guidance to their patients.⁴⁵³ Just telling patients *Watch what you eat*, is unlikely to be particularly helpful, but many primary care physicians may not even go that far. Physical inactivity was rated by physicians as significantly more important than any other cause of obesity, which is far from accurate, as I discuss [here](#). Most physicians said they would spend more time working with patients on weight management if only their time were "reimbursed appropriately."⁴⁵⁴ Maybe we could even offer doctors a bonus to refrain from blaming the victim.⁴⁵⁵ As one pair of commentators wrote in response to the pro-stigmatization camp, "If shaming reduced obesity, there would be no fat people."⁴⁵⁶

Blind, Deaf, Dumb, or Fat

I want to end this stigma section with the jaw-dropping findings of a study I think best illustrates how hard it is to live inside a fat body. If this doesn't foster sympathy among my medical colleagues, I don't know what will. Researchers talked with men and women who had lost and kept off more than 100 pounds to tap into their unique insights, having personally experienced what it was like to be morbidly obese and then, on average, 126 pounds lighter. Forty-seven such individuals were interviewed.

They were asked to think back to when they were heavier and make a choice: "If someone offered you a couple of million dollars if you stayed morbidly obese forever, would you have chosen the money? Or would you have chosen to be normal weight no matter what?"

- **Option 1:** “I would have chosen no money and being normal weight. It would have taken me one second to decide.”
- **Option 2:** “I probably would have chosen being normal weight. But the possibility of having that much money would make me think about the choice.”
- **Option 3:** “I wanted to be normal weight, but I really could use the money. If I would be a multimillionaire I think I could live with being morbidly obese.”

One of the forty-seven people had to think about it, but the other forty-six jumped at Option 1. Not a single person chose Option 3. They all said they would give up being a multimillionaire to be normal weight.⁴⁵⁷

If that shocked you, buckle your seat belt. They were then asked about being obese compared to other disabilities. Normally when you ask people to choose between living with their own disability or switching to a different one, there is a strong proclivity to stay with their own.⁴⁵⁸ For example, even though most people would rather be deaf than blind, blind people prefer to remain blind by a large margin rather than having sight without sound. They already know how to cope with their own disability, so there’s safety in familiarity. The exact opposite happened when the formerly obese were asked.

Each of the forty-seven men and women said they’d rather be deaf for the rest of their lives than obese. Every single one said they’d rather be unable to read, be diabetic, have very bad acne, or have heart disease than be obese. And then the true jaw-dropper: More than 90 percent said they’d rather have a leg amputated, and, similarly, about nine out of ten said they’d rather be *blind* their whole lives than obese. Obesity appears to be the only handicap where nearly everyone wants to switch disabilities no matter what the cost. To quote one study subject, “When you’re blind, people want to help you. No one wants to help when you’re fat.”⁴⁵⁹

How Much Weight Does It Take?

We seem to have become inured to the mortal threat of obesity. If you go back in the medical literature a half century or so, when obesity wasn’t run of the mill, the descriptions are much grimmer: “Obesity is always tragic, and its hazards are terrifying.”⁴⁶⁰ But it doesn’t have to be frank obesity. Of the four million deaths every year attributed to excess body fat, nearly 40 percent of the victims are just overweight, not obese.⁴⁶¹ According to two famous Harvard studies, as little as eleven pounds of weight gain from early adulthood through middle age increases the risk of major chronic disease.⁴⁶²

The flip side is that even modest weight *loss* can have major health benefits.

The good news is the riskiest fat is the easiest to lose. Our bodies appear to preferentially shed the villainous visceral fat first.⁴⁶³ Although it may take losing as much as 20 percent of your weight to realize significant improvements in quality of life for most individuals with severe obesity,⁴⁶⁴ disease risk drops almost immediately. At 3 percent weight loss (only six pounds for someone weighing two hundred), your blood sugar control and triglycerides start to get better.⁴⁶⁵ At 5 percent weight loss, blood pressure and cholesterol improve. Furthermore, a 5 percent weight loss—just ten pounds for someone starting at two hundred—may cut the risk of developing diabetes in half.⁴⁶⁶

What About Weight Cycling?

There was a book originally published in the 1980s and then repeatedly republished ever since entitled *Dieting Makes You Fat*. Since most people who lose weight go on to regain it, the concern is there may be adverse health effects to so-called yo-yo dieting.⁴⁶⁷ This idea emerged from animal studies⁴⁶⁸ that showed, for example, detrimental effects of starving and refeeding obese rats.⁴⁶⁹ This captured the media’s attention, leading to a pervasive

common belief about the “dangers” of weight cycling, discouraging people from even trying.⁴⁷⁰

Even the animal data are inconclusive, though. For example, weight cycling mice makes them live *longer*.⁴⁷¹ Most importantly, other than perhaps a greater risk of gallstones,^{472,473} a review of the human data concluded that “evidence for an adverse effect of weight cycling appears sparse, if it exists at all.”⁴⁷⁴ In fact, as I write this, the current issue of *Obesity*, the official journal of the leading scientific society dedicated to the field, published a commentary entitled “Yo-Yo Dieting Is Better Than None.”⁴⁷⁵

The Skinny on Fat

Let’s take a closer look at the best way to measure and define excess body fat.

BODY MASS INDEX VS. BODY FAT PERCENTAGE

Most of the population studies that have explored the relationship between obesity and disease have relied on BMI,⁴⁷⁶ body mass index. (Calculate your own [here](#).) BMI takes height into account but doesn’t take the *composition* of the weight into account. Bodybuilders are heavy for their heights but can be extremely lean. The gold-standard measure of obesity is percentage of body fat,⁴⁷⁷ but accurate calculations for this can be complicated and expensive.⁴⁷⁸ All that’s needed to measure BMI is a scale and a tape measure, but it may underestimate the true prevalence of obesity.

The World Health Organization⁴⁷⁹ and the American College of Endocrinology⁴⁸⁰ define obesity as a body fat percentage over 25 percent in men or 35 percent in women. At a BMI of 25, which is considered just barely overweight, body fat percentages in a representative U.S. sample of adults varied between 14 and 35 percent in men and 26 and 43 percent in women.⁴⁸¹ So you could be normal weight, but actually obese.⁴⁸² Using the BMI cutoff for obesity, only about one in five Americans were obese back in the 1990s, but based on their body fat, the true proportion back then was closer to 50 percent.⁴⁸³ Even by the ‘90s, half of America was not just overweight but obese.

By using only BMI, doctors may misclassify more than half of obese individuals as being just overweight or even normal weight and miss an opportunity to intervene.⁴⁸⁴ The important thing, however, is not the label but the health consequences. Ironically, BMI appears to be an even better predictor of cardiovascular disease death than body fat percentage.⁴⁸⁵ This suggests that excess weight from any source—fat or lean—may not be healthy in the long run.⁴⁸⁶ The life spans of professional bodybuilders do seem to be cut short. They have about a third higher mortality rate than the general population, with an average age of death around forty-eight years,⁴⁸⁷ but this may be due in part to the toxic effects of anabolic steroids on the heart.⁴⁸⁸

WEIGHT VS. WAIST

Preeminent nutritional physiologist Ancel Keys (after whom K rations were named⁴⁸⁹) suggested the mirror method: “If you really want to know whether you are obese, just undress and look at yourself in the mirror. Don’t worry about our fancy laboratory measurements; you’ll know!”⁴⁹⁰ All fat is not the same, though. There is the pinchable, superficial flab you may see jiggling about your body, and then there’s the riskier, visceral fat that coils around and infiltrates your internal organs, bulging out your belly.⁴⁹¹ Measuring BMI is simple, cheap, and effective, but it doesn’t take into account the distribution of fat on the body—whereas waist circumference can provide a measure of the deep underlying abdominal fat.

Both BMI and waist circumference can be used to predict the risk of death due to excess body fat,⁴⁹² but even at the same BMI, there appears to be nearly a straight-line increase in mortality risk with widening waistlines.⁴⁹³ Someone with “normal-weight central obesity”—meaning someone not even considered to be overweight according to BMI, but who carries fat around the middle⁴⁹⁴—may have up to twice the risk of dying compared to someone who’s overweight or obese according to their weight and height. This is why the World Health Organization,⁴⁹⁵ National Institutes of Health,⁴⁹⁶ and American Heart Association⁴⁹⁷ recommend measuring both BMI and waist circumference. This may be especially important for older women, who lose approximately 13 pounds of bone and muscle as they age from twenty-five to sixty-five, while quadrupling their visceral fat stores. (Men’s visceral fat stores tend only to double.)⁴⁹⁸ So even if a woman doesn’t gain any weight according to the bathroom scale, she may be gaining fat.

What’s the healthy waistline cutoff? ⁴⁹⁹ Increased risk of metabolic complications starts at an abdominal circumference of 31.5 inches in women and 37 inches in most men, but closer to 35.5 inches for Chinese, Japanese, and South Asian men.⁵⁰⁰ The benchmark for substantially increased risk starts at about 34.5 inches for women and 40 inches for men.⁵⁰¹ Once you get greater than an abdominal circumference of about 43 inches in men, mortality rates shoot up about 50 percent compared to men with 8-inch-smaller stomachs, and women suffer 80 percent greater mortality risk at 37.5-inch waists compared to 27.5 inches.⁵⁰² The reading of a measuring tape may translate into years off one’s life span.

Surprisingly, there is no universal protocol for assessing waist circumference. Some guidelines recommend measuring at the level of the last rib, others at the top of the hip bones, and others still suggest halfway between

those landmarks, or at the belly button, or at the narrowest point.⁵⁰³ While the belly button may be the most intuitive and easiest to measure (and the preferred location for a one-time visceral fat assessment),⁵⁰⁴ the halfway point between the top of the hip bones and bottom of the rib cage appears to be the most effective at tracking changes in visceral fat over time.⁵⁰⁵

KEEP YOUR WAIST LESS THAN HALF YOUR HEIGHT

Unlike waist circumference, body mass index has the advantage of taking height into account. Waist-to-height ratio may offer the best of both worlds, and the cutoff value is the simplest to remember: Keep your waist less than half your height.⁵⁰⁶ The goal for adults and children six years or older is to get a waist-to-height ratio under 0.5.⁵⁰⁷

Waist-to-height ratio may be a better predictor of both body fat percentage and visceral fat mass than BMI or waist circumference alone.⁵⁰⁸ In terms of screening for cardiometabolic risk (for example, heart disease and diabetes), waist-to-height ratio appears superior to BMI in adults⁵⁰⁹ and seems to work as well as BMI for assessing body fat in children.⁵¹⁰ So the ideal may be a combination of BMI and a measure of abdominal obesity, such as waist-to-height ratio.⁵¹¹

THE SOLUTIONS

Bringing a Butter Knife to a Gunfight

Now that you have a sense of the causes and consequences of obesity, let's look at the panoply of solutions that have been undertaken to combat excess body fat—and whether or not they actually address the root cause. The treatment of obesity has long been stained by the snake-oil swindlings of profiteers, hustlers, and quacks. Even the modern field of bariatric medicine (derived from the Greek word *baros*, meaning *weight*) is pervaded by an “insidious image of sleaze.”⁵¹² Beguiled by advertising for fairy-tale magic bullets of rapid, effortless weight loss, people blame themselves for failing to manifest the miracle or imagine themselves to be metabolically broken. On the other end of the spectrum are overly pessimistic practitioners of the opinion that “people who are fat are born fat, and nothing much can be done about it.”⁵¹³ The truth lies somewhere in between.

The difficulty of curing obesity has been compared to learning a foreign language; it's an achievement virtually anyone can attain with a sufficient investment of energies, but it always takes considerable time and effort.⁵¹⁴ Research suggests that most obese individuals don't stay in treatment. Of those who do, most don't adhere to it sufficiently to lose the excess weight. But, even among those who try to stick with it, most will regain much of the weight.⁵¹⁵ To me, this speaks to the difficulty, rather than the futility. It may take smokers an average of thirty quit attempts to finally kick the habit.⁵¹⁶ Like quitting smoking, it helps to think of losing excess weight as just something that has to be done. As the chair of the Association for the Study of Obesity put it, it doesn't take willpower to do essential tasks like getting up at night to feed a baby—it's just something that has to be done.⁵¹⁷

Our collective response to the obesity epidemic doesn't seem to match the rhetoric or reality.⁵¹⁸ If obesity is such a “national crisis” “reaching alarming proportions,”⁵¹⁹ dubbed by the post-9/11 Surgeon General as “every bit as devastating as terrorism,” why has our reaction been so tepid?⁵²⁰ For example, governments meekly suggest the food industry take “voluntary initiatives to restrict the marketing of less healthy food options to children.”⁵²¹ Have we just given up and ceded control to Big Business?

Our timid response to the obesity epidemic is encapsulated by a national initiative promulgated by the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council: the “small-changes approach.”⁵²² Since small changes are “more feasible,”⁵²³ suggestions include “using mustard rather than mayonnaise” and “eating 1 rather than 2 doughnuts in the morning.”⁵²⁴ Seems a bit like bringing a butter knife to a gunfight. Proponents of the small-changes approach lament that unlike other addictions, such as alcohol, cocaine, gambling, or tobacco, we can't

counsel our obese patients to give up the addictive element completely, as “no one can give up eating.”⁵²⁵ But just because we have to breathe doesn’t mean it has to be through the end of a cigarette. Similarly, just because we have to eat doesn’t mean we have to eat junk.

Bariatric Surgery

Liposuction Sucks

The first surgical attempt at body fat sculpting was in 1921. A dancer wanted to “improve” the shape of her ankles. The surgeon apparently scraped away too much tissue and tied the stitches too tight, resulting in necrosis, amputation, and the first recorded malpractice suit in the history of plastic surgery.⁵²⁶ Modern liposuction is much safer, killing only about one in five thousand patients.⁵²⁷

Liposuction currently reigns as the most popular cosmetic surgery in the world, and its effects are indeed only cosmetic.⁵²⁸ A study published in *The New England Journal of Medicine* assessed fifteen obese women before and after having about twenty pounds of fat sucked out of their bodies, resulting in nearly a 20 percent drop in their total body fat.⁵²⁹ Normally, if you lose even just 5–10 percent of your body weight in fat, you get significant improvements in blood pressure, blood sugars, inflammation, cholesterol, and triglycerides,⁵³⁰ but none of those benefits materialized after the massive liposuction.⁵³¹

This suggests subcutaneous fat, the fat under our skin, is not the problem. The metabolic insults of obesity arise from the *visceral* fat surrounding or even infiltrating our inner organs, like the fat marbling our muscles and livers. The way you lose that fat, the dangerous fat, is to take in fewer calories than you burn.

Under the Knife

What about bringing a scalpel to the gunfight instead? The use of bariatric surgery has exploded from about forty thousand procedures per year, as noted in the first international survey in 1998,⁵³² to hundreds of thousands now performed each year in the United States alone.⁵³³ The first technique developed, the intestinal bypass, involved carving out about twenty feet of intestines.^{534,535} More than thirty thousand intestinal bypass operations were performed⁵³⁶ before the “catastrophic,”⁵³⁷ “disastrous outcomes” were recognized.⁵³⁸ This included protein deficiency-induced liver disease⁵³⁹ progressing to “fatal hepatic necrosis.”⁵⁴⁰ Its inauspicious start is remembered as “one of the dark blots in the history of surgery.”⁵⁴¹

Today, death rates after bariatric surgery are considered “very low,” occurring on average in perhaps one in three hundred⁵⁴² to one in five hundred patients.⁵⁴³ The most common procedure is stomach stapling, also known as a *sleeve gastrectomy*, in which most of the stomach is permanently removed,⁵⁴⁴ leaving only a narrow sleeve or tube of stomach so as to restrict how much food people can eat at any one time.⁵⁴⁵ It’s ironic that many patients choose bariatric surgery, convinced that “diets don’t work” for them, when, in reality, that’s all the surgery may be—an enforced diet.⁵⁴⁶ Bariatric surgery can be thought of as a form of internal jaw wiring.

Gastric bypass is the second most common bariatric surgery.⁵⁴⁷ It combines restriction—stapling the stomach into a pouch smaller than the size of a golf ball—with malabsorption, by rearranging our anatomy to bypass the first part of our small intestines.⁵⁴⁸ It appears to be more effective than just cutting out most of the stomach—resulting in a loss of 63 percent of excess weight compared to 53 percent with a gastric sleeve⁵⁴⁹—but gastric bypass carries a greater risk of serious complications.⁵⁵⁰ Many are surprised to learn that new surgical procedures don’t require premarket testing or approval by the Food and Drug

Administration (FDA)⁵⁵¹ and are largely exempt from rigorous regulatory scrutiny,⁵⁵² potentially making new surgeries even riskier than new medications.

It's Complicated

The third most common bariatric procedure is a revision to fix a previous bariatric procedure.⁵⁵³ Up to 25 percent of bariatric patients have to go back into the operating room to rectify problems caused by their first bariatric surgery or for additional procedures. Reoperations are riskier, carrying up to ten times the mortality rate,⁵⁵⁴ and offer no guarantee of success.⁵⁵⁵ Complications include leaks,⁵⁵⁶ fistulas, ulcers, strictures, erosions, obstructions, and severe acid reflux.⁵⁵⁷

The extent of risk may depend on the skill of the surgeon. In a study published in *The New England Journal of Medicine*, bariatric surgeons voluntarily submitted videos of themselves performing surgery to a panel of their peers for evaluation. Technical proficiency varied widely and was related to the rates of complications, hospital readmissions, reoperations, and death. Patients operated on by the less competent surgeons suffered nearly three times the complications and five times the risk of death.⁵⁵⁸

As with athletes and musicians, some surgeons may simply be more talented than others, but practice may help make perfect.⁵⁵⁹ Gastric bypass is such a complicated procedure that its learning curve may require hundreds of cases for a surgeon to master it. Risk of complications plateaus after about five hundred cases, with the lowest risk found among surgeons who've performed more than six hundred bypasses.⁵⁶⁰ So if you do choose to undergo the procedure, I'd recommend asking your surgeon how many they've done and also choosing an accredited Bariatric Center of Excellence, since surgical mortality appears to be two to three times lower at those institutions than at nonaccredited ones.⁵⁶¹

Even if the surgery goes perfectly, lifelong nutritional replacement and monitoring are required to avoid vitamin and mineral deficits⁵⁶²—the consequences of which include more than just a little anemia, osteoporosis, or hair loss.⁵⁶³ Bariatric surgeries have resulted in full-blown cases of potentially life-threatening deficiencies, such as beriberi, pellagra, kwashiorkor, and nerve damage⁵⁶⁴ that can manifest as vision loss years or even decades after surgery (in the case of copper deficiency).⁵⁶⁵ Tragically, in cases of severe deficiency of a B vitamin called thiamine, nearly one in three patients progressed to permanent brain damage before they were even diagnosed.⁵⁶⁶

The malabsorption of nutrients is on purpose for procedures like gastric bypass. By cutting out segments of the intestine, we can successfully impair the absorption of calories—but at the expense of impairing the absorption of necessary nutrition. Even people who simply undergo restrictive procedures like stomach stapling can be at risk for life-threatening nutrient deficiencies because of persistent vomiting.⁵⁶⁷ Indeed, vomiting is reported by up to 60 percent of patients after bariatric surgery due to “inappropriate” eating behaviors—that is, by trying to eat normally.⁵⁶⁸

“Dumping syndrome” can work the same way. A large percentage of gastric bypass patients can suffer from abdominal cramps, diarrhea, nausea, bloating, fatigue, or palpitations after eating calorie-rich foods as they bypass the stomach and dump straight into the intestines. As surgeons describe it, this is a feature, not a bug: “Dumping syndrome is an expected and desired part of the behavior modification caused by gastric bypass surgery; it can deter patients from consuming energy-dense food.”⁵⁶⁹

Bariatric Surgery: Metabolic or Hyperbolic?

The surgical community objects to the characterization of bariatric surgery as internal jaw wiring, the cutting up of healthy organs just to discipline people's behavior. The field has gone as far as to rename it “metabolic surgery,” suggesting the anatomical rearrangements cause changes in digestive hormones that offer unique physiological

benefits.⁵⁷⁰ As evidence, the surgical community points to the remarkable remission rates for type 2 diabetes.

After bariatric surgery, about 55 percent of obese diabetics and 75 percent of “super-obese” diabetics go into remission, meaning they have normal blood sugars off all diabetes medications.⁵⁷¹ The normalization in blood sugars can happen within just days after the surgery.⁵⁷² Fifteen years after surgery, 30 percent may remain diabetes-free (compared to a 7 percent cure rate in a nonsurgical control group).⁵⁷³ But are we sure it was the surgery that did this? Could their improvement in blood sugars just be from the extreme caloric restriction that typically precedes and also follows surgery, rather than some surgical sort of metabolic magic? Researchers decided to put it to the test.

At a bariatric surgery clinic at the University of Texas, patients with type 2 diabetes scheduled for a gastric bypass volunteered to first undergo an identical period of caloric restriction. They were placed in the hospital and, for ten days, were put on the same diet they would be on immediately before and after the surgery, averaging fewer than five hundred calories a day to mimic the surgical situation. The researchers then waited a few months so the subjects would gain back the weight before putting them through the actual surgery, matched day for day to the diets they had been on before. Some patients, same diets—just with or without the actual surgery. If there were some sort of metabolic benefit to the anatomical rearrangement, they would have done better with the actual surgery, but in some ways, they actually did worse. The caloric restriction alone resulted in similar improvements in blood sugar, pancreatic function, and insulin sensitivity, but several measures of diabetic control improved significantly more *without* the surgery.⁵⁷⁴ So, if anything, the surgery seemed to put them at a metabolic disadvantage.

The bottom line is that type 2 diabetes is reversible with weight loss if you catch it early enough. With the loss of 15 percent of body weight, nearly 90 percent of those who’ve had type 2 diabetes for fewer than four years can achieve remission, whereas it may only be reversible in 50 percent of those who’ve lived with the disease for longer than eight years.⁵⁷⁵ That’s losing weight with diet alone, though. The remission numbers for diabetics losing more than twice as much weight with bariatric surgery may only be around 62 percent and 26 percent, respectively.⁵⁷⁶ So losing weight with your fork can be more than twice as effective as the surgeons’ knives.

Losing weight without resorting to surgery may offer other benefits as well. In the Anti-Inflammatory section, I’ll discuss the slimming hormone leptin. Losing weight with diet alone can improve leptin sensitivity,⁵⁷⁷ but losing weight from gastric bypass apparently does not.⁵⁷⁸ Diabetics losing weight with diet alone can also improve markers of systemic inflammation, such as tumor necrosis factor, whereas levels significantly worsened when about the same amount of weight was lost from a gastric bypass.⁵⁷⁹

The Blind Leading the Blind

What about diabetic complications? Two of the reasons we don’t want diabetes are that we don’t want to go blind and we don’t want to go on dialysis. Reversing diabetes with bariatric surgery can improve kidney function⁵⁸⁰ but, surprisingly, may not prevent the appearance⁵⁸¹ or progression of diabetic vision loss.⁵⁸² Perhaps this is because bariatric surgery affects diet quantity but not necessarily diet quality. This reminds me of a famous study published in *The New England Journal of Medicine* that randomized thousands of diabetics to an intensive lifestyle program that focused on weight loss. Ten years in, the study was stopped prematurely because the diabetics weren’t living any longer or having any fewer heart attacks.⁵⁸³ This may be because they remained on the same heart-clogging diet, but just with smaller portions.

There is a diet that has been shown to reverse diabetic eye disease: Dr. Kempner’s rice and fruit diet. More than a half century ago, Walter Kempner at Duke University showed

that his plant-based diet, ultralow in sodium, fat, cholesterol, and animal protein, could not only reverse advanced heart and kidney failure⁵⁸⁴ but diabetic retinopathy as well, with some patients going from not even being able to read headlines to having normal vision.⁵⁸⁵

How do we treat severe diabetic retinopathy these days? With intravitreal drugs (meaning injections straight into your eyeball). If those don't work, there's always panretinal laser photocoagulation, in which laser burns are etched over nearly the entire back of your eye⁵⁸⁶ in the hope that the little pieces left behind may get more of the blood flow.⁵⁸⁷ When I see this, along with Kempner's work, I can't help but feel like history has been reversed. It would be one thing if, a half century ago, the best we had was a barbaric burn-out-your-eye-socket surgery but, thankfully, we've since learned that we can reverse the vision loss through dietary means alone. But instead of learning, medicine seems to have forgotten.

Kempner also proved massive obesity could be corrected "without drastic intervention," showing people could lose hundreds of pounds through lifestyle changes alone, without resorting to hospitalization, drugs, or surgery.⁵⁸⁸ His diet was itself pretty drastic (certainly not to be undertaken without medical supervision),⁵⁸⁹ but at least it didn't entail getting one's internal organs cut open and stapled. "Even if surgery proves sustainably effective," wrote the founding director of the Yale-Griffin Prevention Research Center, "the need to rely on the rearrangement of natural gastrointestinal anatomy as an alternative to better use of feet and forks [exercise and diet] seems a societal travesty."⁵⁹⁰

Through Thick and Thin

How sustainable is weight loss with bariatric surgery? Over the first year or two after the procedure, most gastric bypass patients do end up regaining some of the weight they had lost,⁵⁹¹ but five years later, three-quarters maintain at least a 20 percent weight loss.⁵⁹² The typical trajectory for someone who starts out obese at 285 pounds, for example, would be to drop to an overweight 178 pounds two years after bariatric surgery but then regain back up to an obese 207 pounds.⁵⁹³ This has been chalked up to "grazing" behavior, where compulsive eaters may shift from bingeing, which becomes more difficult post-surgery, to constantly eating smaller amounts throughout the day.⁵⁹⁴ Eight years out, about half of gastric bypass patients continue to describe episodes of disordered eating.⁵⁹⁵ As one pediatric obesity specialist described, "I have seen many patients who put chocolate bars into a blender with some cream, just to pass technically installed obstacles" such as a gastric band.⁵⁹⁶

Bariatric surgery advertisements are filled with happily-ever-after fairy-tale narratives of cherry-picked outcomes, offering, as one ad analysis put it, "the full Cinderella-romance happy ending."⁵⁹⁷ This may contribute to the finding that patients often overestimate the amount of weight they're going to lose and underestimate the difficulty of the recovery process.⁵⁹⁸ Surgery forces profound changes in eating habits, requiring slow, small, thoroughly chewed bites. The stomach goes from the volume of two softballs down to about the size of half a tennis ball in stomach stapling and about half a Ping-Pong ball in the case of gastric bypass or banding.⁵⁹⁹

As you can imagine, weight regain after surgery can have devastating psychological effects, as patients may feel they failed their last resort.⁶⁰⁰ This could help explain why bariatric surgery patients are at a higher risk of depression⁶⁰¹ and suicide.⁶⁰² Severe obesity alone may increase risk of suicidal depression,⁶⁰³ but even at the same weight, those going through surgery appear to be at higher risk.⁶⁰⁴ At the same BMI, age, and gender, bariatric surgery recipients have about four times the odds of suicide.⁶⁰⁵ Most convincingly, before-and-after "mirror-image analysis" shows the risk of serious self-harm increases post-surgery in the same individuals.⁶⁰⁶

Nearly one in fifty bariatric surgery patients ends up being hospitalized for self-harm or attempted suicide.⁶⁰⁷ Furthermore, this only includes confirmed self-harm episodes, excluding masked attempts⁶⁰⁸ such as overdoses of “undetermined intention.”⁶⁰⁹ Bariatric surgery patients also have an elevated risk of “accidental death,”⁶¹⁰ though some of this may be due to changes in alcohol metabolism. When gastric bypass patients have two shots of vodka, for example, because of their altered anatomy, their blood alcohol levels shoot up past the legal driving limit within minutes.⁶¹¹ It’s unclear, however, whether this plays a role in the 25 percent increase in prevalence of alcohol problems noted during the second postoperative year.⁶¹²

Even those who successfully lose the excess weight and keep it off appear to have a hard time coping. Ten years out, though health-related quality of life improves, general mental health tends to significantly deteriorate compared to presurgery levels—even among the biggest losers.⁶¹³ Ironically, there’s a common notion that bariatric surgery is for “cheaters”⁶¹⁴ who take the “easy way” out by choosing the “low-effort” method of weight loss.⁶¹⁵ Shedding the pounds may not shed the stigma of even prior obesity. Studies suggest that, in the eyes of others, knowing someone was fat in the past leads them to always be treated more like a fat person. And there’s a strong anti-surgery bias on top of that, such that those who choose the scalpel to lose weight are rated most negatively (for example, thought of as least physically attractive).⁶¹⁶ One can imagine how remaining a target of prejudice even after joining the “in-group” could potentially undercut psychological well-being.

Weighing the Options

In the Middle Ages, starving peasants dreamed of gastronomic utopias where food rained down from the sky. The English called it the Kingdom of Cockaigne. Little could medieval fabulists predict that many of their descendants would not only take permanent residence there but also cut out parts of their stomachs and intestines to combat the abundance.⁶¹⁷

A body gaining weight when excess calories are available for consumption is behaving as it should.⁶¹⁸ Efforts to curtail such weight gain with drugs or surgery are not efforts to correct an anomaly in human physiology but rather to deconstruct and reconstruct its normal operations at the core. Critics have pointed out this irony of surgically altering healthy organs to make them dysfunctional (“malabsorptive”) on purpose,⁶¹⁹ especially when it comes to operating on children. Bariatric surgery for kids and teens is becoming widespread⁶²⁰ and is being performed in children as young as five years old.⁶²¹ Surgeons defend the practice by arguing that growing up fat can leave emotional scars and “lifelong social retardation.”⁶²²

Promoters of preventive medicine argue that bariatric surgery is the proverbial “ambulance at the bottom of the cliff.”⁶²³ In response, a proponent of pediatric bariatric surgery said, “It is often pointed out that we should focus on prevention. Of course, I agree. However, if someone is drowning, I don’t tell them, ‘You should learn how to swim’; no, I rescue them.”⁶²⁴

A strong case can be made that the benefits of bariatric surgery far outweigh the risks if the alternative is remaining morbidly obese, which is estimated to shave off up to thirteen years of one’s life.⁶²⁵ Although there are no data from randomized trials yet to back it up, compared to obese individuals who hadn’t been operated on, those getting bariatric surgery would be expected to live significantly longer on average.⁶²⁶ It’s no wonder surgeons consistently frame the elective surgery as a life-or-death necessity,⁶²⁷ but this is a false dichotomy. The benefits only outweigh the risks if there are no other alternatives.

Like Lead Balloons

With much fanfare, the 1980s brought us intragastric balloons that could be implanted into the stomach and inflated with air or water to fill up much of the space.⁶²⁸ Sadly, surgical devices are often brought to market before there is adequate evidence of safety and effectiveness,⁶²⁹ and the balloons were no exception.

The “Gastric Bubble” had its bubble burst when a study at the Mayo Clinic found that eight out of ten balloons spontaneously deflated (which is potentially dangerous, as they could pass into the intestines and cause an obstruction⁶³⁰), but not before causing gastric erosions—that is, damage to the stomach lining—in half the patients.⁶³¹ The kicker is that, in terms of inducing weight loss, the device didn’t even work.⁶³² It was eventually pulled from the market, but now balloons are back.

After a thirty-three-year hiatus, the FDA started approving a new slew of intragastric balloons in 2015,⁶³³ resulting in more than five thousand placements.⁶³⁴ By then, the Sunshine Act had been passed in order to shine a disinfecting light on industry enticements by forcing drug companies and the surgical and medical device industry to disclose any payments they were making to physicians.⁶³⁵ Most people now know about the overly cozy financial relationships doctors can have with Big Pharma, but fewer realize that surgeons can also get payments from the companies manufacturing the devices they use.⁶³⁶ The hundred top recipients of industry payments received an unbelievable \$12 million from device companies in a single year. Yet when these doctors published papers, only a minority disclosed the blatant conflict of interest.⁶³⁷

The benefit of balloons over most types of bariatric surgery is that they’re reversible, but that doesn’t mean they’re benign. The FDA has released a series of advisories about their risks, which includes cases of patient fatalities due to a stomach rupture.⁶³⁸ How could someone suffer a gastric perforation from a smooth, rounded object? By causing the patient to puke so much they rip open their stomach and die.⁶³⁹ Nausea and vomiting are unsurprising and very common side effects, affecting the majority of those who have balloons placed.⁶⁴⁰ Persistent vomiting likely also explains cases of life-threatening nutrient deficiencies after balloon implantation.⁶⁴¹

Some complications, such as bowel obstruction, are due to the balloon deflating,⁶⁴² but others, oddly enough, are due to the balloons suddenly overinflating,⁶⁴³ causing pain, vomiting, and abdominal distention.⁶⁴⁴ This was first noticed in breast implants, as documented in reports such as “The Phenomenon of the Spontaneously Autoinflating Breast Implant.”⁶⁴⁵ Out of nowhere, the implants just started growing, increasing breast volume by an average of more than 50 percent.⁶⁴⁶ “It remains,” one review noted, “an underreported and poorly understood phenomenon.”⁶⁴⁷ (Interestingly, breast implants were actually used as some of the first failed experimental intragastric balloons.⁶⁴⁸)

As with any medical decision, though, it’s all about risks versus benefits. Industry-funded trials display notable weight loss, but it’s hard to tease out the effect of the balloon alone from the accompanying supervised diet and lifestyle changes prescribed along with the devices in the studies.⁶⁴⁹ In drug trials, you can randomize subjects to sugar pills, but how do you eliminate the placebo effect of undergoing a procedure? You perform sham surgery.

In 2002, a courageous study was published in *The New England Journal of Medicine*. Knee arthroscopy, the most common orthopedic surgery, was put to the test. Billions of dollars are spent sticking scopes into knee joints and cutting away damaged tissue in osteoarthritis and knee injuries, but does the surgery actually work? Knee pain sufferers were randomized to get either the real surgery or a sham surgery in which surgeons sliced into people’s knees and pretended to perform the procedure, complete with splashing saline, but never actually did anything within the joint.

The trial caused an uproar. How could anyone randomize people to get cut open for fake surgery? Professional medical associations questioned the ethics of the surgeons and the sanity of the patients who agreed to be part of the trial.⁶⁵⁰ But guess what happened? Yes,

the surgical patients got better, but so did the placebo patients. The surgeries had no actual effect.^{651,652} Currently, heart stents⁶⁵³ and rotator cuff shoulder surgery are facing the same crisis of confidence.⁶⁵⁴

When intragastric balloons were put to the test, sham controlled trials show both older⁶⁵⁵ and newer⁶⁵⁶ devices sometimes fail to offer any weight-loss benefit. Even when they do work,⁶⁵⁷ the weight loss may be temporary because balloons are only allowed to stay in for six months, at which point the deflation risk gets too great. Why can't we keep putting in new ones? That's been tried, and it failed to improve long-term weight outcomes.⁶⁵⁸ A sham controlled trial showed that any effects of the balloon on appetite and satiety may vanish with time,⁶⁵⁹ perhaps as our bodies get used to the new normal.

What sham-surgery trials have shown us is that some of our most popular surgeries are themselves shams. Doctors like to pride themselves on being men and women of science. We rightly rail against the anti-vaccination movement, for example. Many of us in medicine have been troubled by the political trend of people choosing their own "facts." When I read that some of these still-popular surgeries are not only useless⁶⁶⁰ but may actually make things worse—for example, increasing the risk of progression to a total knee replacement⁶⁶¹—I can't help but think we doctors are not immune to our own versions of "fake news" and "alternative facts."⁶⁶²

Diet Drugs

One Pill Makes You Smaller

We worship medical magic bullets in this country. Yet, despite the full menu of FDA-approved medications for weight loss these days, they've only been prescribed for about one in fifty obese patients.⁶⁶³ What gives? One of the reasons anti-obesity drugs are so highly stigmatized⁶⁶⁴ is that, historically, they've been anything but magical; the bullets have been blanks, or worse.⁶⁶⁵

To date, most weight-loss drugs, despite their initial approval, have been pulled from the market for unforeseen side effects that turned them into a public threat.⁶⁶⁶ As I explore in the Fat Burners section, it all started with DNP, a pesticide with a promise to safely melt away fat⁶⁶⁷—but instead melted away people's eyesight.⁶⁶⁸ (The DNP disaster, in fact, helped lead to the passage of the Federal Food, Drug, and Cosmetic Act in 1938.⁶⁶⁹) Thanks to online accessibility, DNP has made a comeback with predictably lethal results.⁶⁷⁰

Then came the amphetamines. Currently, more than half a million Americans are addicted to amphetamines like crystal meth,⁶⁷¹ but the original amphetamine epidemic was generated by doctors and drug companies.⁶⁷² By the 1960s, pharmaceutical companies were churning out about eighty thousand kilos a year, which is nearly enough for a weekly dose for every man, woman, and child in the United States. Literally billions of doses were taken each year, and weight-loss clinics were raking in huge profits. A dispensing diet doctor could buy one hundred thousand amphetamine tablets for less than \$100 and turn around and sell them to patients for \$12,000.⁶⁷³

At a 1970 Senate hearing, Senator Thomas Dodd, father of Dodd-Frank senator Chris Dodd, suggested America's speed freak problem was no "accidental development." He said the pharmaceutical industry's "multihundred million dollar advertising budgets, frequently the most costly ingredient in the price of a pill, have, pill by pill, led, coaxed and seduced post-World War II generations into the 'freakedout' drug culture."⁶⁷⁴ I'll leave drawing the Big Pharma parallels to the current opioid crisis as an exercise for the reader.

Aminorex was a widely prescribed appetite suppressant before it was pulled for causing lung damage.⁶⁷⁵ Eighteen million Americans were on fen-phen before it was pulled⁶⁷⁶ for causing severe damage to heart valves.⁶⁷⁷ Meridia was pulled for heart attacks and strokes,⁶⁷⁸ Acomplia for psychiatric side effects including suicide,⁶⁷⁹ and the list goes on.⁶⁸⁰

The fen-phen debacle resulted in some of the largest litigation payouts in the industry's history, but it's all baked into the formula.⁶⁸¹ A new weight-loss drug may injure and kill so many that "expected litigation cost" could exceed \$80 million, but Big Pharma consultants estimated in the journal *PharmacoEconomics* that, if successful, the drug could bring in excess of \$100 million.⁶⁸² You do the math.

Think Outside the Black Box

Current options for weight-loss medications include Qsymia, a combination of phentermine, the *phen* in fen-phen, and topiramate, a drug that can cause seizures if you abruptly stop taking it.⁶⁸³ Qsymia was explicitly rejected multiple times for safety reasons in Europe but remains for sale in the United States. Belviq (lorcaserin) is in a similar boat, allowed here but not in Europe out of concerns about it possibly causing cancers, psychiatric disorders, and heart valve problems.⁶⁸⁴ It's sold in the United States for about \$200 a month, a bargain compared to the latest addition: Saxenda (liraglutide).

A drug requiring daily injections, Saxenda is listed at \$1,281.96 for a thirty-day supply.⁶⁸⁵ It carries a black box warning—FDA's strictest caution about potentially life-threatening hazards—for thyroid cancer risk.⁶⁸⁶ Paid consultants and employees of the company that makes it argue the greater number of breast tumors found among drug recipients may be due to "enhanced ascertainment," meaning easier breast cancer detection due to the drug's effectiveness.⁶⁸⁷ Contrave (bupropion/naltrexone) is another option if you choose to ignore its own black box warning about a potential increase in suicidal thoughts.⁶⁸⁸

Alli (orlistat) is the final choice. That's the drug that blocks fat absorption and causes side effects such as "flatus with discharge."⁶⁸⁹ The drug evidently "forces the patient to use diapers and to know the location of all the bathrooms in the neighborhood in an attempt to limit the consequences of urgent leakage of oily fecal matter."⁶⁹⁰ A Freedom of Information Act exposé found that although company-sponsored studies claimed "all adverse events were recorded,"⁶⁹¹ one trial apparently conveniently failed to mention 1,318 of them.⁶⁹²

What's a little bowel leakage compared to the ravages of obesity, though? ⁶⁹³ As always, risks versus benefits, right? But in an analysis of more than one hundred clinical trials of anti-obesity medications lasting up to forty-seven weeks, drug-induced weight loss never exceeded nine pounds.⁶⁹⁴ Since you're not treating the underlying cause—a fattening diet—the weight tends to come right back when people stop taking these drugs,⁶⁹⁵ so you'd have to take them every day for the rest of your life. How well are people able to stay on them? Using pharmacy data from a million people, most Alli users stopped after the first purchase, and most Meridia users didn't even make it three months. Taking weight-loss meds is so disagreeable that 98 percent of people stopped taking them within the first year.⁶⁹⁶

Studies show many doctors tend to overestimate the amount of weight loss caused by these drugs.⁶⁹⁷ One reason may be that some clinical practice guidelines, like those of the Endocrine Society, go out of their way to advocate pharmacotherapy for obesity.⁶⁹⁸ Are they seriously recommending drugging 40 percent of Americans—more than one hundred million people? ⁶⁹⁹ At this point, you will not be surprised to learn that the principal author of the guidelines had a "significant financial interest or leadership position" in six separate pharmaceutical companies that all, coincidentally, work on obesity drugs.⁷⁰⁰ In contrast, independent expert panels, like the Canadian Task Force on Preventive Health Care, explicitly recommend against weight-loss drugs given their poor track records of safety and efficacy.⁷⁰¹

Weight-Loss Supplements

Bad Manufacturing Practices

According to a national survey, a third of adults who've made serious efforts at weight loss have tried using dietary supplements,⁷⁰² for which Americans spend literally billions of dollars every year.⁷⁰³ Most people surveyed mistakenly thought that over-the-counter appetite suppressants, herbal products, and weight-loss supplements had to be approved for safety by a government agency like the FDA before being sold to the public—or at least include some kind of warning on the label about potential side effects. Nearly half even thought they had to demonstrate some sort of effectiveness.⁷⁰⁴ None of that is true.

The FDA estimates that dietary supplements in general cause fifty thousand adverse events annually,⁷⁰⁵ most commonly liver and kidney damage.⁷⁰⁶ Meanwhile, prescription drugs don't just adversely affect but actually kill more than one hundred thousand Americans every year.⁷⁰⁷ But at least with prescription meds, you notionally have the opportunity to parse out the risks versus the benefits, thanks to testing and monitoring requirements typically involving thousands of individuals.⁷⁰⁸ When the manufacturer of the ephedrine-containing dietary supplement Metabolife 356 had it tested in a study that ended up with just twenty-four people, only minor side effects were found (like dry mouth, headache, and insomnia).⁷⁰⁹ However, once unleashed on the populace, nearly fifteen thousand adverse effects were reported before it was pulled from the market, including heart attacks, strokes, seizures, and deaths.⁷¹⁰

Given the lack of government oversight, there's no guarantee that what's on the label is even inside the bottle. FDA inspectors have found that 70 percent of supplement manufacturers violated so-called Good Manufacturing Practices, which are considered the *minimum* quality standards,⁷¹¹ such as basic sanitation and ingredient identification. Not 7 percent, but 70 percent.

DNA testing of herbal supplements across North America found that most could not be authenticated. In 68 percent of the supplements tested, the main labeled ingredient was missing completely and substituted with something else. For example, a "St. John's Wort" supplement contained nothing but senna,⁷¹² a laxative that can cause anal blistering.⁷¹³ Only two out of twelve supplement companies had products that were accurately labeled.⁷¹⁴

The problem isn't limited just to fly-by-night phonies in some dark corner of the internet. The New York State Attorney General commissioned DNA testing of seventy-eight bottles of commercial herbal supplements sold by Walgreens, Walmart, Target, and GNC. Four out of five bottles didn't contain any of the herbs listed on their labels. Instead, capsules were often stuffed with little more than cheap fillers like powdered rice "and houseplants."⁷¹⁵

Getting More Than You Paid For

Weight-loss supplements are also infamous for being adulterated with drugs.⁷¹⁶ Of 160 "100% natural" weight-loss supplements sampled, more than half were tainted with drugs, ranging from antidepressants to erectile dysfunction meds.⁷¹⁷ Diuretic drugs are frequent contaminants, which makes sense.⁷¹⁸ In the Intermittent Fasting section, I talk about rapid water loss as the billion-dollar gimmick that has sold low-carb diets for more than a century.

Researchers in Denver tested every weight-loss supplement they could find within a ten-mile radius and alarmingly found a third were adulterated with *banned* ingredients, and 90 percent contained "discouraged-use" components.⁷¹⁹ The most common illegal adulterant of weight-loss supplements is sibutramine, the Meridia drug that was yanked off the market back in 2010 for heart attack and stroke risk,⁷²⁰ and is now blamed for cases of slimming supplement-induced psychosis.⁷²¹ An analysis of weight-loss supplements bought off the internet and advertised with claims such as "purely natural," "harmless," or "traditional herbal" found that a third contained a high dose of sibutramine and the rest contained caffeine. Wouldn't we be able to tell if caffeine were added to a supplement? Perhaps not if

the supplement also contained temazepam, a controlled-substance benzodiazepine downer sedative found in half of the caffeine-tainted supplements.⁷²²

Doesn't the FDA demand recalls of adulterated supplements? Yes, but the pills just pop up again on store shelves. Twenty-seven supplements purchased at least six months after recalls were retested, and two-thirds still contained banned substances. At the follow-up testing, seventeen supplements out of twenty-seven had the same pharmaceutical adulterant found originally, and six contained one or more *additional* banned ingredients.⁷²³ And unfortunately, the manufacturers aren't sufficiently penalized for noncompliance. As a founding fellow of the Institute for Science in Medicine put it, "Fines for violations are small compared to the profits."⁷²⁴

Slim Pickings

One of the ways supplement makers can skirt the law is by labeling them "not intended for human consumption," for example, labeling the fatal fat-burner DNP as an industrial or research chemical.⁷²⁵ That's how designer street drugs can be sold openly at gas stations and convenience stores as "bath salts."⁷²⁶ Another way is to claim that synthetic stimulants added to slimming supplements are actually natural food constituents, like listing the designer drug dimethylamylamine as "geranium oil extract." The FDA banned dimethylamylamine in 2012 after it was determined DMAA was "not found in geraniums." (Who eats geraniums anyway?⁷²⁷) Despite being tentatively tied to cases of sudden death⁷²⁸ and hemorrhagic stroke,⁷²⁹ DMAA has continued to be found in weight-loss supplements with innocuous names like Simply Skinny Pollen made by Bee Fit with Trish.⁷³⁰

There is little doubt that certain banned supplements like ephedra could help people lose weight.⁷³¹ "There's only one problem," wrote a founding member of the American Board of Integrative Medicine. "This supplement may kill you."⁷³²

Are there any safe and effective dietary supplements for weight loss? When nine popular slimming supplements were put to the test in a randomized placebo-controlled trial, not a single one could beat out placebo sugar pills.⁷³³ A systematic review of diet pills came to a similar conclusion: None appears to generate appreciable impacts on body weight without undue risks.⁷³⁴ One such systematic review of "nutraceutical" supplements out of the Weight Management Center at Johns Hopkins University ended with this:

*In closing, it is fitting to highlight that perhaps the most general and safest alternative/herbal approach to weight control is to substitute low-energy density foods for high-energy density and processed foods, thereby reducing total energy intake. By taking advantage of the low-energy density and health-promoting effects of plant-based foods, one may be able to achieve weight loss, or at least assist weight maintenance without cutting down on the volume of food consumed or compromising its nutrient value.*⁷³⁵

Licensed to Swill

Even if harmless, there's a way weight-loss supplements could actually make you gain weight, thanks to a fascinating glitch of human psychology called *self-licensing*.⁷³⁶ This is when we unwittingly justify doing something that pulls us away from our goals, right after we've done something that moves us toward them. We reward ourselves with an indulgence that sets us back.

When smokers were told they were given "vitamin C" supplements, they subsequently smoked more cigarettes than if they had been given what were identified as "placebo" pills—even though both groups had been given identical sugar pills. The "vitamin C" group smoked nearly twice as much, perhaps thinking at some subconscious level that since they had just done something good for their health by taking a "supplement," they could afford to "live a little," when, in effect, it may have indeed occasioned them to live a little ... less.⁷³⁷

You can see how self-licensing can translate into other lifestyle arenas. Other studies have shown that those given placebo pills they believed to be dietary supplements not only expressed less desire to subsequently engage in exercise but followed through by walking about a third less. Compared to those who were told the pills were

placebos, misled participants were also more likely to choose a buffet over a “healthful, organic meal.”⁷³⁸ Would they eat more too? A seminal study entitled “The Liberating Effect of Weight Loss Supplements on Dietary Control” put it to the test.

Participants were randomized to take a known placebo or a purported weight-loss supplement that was actually just the same placebo, and they were later covertly observed at a buffet. Not only did the “supplement” subjects eat more foods, they chose less-healthy items.⁷³⁹ They also ate about 30 percent more candy in a bogus “taste test” and ordered more sugary drinks.⁷⁴⁰ “Hence,” the investigators concluded, “people who rely on dietary supplements for health protection may pay a hidden price: the curse of licensed self-indulgence.”⁷⁴¹

Policy Approaches

System Failure

The public health community appears to have all but given up on ending the obesity epidemic. The latest World Health Organization goals include a 2025 obesity target of just trying to shoot for a zero increase in further prevalence.⁷⁴² Even such a modest-sounding low bar may represent one of the greatest challenges facing global health. Though there have been isolated pockets of patchy progress, no country has yet reversed the epidemic.

The promotion of the overconsumption of high-calorie, low-nutrient foods and beverages has been identified as the major driver of the obesity pandemic.⁷⁴³ Now that we have rid much of the world of pestilence and famine, some public health proponents have gone as far as to suggest that the “new vectors of disease” are taking the form of “trans-national food corporations that market salt, fat, sugar, and calories in unprecedented quantities.”⁷⁴⁴ Blame has been laid at the feet of lobbying efforts of the food industry,⁷⁴⁵ which is considered the world’s biggest industry.⁷⁴⁶ The processed food makers alone may bring in trillions.⁷⁴⁷ “Put simply,” concluded a senior director at the George Institute for Global Health, “the enormous commercial success enjoyed by the food industry is now causing what promises to be one of the greatest public health disasters of our time.”⁷⁴⁸

But remember—corporations just do what they’re set up to do. Their goal is not to make people fat but to make people money.⁷⁴⁹ The food industry manipulates ingredients like salt, sugar, and fat and throws in caffeine and flavor-enhancing chemicals for reasons no more nefarious than maximizing profits. Markets often incentivize companies to cater to, and take advantage of, human weaknesses.⁷⁵⁰ The food and beverage CEOs simply have a fiduciary responsibility to maximize quarterly profits for their shareholders.

But why not sell apples instead of Apple Jacks or oranges instead of Orange Crush? To quote from Slick Willie Sutton’s apocryphal answer to why he robbed banks: “That’s where the money is.” The reason some of the unhealthiest foods are marketed is one of simple economics: Real food goes bad.⁷⁵¹ Fruits and vegetables are perishable. What shareholders want is a snack cake that lasts for weeks on the shelf.

On top of that, real food doesn’t have brand names. Why would a broccoli grower put an ad on TV when you’d just as likely buy their competitor’s broccoli? The system is simply not set up to reward the sale of health-promoting food.

And finally, real food costs money to grow. Shareholders don’t want dirt—they want dirt-cheap commodities such as corn syrup, preferably discounted by taxpayer subsidies, that they can then mix with carbonated water and sell for a few bucks a bottle. Burgers on the Dollar Menu are there thanks in part to hundreds of billions of dollars of federal subsidies for cheap animal feed.⁷⁵² Those who resist calls for “heavy-handed” government regulation may not realize those heavy hands are already pressing down the scale on the side of Big Business.

Using the Anti-Tobacco Playbook

What we learned from the tobacco experience, wrote two preeminent public health scholars, is how powerfully profits can motivate “even at the cost of millions of lives and

unspeakable suffering.” Here they quote a U.S. district judge ruling on a tobacco case:

*All too often in the choice between the physical health of consumers and the financial well-being of business, concealment is chosen over disclosure, sales over safety, and money over morality. Who are these persons who knowingly and secretly decide to put the buying public at risk solely for the purpose of making profits, and who believe that illness and death of consumers is an apparent cost of their own prosperity?*⁷⁵³

Tobacco is one of our great public health victories. The share of adults who smoke declined from 42 percent in 1965⁷⁵⁴ down to just 15 percent today.⁷⁵⁵ That’s about five out of twelve down to fewer than two out of twelve. Thanks to the decline, cigarettes now only kill about a half million Americans a year, whereas our diets kill many thousands more. Currently, the leading cause of death in America is the American diet.⁷⁵⁶

Might we be able to use the same strategies that were so successful in the battle against Big Tobacco? It may be no coincidence that three of the most cost-effective policy interventions against obesity seem to be taken straight from the tobacco wars: (1) taxes on unhealthy products, (2) front-of-pack labeling, and (3) a restriction on advertising to children.⁷⁵⁷

Death and Taxes

Excise taxes on cigarettes have been cited as the single most effective weapon in slashing smoking rates.⁷⁵⁸ A twenty-five-cents-per-pack tax to help deal with some of the societal costs of smoking was tied to as much as a 9 percent decrease in smoking rates.⁷⁵⁹ The World Health Organization has estimated that a 70 percent global increase in the price of cigarettes could prevent up to a quarter of all tobacco-related deaths worldwide.⁷⁶⁰

Extending taxes on alcohol and tobacco to foodstuffs was proposed by none other than Adam Smith in his 1776 *Wealth of Nations*: “Sugar, rum, and tobacco, are commodities which are nowhere necessities of life, which are become objects of almost universal consumption, and which are, therefore, extremely proper subjects of taxation.”⁷⁶¹ People have the right to smoke, drink, and eat fattening foods, the logic goes, but perhaps they should help defray some of the publicly funded medical costs that result from their unhealthy habits.⁷⁶²

A penny-per-ounce tax on sugar-sweetened beverages could bring in more than a billion dollars a year in states like Texas and California.⁷⁶³ A 10 percent tax on fattening foods on a national level could yield half a trillion dollars over ten years.⁷⁶⁴ Even if such a tax were combined with a subsidy that lowered the cost of fruits and vegetables by 10 percent, it would be expected to net hundreds of billions of dollars. But would it change anyone’s eating habits? Just a small price differential of about 10 percent between unleaded and leaded gas was able to shift the entire auto industry away from lead.⁷⁶⁵ What we want to know now is whether such a price difference could also shift Americans to apples from apple pie.

A systematic review of the available evidence suggests that dietary financial incentives and disincentives do work. The cheaper we make fruits and vegetables, the more people said they’d buy, and the more we tax unhealthy foods, the lower their consumption drops.⁷⁶⁶ Based on this kind of modeling, a tax on saturated fat (found mostly in fatty meat, dairy, and junk) could potentially save thousands of lives a year.⁷⁶⁷

But wouldn’t such a tax disproportionately affect the poor? Yes, in that we would expect the impoverished to *benefit* the most. It’s like cigarette taxes.⁷⁶⁸ The classic tobacco industry argument is that cigarette taxes are “unfair” and “regressive,” burdening the poor the most, to which the public health community responded: “Cancer is unfair.” Indeed,

cancer disproportionately burdens the poor,⁷⁶⁹ so these types of taxes would be expected to affect the greatest health gains for the least well-off.

The fact that the tobacco industry fought tooth and nail against cigarette taxes—doing everything from inventing industry front groups to overtly buying off politicians⁷⁷⁰—suggests that taxes can indeed be a powerful tool to shift people’s habits, but much of the evidence on changing food behaviors has not been based on real-life data. When people are put through high-tech, 3-D supermarket simulators, researchers have shown that a 25 percent discount on fruits and vegetables appears to boost produce purchasing by the same amount—up to nearly two pounds a week.⁷⁷¹ Virtual vegetables, however, don’t actually do you any good. Does this work in the real world with real food?

South Africa’s largest private health insurer started offering up to 25 percent cash back on healthy food purchases to hundreds of thousands of households, up to the U.S. equivalent of \$799 per month.⁷⁷² Why would the insurer give money away? Because it apparently increases consumption of fruits, vegetables, and whole grains, while at the same time decreasing consumption of foods high in added sugar, salt, and fat, including processed meats and fast food—which then would be expected to translate into reduced disease rates, saving the insurer money.⁷⁷³

Why not just pay people to lose weight directly? A systematic review found that eleven out of twelve studies on financial incentives for weight loss described positive results.⁷⁷⁴ The one that failed to find a benefit of direct monetary inducements had only offered \$2.80 a day.⁷⁷⁵ With kids, you can get away with just giving them a nickel or a sticker to get them to choose dried fruit over a cookie as an afterschool snack, but as soon as the enticements ended, so did the change in behavior.⁷⁷⁶

Even if the incentives have to be made permanent, they might still pay for themselves. In the United States, every \$1 spent taxing processed foods or milk might net an estimated \$2 in health-care cost savings. Every \$1 spent making vegetables cheaper could net \$3, and subsidizing whole grains might offer more than a 1,000 percent return on investment.⁷⁷⁷ Even a 1 percent decrease in the average price of all fruits and vegetables might prevent nearly ten thousand heart attacks and strokes every year.⁷⁷⁸

From Coke to Coors: Unintended Consequences

Sometimes dietary policy decisions can have unintended consequences. Swapping out sugary cookies for salty chips, for example, might not do the public’s health many favors. One field study of a tax on soda found that it can drop soft drink purchases, but households may just end up buying more beer.⁷⁷⁹ Another study found that, ironically, calorie labeling of sugary drinks led to an *increase* in consumption, presumed to be because the consumers may have previously overestimated their caloric content.⁷⁸⁰

Stark warnings about the risks of unintended, negative consequences of obesity-targeted health policies are trumpeted by those with ties to the likes of Coca-Cola, Kraft, PepsiCo, Wrigley, Red Bull, the World Sugar Research Organisation, the National Cattlemen’s Beef Association, Mars, and corn syrup giant Archer Daniels Midland (and that is just a single scientist’s list of funding sources).⁷⁸¹ The concern shouldn’t paralyze our efforts, but it should serve up a healthy dose of humility when considering policy proposals.⁷⁸²

How about releasing a video game for kids that promotes fruit? Sounds good, right? Well, what do you think happened when kids were seated in front of bowls of fruit and candy, and randomized to play one of three different computer “advergames” (advertising-game hybrids incorporating product placements) that promoted either candy, fruit, or toys? The pro-candy game group ate more candy, but, disappointingly, the pro-fruit group didn’t eat more fruit. Then it got interesting. The kids in the pro-fruit group *also* ate more candy. Compared to the pro-toy control group, having a kid play a video game promoting fruit led them to eat more candy. Presumably both the candy and fruit games just made the kids think about food, and they naturally gravitated to their preferred snacks.⁷⁸³

Among the most fascinating phenomena I’ve come across is the boomerang effect of “remedy messaging.” One might presume that the advertising of smoking cessation aids like nicotine gum would help make quitting easier. After all, the vast majority of smokers want to quit,⁷⁸⁴ so availing them of helpful options couldn’t help but help, right? Instead, such remedy marketing can create a vicarious get-out-of-jail-free card that ends up reinforcing risky behavior. Exposure to nicotine replacement product advertising was found to undermine quitting intentions, especially among the heaviest smokers, the very ones who needed it the most. The thought is that smokers may subconsciously interpret the remedy as evidence that the hazards of smoking are more manageable and, therefore, less risky, which thereby helps to justify their habit.⁷⁸⁵

You can see how easily this would translate to the weight-loss arena. We explored how self-licensing could cause those taking slimming supplements to inadvertently eat more, but merely being exposed to an ad for a “fat-fighting pill” appeared to have a similar type of effect. So even when companies are ostensibly selling health rather than disease, they still may be inadvertently making the problem worse. And in the marketplace, there’s just no incentive for risk-avoidance messaging. Nobody makes money selling *just say no* unless it can somehow be linked to salable products and services.⁷⁸⁶

A policy in France—where burgers now outsell baguettes⁷⁸⁷—may represent an interesting real-world example of the counterintuitive remedy-messaging effect. Industry lobbying took a valiant effort to ban the advertising of junk and morphed it into a mandate for preventive health messaging on junk food advertisements.⁷⁸⁸ On products like Lay’s Chips Saveur Poulet Rôti (chicken-flavored potato chips), you’ll now see messages like *Pour votre santé, pratiquez une activité physique régulière* (For your health, practice regular physical activity).⁷⁸⁹ Sounds good, right? Not so fast. Anytime an industry agrees to a regulation, one should get skeptical as to its effectiveness.

To see if such messaging might lead to a boomerang effect, research subjects were randomized to view a Big Mac advertisement with or without the preventive health message *For your health, eat at least five fruits and vegetables per day*. (After all, wouldn’t it be great if McDonald’s were forced to advertise healthy food?) The subjects then filled out a general questionnaire and, before they left, were allowed to choose one of two McDonald’s coupons as a reward for their participation: a free sundae or a free bag of fruit.⁷⁹⁰ Guess who was more likely to pick the fruit?

Only one in three who had just seen the straight burger advertisement, the one without the preventive health message, chose the fruit over the sundae, but that number fell to only about one in six among those who had been prompted to eat healthier.⁷⁹¹ Isn’t that wild? The *absence* of the healthy message doubled the number of people choosing the healthy snack. The health message made things worse. This may be the remedy-messaging boomerang effect in action. Simultaneously offering a temptation with a reminder about how they can dig themselves out justifies the excuse to indulge. Subconsciously, it may give the chicken-y chip eater the rationalization that they can just work it off the next day at the gym, even if that day never comes.

The recommended antidote to avoid justification effects is to instead use negative framing.⁷⁹² That is, instead of offering a way out to compensate for indulging “just this one time,” cautionary messages may be more effective. For example, imagine reading *Pour votre santé, évitez de manger trop gras, trop sucré, trop salé* (For your health, avoid foods that are too fatty, too sweet, or too salty) on your next chocolate-filled or ham-and-cheese croissant. That’s a message for which I doubt Le McDonald’s would be quite as enthusiastic.

Truth in Advertising

A tried-and-true method used by alcohol, tobacco, and food-related corporate interests to deflect attention away from health is to reframe something like a fat tax or soda tax as an issue of freedom, railing against the “nanny state” for restricting consumers’ rights.⁷⁹³ However, those complaining about the governmental manipulation of people’s choices hypocritically tend to be fine with corporations doing the very same thing.⁷⁹⁴ Case in point: former New York City mayor Michael Bloomberg’s attempt to cap soft drink sizes. How dare he try to manipulate consumer choice! But isn’t that just what the industry’s done? In 1950, a twelve-ounce soda was the “king-sized” option.⁷⁹⁵ Today, it’s marketed as a child’s portion. “King-sized” became “kid-sized.”

The tobacco industry’s classic “personal responsibility” trope does have a certain philosophical appeal.⁷⁹⁶ As long as people understand the risks, shouldn’t they be free to do whatever they want with their bodies? Sure, risk-taking affects others, but if you have the right to put your own life at risk, shouldn’t you have the right to aggrieve your parents, widow your spouse, and orphan your children?⁷⁹⁷ There is a social cost argument: People’s bad decisions can cost society as a whole, and our tax dollars may have to care for them. As some health law scholars eloquently put it, “The independent individualist [motorcyclist], helmetless and free on the open road, becomes the most dependent of individuals in the spinal injury ward.”⁷⁹⁸

For the sake of argument, though, let’s forget these spillover effects. If someone understands the hazards, shouldn’t they be able to do as they please? This assumes consumers have access to accurate and balanced information. How could smoking be a fully informed choice when tobacco companies spent decades *deliberately* suppressing, manipulating, and undermining the scientific evidence?⁷⁹⁹ “Don’t worry your pretty little head,” said the nanny companies.

Is the food industry any different? We are bombarded with conflicting nutrition messages.⁸⁰⁰ People love hearing good news about their bad habits, so clickbait headlines like “Butter Is Back” may sell a lot of magazines, but they sell the public short.

“It is not just Big Tobacco anymore,” declared the director-general of the World Health Organization.⁸⁰¹ “Public health must also contend with Big Food, Big Soda, and Big Alcohol. All of these industries fear regulation, and protect themselves by using the same tactics ... front groups, lobbies, promises of self-regulation, lawsuits, and industry-funded research that confuses the evidence and keeps the public in doubt.” It’s like that infamous tobacco industry memo that read: “Doubt is our product since it’s the best means of competing with the body of fact that exists in the mind of the general public.”⁸⁰² The tobacco industry didn’t have to convince the public that smoking was healthy to get people to keep consuming its products. It just needed to establish a controversy: Some science says it’s bad, some says it’s not so bad.

Conflicting messages in nutrition cause people to become so frustrated and confused they may just throw their hands up in the air and eat whatever’s put in front of them, which is exactly what the industry wants.

No purveyor of unhealthy products wants the public to know the truth. An extraordinary example of this is the tobacco industry’s 1967 response to the Fairness Doctrine. A court ruled that TV and radio stations had to run one health ad about smoking for every four tobacco ads they ran. Rather than risk the public being informed—even on a one-to-four basis—the tobacco companies withdrew all their own advertising from television.⁸⁰³ They knew they couldn’t compete with the truth. They needed to keep the public in the dark.

Now there are health warnings on each pack of cigarettes. Global travelers will notice, though, that while the U.S. mandate is met with simple, black-and-white text, other countries plaster evocative images, such as rotting gums, on their cigarette packs.⁸⁰⁴ Canadian smokers are forced to look at a drooping cigarette with the caption TOBACCO USE CAN MAKE YOU IMPOTENT. Similarly, U.S. food packaging just has the inscrutable bring-your-calculator-to-the-grocery-store nutrition facts label on the back. I don’t expect pictures of flaccid frankfurters, but other countries have tried to impose clear and simple front-of-package graphics to convey the health risks of fattening foods.⁸⁰⁵

“Signpost labeling” offers easy-to-understand traffic-light symbols alerting shoppers to the salt, sugar, and saturated fat content of products right on the front of every package.⁸⁰⁶ When it’s been tried, investment analysts at Citibank concluded, “The magnitude of the sales impacts is such that we are left with the inescapable conclusion that the increased prevalence of front-of-pack signposts may lead to marked changes in consumer buying habits.” It works so well that green, yellow, and red traffic-light labeling poses “dire consequences” for certain food categories.⁸⁰⁷ No wonder the food industry fought it fiercely, spending more than a billion dollars to defeat it in Europe, an amount that’s ten times more than the drug industry lobby spends annually in the United States.⁸⁰⁸

It’s in the food industry’s interest to have the public confused about nutrition.

Vicarious Goal Fulfillment

What about labeling menus with calorie counts? Just as one might divine the significance of front-of-pack signpost labeling from the ferocity of the industry response, one could probably gauge the futility of calorie labeling by the ease at which such regulations have been passed. McDonald’s voluntarily started doing it nationally in 2012⁸⁰⁹ after a labeling mandate in New York City was found to have no overall effect on consumer behavior.⁸¹⁰ Studies suggest such voluntary labeling could boost “perceptions of the restaurant’s concern for customers’ well-being,”⁸¹¹ while not stopping any Big Mac attacks.

At the same time, McDonald’s announced plans for adding seasonal produce to its menu.⁸¹² How cynical do you have to be to not at least recognize that as a good thing? Well, ironically, adding a healthy option can actually sway people to make even worse choices.

If you offer people with high self-control a choice of side dishes—something unhealthy like french fries or something more neutral like a baked potato—only about 10 percent of them will splurge for the fries. French fries are so unhealthy, though, that as a public health do-gooder, you add a third option, an even healthier one—a side salad—to appeal to their better natures. Even if they don’t choose the salad, perhaps more will elect the middle-ground baked potato. So how much further does french-fry fancying fall by adding the salad option to the mix? It

shoots *up* to more than 50 percent. Without the salad option, only one in ten chose the fries over the baked potato, but it jumped to more than half of the people just at the *sight* of salad.

The same thing happens when you offer people the choice of a bacon cheeseburger, a chicken sandwich, or a veggie burger. In a “No Healthy Option” scenario where people were offered the bacon cheeseburger, a chicken sandwich, or a fish sandwich, 17 percent chose the burger. When the fish sandwich was replaced with a veggie burger, however, the bacon cheeseburger preference more than doubled, up to 37 percent. How can just *seeing* a healthy option push people to make unhealthier choices? The title given to the paper describing these series of experiments is “Vicarious Goal Fulfillment: When the Mere Presence of a Healthy Option Leads to an Ironically Indulgent Decision.” The thinking is that just by seeing the salad or plant-based option, people make the mental note to choose that the *next* time, thereby giving them the excuse to indulge now. Remember the self-licensing effect, where people making progress toward a goal rationalize making decisions that undermine it? These experiments suggest that even merely *considering* making progress can have a similar licensing effect.⁸¹³

Note that the study participants weren’t just moved to make the unhealthier choice, but the *unhealthiest* one. Even if people don’t go for the salad or veggie burger option, you’d think that the presence of a healthier alternative might, at the very least, encourage people to choose something in between. Instead, it moved people in the opposite direction altogether. Compared to the “No Healthy Option” scenario of chocolate-covered Oreos, regular Oreos, or golden Oreos, adding a “lower-calorie” Oreo option doubled the likelihood study participants would go straight for the most indulgent chocolate-covered option. This is attributed to another illogical quirk of human psychology, the indelicately named *what-the-hell effect*. This is when one forbidden cookie can lead dieters to eat the whole bag. Once you’ve already strayed from your goals, why not go all the way? So once people decide they are going to get the salad the next time and spoil themselves “just this once,” they might as well go for the most indulgent choice.⁸¹⁴

The halo of healthy foods can even warp our perceptions. When weight-conscious people were shown a burger on its own and asked to estimate its calories, the average answer was 734 calories. What happened when people were shown the exact same burger, but this time, it was accompanied by three celery sticks? The estimated number of calories dropped to 619. Did they think the celery had negative calories? No, most knew the celery had calories, too, but just the juxtaposition made the burger seem healthier. The same thing happens when you add an apple next to a bacon-and-cheese waffle sandwich, a side salad to beef chili, or some carrots next to a cheesesteak. About one hundred calories appear to disappear.⁸¹⁵ Health halo effects may explain why people are more likely to order a dessert and more sugary drinks with a “healthier” sub at Subway versus a Big Mac at McDonald’s, even though the sub used in the study (filled with ham, salami, and pepperoni) had 50 percent more calories than the Big Mac.⁸¹⁶

Even just a reference to healthy foods can cause this unhealthy behavior. Remember that crazy Big Mac study where the eat-your-fruits-and-veggies message steered people toward the sundae instead of the fruit? The findings get even wackier. When asked to estimate the calorie content of the burger pictured in the ad without any health messaging, people guessed 646 calories.⁸¹⁷ What happened when the text *For your health, eat at least five fruits and vegetables per day* was added to the ad? All of a sudden, the same burger in the same ad appeared to only have 503 calories. So offering and even promoting salads and fruit can bring McDonald’s accolades and bolster consumer loyalty without, ironically, helping their waistlines.⁸¹⁸

Ad Nauseam

The third strategy taken from the anti-tobacco playbook, after taxes and front-of-pack labeling, is restricting advertising to children.⁸¹⁹ The food industry spends more money on advertising than any other industry,⁸²⁰ with more than \$10 billion in ads targeting American children and teens every year.⁸²¹ As a case study example, allow me to profile the number-one food advertised to kids: breakfast cereals.

There have been calls for nearly a half century to ban the advertising of sugary cereals to children, which Harvard nutrition professor Jean Mayer referred to as “sugar-coated nothings.”⁸²² In a Senate hearing on nutrition education, he said, “Properly speaking, they ought to be called cereal-flavored candy, rather than sugar-covered cereals.”⁸²³

The Senate committee had invited the major manufacturers of children’s cereals to testify. They initially agreed to participate—until they heard the kinds of questions that were going to be asked. One cereal industry representative candidly admitted why he decided to boycott the hearing: He simply didn’t have “persuasive answers” for why the industry tries to sell kids candy for breakfast.⁸²⁴

In the *Mad Men* age before the consumer movement was in bloom, advertising company executives were more willing to talk frankly about the purpose of their ads and how they felt about aiming them at the “child market.”⁸²⁵ For example, consider this 1965 quote from an ad executive for Kellogg’s and Oscar Mayer:

*Our primary goal is to sell products to children, not educate them. When you sell a woman a product and she goes in to the store and finds your brand isn't in stock, she will probably forget about it. But when you sell a kid on your product, if he can't get it, he will throw himself on the floor, stamp his feet and cry. You can't get a reaction like that out of an adult.*⁸²⁶

To preempt federal regulations, the industry pledged to self-regulate and launched the Children's Food and Beverage Advertising Initiative, in which all the big cereal companies promised they would only market healthier dietary choices to kids.⁸²⁷ The candy industry signed on too. How did that go? Well, how do you think it went? They pledged not to advertise to children, yet after the initiative went into effect, kids actually saw *more* candy ads. Hershey, for example, more than doubled its advertising to children, while, at the same time, pledging not to advertise to children at all.⁸²⁸

The cereal companies got to decide for themselves their own definitions of "healthier dietary choices," and what they chose should give a sense of how serious they are about protecting children: They classified Froot Loops and Reese's Peanut Butter Puffs, which consist of up to 44 percent sugar by weight, as "healthier dietary choices."⁸²⁹ In that case, what are their *unhealthy* choices?! Rather than base it on what might be best for children, they basically set the limit based more on the sugar content of everything they were already selling.⁸³⁰

The industry has since revised the "healthier dietary choices" criteria to allow only cereals that are below 38 percent sugar by weight.⁸³¹ Even if they're "only" one-third sugar, that means kids effectively are eating at least one spoonful of sugar in every three spoonfuls of cereal.⁸³² I wouldn't call that a healthy dietary choice.

The Federal Trade Commission (FTC) tried stepping it back in 1978, but industry poured in millions to fight it, and, with enough campaign contributions, Congress essentially threatened to yank the entire agency's funding if it continued to pursue industry regulations.⁸³³ This demonstrated to a former CDC nutrition director "just how powerful market forces are compared to those that can be mobilized on behalf of children."⁸³⁴ The political post-traumatic stress induced by the industry backlash delayed further federal efforts to rein in food marketing aimed at children for decades.

But then, enter the Interagency Working Group.⁸³⁵ In 2011, FTC, CDC, FDA, and U.S. Department of Agriculture (USDA) all came together to propose *voluntary* principles designed to encourage stronger and more meaningful self-regulation. Their radical suggestion? Don't market cereal that is more than 26 percent sugar to children.⁸³⁶

Not a single one of the top ten breakfast cereals marketed to children would meet that standard.⁸³⁷ General Mills shot back that the proposed nutrition standards were "arbitrary, capricious, and fundamentally flawed." After all, it pleaded, "literally *all* cereals marketed by General Mills would be barred from advertising."⁸³⁸ One grocers' association called the proposed nutrition principles the "most bizarre and unconscionable" it had ever seen.⁸³⁹ Cereal manufacturers charged that the suggested recommendations for voluntary self-regulation would unconstitutionally violate their "free speech rights" under the First Amendment,⁸⁴⁰ to which the FTC basically offered to get them a dictionary so they could look up the meaning of the word *voluntary*.⁸⁴¹ All this gives you a sense of how freaked out the food industry got at even the *notion* of meaningful guidelines.

So what happened? Again, agency funding was put into jeopardy, so the interagency proposal was called off.⁸⁴² "We just got beat," one of the child advocacy organizations said. "Money wins." It apparently took \$175 million of Big Food lobbying to buy the White House's silence as the interagency proposal got killed. As one Obama adviser put it, "You can tell someone to eat less fat, consume more fiber, more fruits and vegetables and less sugar. But if you start naming foods, you cross the line."⁸⁴³

“I’m upset with the White House,” the chair of the Senate Health Committee said.⁸⁴⁴ “They went wobbly in the knees, and when it comes to kids’ health, they shouldn’t go wobbly in the knees.”

How We Won the Trans Fat Fight

In 2012, a prize-winning⁸⁴⁵ exposé on corporate lobbyists found that the food and beverage industries had never lost a significant political battle in the United States, winning fight after fight at every level of government.⁸⁴⁶ That all changed in 2018 with the successful ban on added trans fat in the American food supply. Trans fat, found largely in vegetable oils partially hydrogenated to mimic the qualities of animal fats in snack foods, was implicated in the deaths of tens of thousands of Americans every year.⁸⁴⁷ So how did the public health movement finally triumph?

There are three broad approaches to mediating the ruin of risky choices: inform people (such as through labeling), nudge people (perhaps with financial incentives), or directly intervene to make the activity less harmful.⁸⁴⁸ Which do you think prevented more car fatalities: mandating driver education, labeling cars about crash risk, or removing the human element by just making sure airbags are installed?⁸⁴⁹ There are public education nutrition campaigns—from “sugar pack” ads on public transit informing consumers how much sugar there is in soft drinks⁸⁵⁰ to “Hot Dogs Cause Butt Cancer” billboards educating people about the link between processed meat and colorectal cancer.⁸⁵¹ But just warning people about trans fat wasn’t working.

We learned about the dangers of trans fat in 1993, when the Harvard Nurses’ Health Study reported that high intake of trans fat may increase the risk of heart disease by 50 percent.⁸⁵² That’s where the trans fat story started in Denmark—a story that ended a decade later with a ban on added trans fat in 2003.⁸⁵³ It took another ten years before the United States even started considering a ban.⁸⁵⁴ All the while, trans fat continued to kill the estimated tens of thousands of Americans every year,⁸⁵⁵ resulting in as many years of healthy life lost as conditions like meningitis, cervical cancer, and multiple sclerosis.⁸⁵⁶ If so many people were suffering and dying, why did it take so long for the United States to even *suggest* taking action?

One can look at the fight over New York City’s trans fat ban for a microcosm of the national debate. Opposition came down hard from the food industry, complaining about “government intrusion” and likening the city to a “nanny state.”⁸⁵⁷ The livestock industries echoed⁸⁵⁸ the everything-in-moderation argument made by the Institute of Shortening and Edible Oils⁸⁵⁹ (since trans fat is present naturally in meat and dairy).⁸⁶⁰ Another argument went: If “food zealots” get their wish in banning added trans fat, what’s next?⁸⁶¹ Critics styled proposals for a trans fat ban as the “rise of food fascism,”⁸⁶² but it was really the restaurant and food industry that was limiting consumer choice, by so broadly fouling the food supply with these dangerous fats.⁸⁶³

Vested corporate interests tend to rally around these kinds of “slippery slope” arguments to distract from the fact that people are dying.⁸⁶⁴ What if the government tries to make us eat broccoli? Unbelievably, that actually came up in a Supreme Court case over Obamacare. Chief Justice Roberts suggested Congress could start “ordering everyone to buy vegetables,” a fear Justice Ginsburg dubbed “the broccoli horrible.” Technically, Congress could compel the American public to eat more plant-based, Justice Ginsburg wrote, yet one can’t “offer the ‘hypothetical and unreal possibilit[y]’ ... of a vegetarian state as a credible [argument].”⁸⁶⁵ As one legal scholar put it, “Judges and lawyers [may] live on the slippery slope of analogies; [but] they are not supposed to ski it to the bottom.”⁸⁶⁶

But New York City eventually won its trans fat fight in 2006, preserving its status as a public health leader. New York, for example, banned lead paint eighteen years before

federal action was taken despite decades of unequivocal evidence for harm.⁸⁶⁷ Comparing stroke and heart attack rates before and after the rollout of the trans fat ban in different New York counties, researchers estimate the ban successfully reduced cardiovascular death rates by about 5 percent.⁸⁶⁸ This then became the model for the nationwide ban in 2018.

How was public health able to triumph when past attempts to regulate the food industry failed? If you would have asked me back then about the odds of a trans fat ban, I would have answered: *Fat chance*.

In Denmark, as a leading Danish cardiologist put it, “Instead of warning consumers about trans fats and telling them what they are, we’ve simply removed them.” The cardiologist continued, “As they say in North America, ‘You can put poison in food if you label it properly.’”⁸⁶⁹ And in America, things do seem to work differently. The belief is if people know the risks, they should be able to eat whatever they want—but that’s assuming they’re given all the facts. Unfortunately, this isn’t always the case, especially given the food industry’s “model of systemic dishonesty,” as one health ethics professor put it.⁸⁷⁰

Because of the predilection for predatory deception and manipulation, government intervention was deemed necessary when it came to trans fat. But how did the ban get passed? First there was a labeling requirement. Manufacturers had to start adding trans fat content to the nutrition facts labels. This ostensibly was to influence consumers, but it may have had a bigger impact on producers. Now that they had to divulge the truth, companies scrambled to reformulate their products to gain a “no trans fat” competitive edge.

Within a year of the mandatory disclosure, more than five thousand products were introduced touting low or zero trans fat on their labels.⁸⁷¹ Kentucky Fried Chicken went from being sued for having some of the highest trans fat levels⁸⁷² to running an ad campaign where the mom tells the dad in front of the kids that KFC now has zero grams of trans fat. The father yells, “Yeah, baby! Whoooo!”—and begins eating fried chicken by the bucketful.⁸⁷³ That was the secret to passing the ban. Once the major food industry players had already reformulated their products and bragged about it, once there wasn’t so much money at stake, then there was insufficient political will to block the ban.

Leveling the Playing Field

Even without regulations, the market can be rapidly responsive, but only within certain parameters. The gluten-free craze is a great example. Ten years ago, how many people had even heard the word *gluten*? And now, some surveys suggest as many as 25 percent of the population is trying to avoid it.⁸⁷⁴ This has led to an explosion of more than ten thousand products labeled as gluten-free,⁸⁷⁵ including ones from major players, such as Tyson Foods launching gluten-free bacon and lunch meat.⁸⁷⁶ Ironically, gluten-free products may be less healthy, with more sugar and salt, less fiber, and fewer nutrients, so they’re mostly just different shades of the same processed junk.⁸⁷⁷ A gluten-free donut is still a donut. And a nutritional analysis of foods marketed to children found that about 90 percent of products—both gluten-free and not—were classified as “unhealthy.”⁸⁷⁸

That’s the limit of the market. The invisible hand is more than happy to hand us any kind of junk we want—from SnackWell’s to keto cookies. The industries can make money off any fad, except real food. Shareholders can profit off any kind of Funyuns but can’t do much with real onions. Within a narrow scope of commodity components and chemicals, endless reformulations can fit any fashionable flavor of the month, but produce will never be as profitable.

The market even prevents food manufacturers from taking small steps to make their products less detrimental, such as lowering salt or sugar content. Any deviation from the levels perfectly engineered for maximum craveability could get you immediately undercut by your competitors. How then was England able to so successfully lower sodium intake, which has been associated with dramatic drops in stroke and heart disease deaths?⁸⁷⁹

Because it was done across the board. McDonald's Chicken McNuggets have two and a half times more salt in the United States than in the United Kingdom, but that's because Burger King UK was cutting down too.⁸⁸⁰

In the best-documented population-level sodium reduction to date,⁸⁸¹ the British government formed public-private partnerships with major food manufacturers, retailers, and restaurant chains to simultaneously reduce sodium levels so slowly over the years that no one would notice.⁸⁸² The secret sauce may be the level playing field, so no company could gain a commercial advantage by outsalting competitors.⁸⁸³ Analogous proposals have called for the stepwise, gradual, unobtrusive reduction in sugar in soft drinks to effect a similar shift in taste preferences on a population-wide scale.⁸⁸⁴

If this all sounds a bit Big Brother-y, realize that people can still season and sweeten to their heart's desire (or rather, detriment). Salt your nuggets all you want. Dump the whole shaker on them and wash it down with a bottle of corn syrup—it's still your body, your choice. It's like the proposed cap on soft drink sizes. You can still drink all the soda you want. The idea is just to try to make the default options a little healthier. It's easier to add salt to food on your plate than it is to remove it.

The lifesaving success of the trans fat ban and society-wide sodium reduction may lie in the convenience of improving consumers' diets without them having to change their behaviors.⁸⁸⁵ Some view this as government overreach, but the slipperiest slope may be that of inaction. As the director of the Rudd Center for Food Policy and Obesity has pointed out, governments initially defaulted to business interests in the case of tobacco to try to counter all the industry lies with weak and ineffective attempts at consumer education. And look what happened: "The unnecessary deaths could be counted in the millions," he wrote. "The U.S. can ill afford to repeat this mistake with diet."⁸⁸⁶

Until the political will is summoned to make industry-wide changes in our food supply, we need to take personal responsibility for our own health and for our families' health because it looks to be a matter of life and death. So what does that best personal solution look like in the interim? That's what the rest of this book is all about.

II. Ingredients for the Ideal Weight-Loss Diet

INTRODUCTION

Fad Diet du Jour

The \$50 billion weight-loss industry has been fed by an endless parade of fad diets offering quick-fix solutions. Dr. David L. Katz said it well, as he so often does: “In a market where buyers reject the tried and true in favor of false promises and pixie dust and in a culture where scapegoats and silver bullets are preferred over a prosaic blend of science and sense, the sellers respond accordingly.”⁸⁸⁷ Indeed, Amazon now lists more than thirty *thousand* weight-loss books.⁸⁸⁸

One of the defining characteristics of fad diets is their reliance on testimonials rather than scientific evidence,⁸⁸⁹ but what’s particularly insidious, beyond the nonsense and nonscience, is the pseudoscience—when the trappings of science are used to gain a false air of legitimacy. Confident, perhaps, that no one will actually check, some diet book authors (or likely their ghostwriters) cite scientific studies that either don’t support their thesis or, at the very least, fail to accurately represent the best available balance of evidence.

When people have taken the time to check the primary sources, it is often to devastating effect.⁸⁹⁰ See, for example, Seth Yoder’s footnote-by-footnote review of *The Big Fat Surprise* on his blog, *The Science of Nutrition*.⁸⁹¹ Similarly, when researchers looked through *The South Beach Diet*, they didn’t just find a few mistakes: Two-thirds of the nutrition “facts” they checked did not appear to be supported by peer-reviewed science.⁸⁹² You can always sell more books offering people good news about their bad habits, but at what human cost?

It’s worth repeating that every penny I receive from all my books is donated directly to charity. It’s written right into my publishing contracts. My overriding motivation is to provide the most accurate information possible. I’m such a stickler for veracity that I hired nine fact-checkers to go through every citation of the *How Not to Die* manuscript, and I committed to the same rigor with this book.

My original intention with *How Not to Diet*, consonant with the title, was to have chapters offering critical analysis on each of the leading popular diets, but I realized that would be like playing a game of Whac-A-Mole. I’m a member of the *U.S. News & World Report* Best Diets expert panel, tasked with scoring dozens of trending diets based on set criteria, and so I’m especially aware how many new diets pop up every year. I didn’t want this book to be out of date before it even came out.

Thus, rather than taking a reactionary tactic and wasting page space on Dr. Quack’s here-today-gone-tomorrow **New Snake Oil Diet** (now with added tricky pixie dust!), I decided upon a more timeless, proactive approach: build an optimal weight-loss diet from the ground up. Based on the most compelling evidence my research team and I could find, I sought to generate a list of dietary attributes and components most effectual for weight loss. The best ingredients, if you will.

I’ve distilled this research into a list of seventeen key ingredients for an ideal weight-loss diet, which we’ll explore one by one over the course of part II. These components can then

be used to construct a portfolio of dietary changes to attack excess body fat on multiple fronts, as well as offer a template by which to compare any new diet that comes down the pike.

Many popular diets exist in an evidence-free zone powered by personal biases and aggrandizement, free from the bonds of scientific accountability.⁸⁹³ A few large proprietary programs have been put under scientific scrutiny, though. So before we build an ideal weight-loss diet from scratch, let's briefly assess the current state of affairs.

Anecdotes as Evidence

Most Americans have tried to lose weight at some point in their lives, and as many as around one in three is actively making the attempt at any given moment.⁸⁹⁴ This has spawned a massive weight-loss industry valued at more than \$50 billion.⁸⁹⁵ With so much money at stake, it comes as no surprise that there are so many different flavors of snake oil on tap. The history of weight-loss quackery includes everything from body jiggers to suction-cupped rolling pins. There was the Relax-a-cizor, an ironic name for a device that delivers electric shocks,⁸⁹⁶ and wearing the Fat-Be-Gone ring promised the "same benefits as jogging up to six miles per day!"⁸⁹⁷ "Unwanted pounds and inches scrub right off" with the Amazing Seaweed Weight Loss Soap,⁸⁹⁸ and don't forget the "amazing new super-formula" that will "overwhelm fat like Cary Grant overwhelmed your grandmother!"⁸⁹⁹

A major conclusion of congressional hearings on fraud in the diet industry was that the entire sector was characterized by deceptive and misleading advertising, rife with puffed-up promises.⁹⁰⁰ In an analysis of hundreds of weight-loss advertisements, the FTC found that most ads made at least one claim that was very likely to be false or, at the very least, lacking adequate substantiation. Some were "grossly exaggerated," "obviously false claims" that were simply not "physiologically possible," like the product that guaranteed weight-loss efficacy comparable to "running a 20 mile marathon while you sleep." And it appears to be getting even worse. Compared to a similar analysis of ads in the 1990s, the FTC noted a "downward spiral to deception in weight-loss advertising."⁹⁰¹ The FTC has recovered millions for conned consumers, but a law journal article described the agency's actions as a "mere slap on the wrist" for an industry worth billions.⁹⁰²

By 2001, nearly 80 percent of all ads for weight-loss products or programs featured at least one testimonial.⁹⁰³ Who doesn't love a good story?⁹⁰⁴ Scientists often assert "anecdotes aren't data," but human nature may favor the opposite view—numbers are nice, but narratives can carry more meaning. Fund-raisers know this. They know to tug at the heart, not the head. It may not be surprising that people are more willing to donate to an African relief program after hearing a story of a starving little girl rather than give to an appeal outlining the dry statistics of the millions in need. But what *is* surprising is that when both the story and the stats are put together in the same appeal, people donate *less* than if they had heard just the anecdote.⁹⁰⁵ We are notoriously prone to embracing anecdotal evidence,⁹⁰⁶ and dietary hucksters rarely fail to exploit this hardwired human instinct.⁹⁰⁷

Researchers have compared the weight-loss claims of commercial programs to the actual results obtained from randomized controlled trials. Weight Watchers, for example, featured a testimonial of a woman who lost more than two hundred pounds after two years on the program⁹⁰⁸—but when Weight Watchers was actually put to the test, the average weight loss after two years was more like six pounds.⁹⁰⁹ The Weight Watchers watched a lot more weight stay on than come off.

The Atkins website boasted a three-hundred-pound weight-loss testimonial, and Jenny Craig a four-hundred-pounder. The average advertised testimonial weight loss across twenty different programs was about fifty pounds, a number far in excess of what even the programs' own published trials have shown.⁹¹⁰ Even if the rare testimonial were true, we

almost never hear what happens next. When researchers actually followed up on some of the people portrayed in the before-and-after pictures, only about one in four had sustained their success.⁹¹¹ The commercial diet program that participated in this study must have suspected as much, as its cooperation with researchers was predicated on the stipulation that the program never be identified.⁹¹² This is consistent with the findings of the Deception and Fraud in the Diet Industry hearings in Congress that concluded most programs actively suppress facts about what to expect regarding chances of success.⁹¹³

Programmed to Fail?

Many real-world diet trials are small in size and short in duration, and most lack control groups and fail to follow through on weight loss over time.⁹¹⁴ However, there are exceptions. Americans spend billions a year on commercial weight-loss programs, such as Weight Watchers, Nutrisystem, and Jenny Craig, and to their credit, these companies have spent some of their largesse on efficacy research to try to promote their respective programs.⁹¹⁵ Nevertheless, the results of their own studies are underwhelming.

A systematic review was conducted of randomized controlled trials of commercial weight-loss programs that used exchange-based meal plans like Weight Watchers, prepackaged meals like Jenny Craig, or meal replacements like SlimFast. All in all, the majority of people enrolled in these commercial weight-loss programs failed to achieve even a modest weight loss, defined as a 5 percent reduction of their initial body weights (for example, a ten-pound loss for someone weighing two hundred pounds).⁹¹⁶

On average, so little weight was lost on these types of programs that cost estimates range up to nearly \$200 per pound lost.⁹¹⁷ Most people don't chalk up that high of a bill, though, because most don't stick with the program for very long. For example, a study of more than sixty thousand men and women enrolled in Jenny Craig found that fewer than 7 percent remained at the end of one year.⁹¹⁸ The largest, longest, best-designed randomized trial of a commercial program was funded by Weight Watchers,⁹¹⁹ and after two years, the best it could show was an average weight loss of only about 3 percent compared to a "self-help" control group given informational resources and a couple of nutrition counseling sessions.⁹²⁰ Imagine all that time and energy spent in weekly Weight Watchers meetings to lose only an average of about three pounds a year.

Programs that include group sessions offer the advantage of social support and accountability,⁹²¹ but since some of the plans from leading companies seem to result in similar weight loss,⁹²² one might as well choose the least expensive. Take Off Pounds Sensibly (TOPS) is a nonprofit, peer-led weight-loss program that has been publishing its results for more than fifty years.⁹²³ Not having to siphon off money for shareholders, TOPS is five times cheaper than Weight Watchers and may be fifty times less expensive than other leading programs such as Nutrisystem or Jenny Craig.⁹²⁴

TOPS was the first national program to publish data on all its completers. Only a tiny percentage stayed enrolled over the entire seven-year study period, but the thousands who did maintained about an eighteen-pound weight loss.⁹²⁵ Still, that only amounts to a few pounds a year. Is that the best we can do? Sadly, as one obesity research pioneer once put it, "Most obese persons will not stay in treatment for obesity. Of those who stay in treatment, most will not lose weight, and of those who do lose weight, most will regain it."⁹²⁶

As a physician, my priority is getting (and keeping) people healthy, but when people are surveyed about their motivation for dieting, disturbingly, "health" may come in last.⁹²⁷ Dieters want results—they want weight to come off.

So that became my challenge. If I were to construct the ideal weight-loss diet, what characteristics would it have? My research team and I dove headfirst into the nearly half-million papers published in the English-language peer-reviewed medical literature on

weight management and certainly ran into some surprises on the way. What follows is our distilled list of seventeen key ingredients—dietary attributes that could be used to create the most effective eating plan for losing weight.

ANTI-INFLAMMATORY

Meta-Inflammation

One of the most important medical discoveries in recent years was the realization that inflammation appears to play a role in many of our chronic diseases, including at least eight of our top ten leading causes of death.⁹²⁸ The significance of this new understanding has been compared to the discovery of the germ theory, which, centuries ago, revolutionized our prevention and treatment of infectious diseases.⁹²⁹ Throughout most of human history, however, inflammation was considered to be a good thing. When you get a splinter in your finger and it gets red, hot, painful, and swollen, that's inflammation. It's your body's natural reaction to tissue damage or irritation. So if the point of inflammation is to trigger the healing process, not a disease process, what's going on?

That splinter reaction is an example of acute inflammation, a short-term, localized, specific response to infection or injury aimed at resolving a problem. In contrast, chronic inflammation, also called *metabolic inflammation*, or *meta-inflammation* for short, is persistent, systemic, and nonspecific, and it appears to perpetuate disease.⁹³⁰ It has a low-grade, smoldering quality—it's not as though we're red, hot, pained, and swollen all over. Simple blood tests, however, can detect abnormally high levels of inflammatory markers like C-reactive protein so that we can gauge our level of chronic inflammation.

C-reactive protein levels in the blood are ideally under 1 mg/L,⁹³¹ but in the presence of an infection, they can jump to 100 mg/L or more within hours.⁹³² Now that we have highly sensitive C-reactive protein blood tests that can measure levels to a fraction of a point, the medical community has realized that walking around with baseline levels of even just 2 or 3 mg/L appears to set us up for increased risk of catastrophes like heart attacks and strokes.⁹³³ Having a C-reactive protein level under 1 mg/L denotes low risk, yet the levels of most middle-aged Americans exceed this,⁹³⁴ suggesting most suffer from chronic inflammation.

This widespread meta-inflammation appears to be our immune systems' reaction to many unhealthy aspects of our lives—from the broader environment like traffic pollution and toxic chemicals to our day-to-day lifestyle choices, such as cigarettes, chronic stress, and too little physical activity and sleep.⁹³⁵ The primary driver of meta-inflammatory chronic disease, however, may be the portions of the outside world we introduce into our bodies multiple times a day: what we eat.⁹³⁶

The Dietary Inflammatory Index

It's easy to tell if a food is pro-inflammatory or anti-inflammatory: Feed it to people, and see what happens to their levels of C-reactive protein and other markers of inflammation. With this method, you can check the impact of individual nutrients, whole foods, meals, or entire dietary patterns.

To rate people's diets, researchers developed a Dietary Inflammatory Index by scouring thousands of such experiments to come up with a scoring system.⁹³⁷ The more pro-inflammatory foods you eat on a daily basis, the higher your score, and the more anti-inflammatory foods you eat, the lower your score. If you eat more anti-inflammatory than pro-inflammatory foods overall, you could end up with the goal—a net negative score, an anti-inflammatory diet.

Broadly speaking, components of processed foods and animal products, such as saturated fat, trans fat, and cholesterol, were found to be pro-inflammatory, while constituents of whole plant foods, such as fiber and phytonutrients, were strongly anti-inflammatory.⁹³⁸ No surprise, then, that the Standard American Diet rates as pro-inflammatory and has the elevated disease rates to show for it.

Higher Dietary Inflammatory Index scores are linked to a higher risk of cardiovascular disease⁹³⁹ and lower kidney,⁹⁴⁰ lung,⁹⁴¹ and liver function.⁹⁴² Those eating diets rated as more inflammatory also experienced faster cellular aging.^{943,944} In the elderly, pro-inflammatory diets are associated with impaired memory⁹⁴⁵ and increased frailty.⁹⁴⁶ Inflammatory diets are also associated with worse mental health, including higher rates of depression, anxiety, and impaired well-being.⁹⁴⁷ Additionally, eating more pro-inflammatory foods has been tied to higher prostate cancer risk in men^{948,949,950} and higher risks of breast cancer,^{951,952} endometrial cancer,⁹⁵³ ovarian cancer,⁹⁵⁴ and miscarriages in women. Higher Dietary Inflammatory Index scores are also associated with more risk of esophageal,⁹⁵⁵ stomach,⁹⁵⁶ liver,⁹⁵⁷ pancreatic,⁹⁵⁸ colorectal,⁹⁵⁹ kidney,⁹⁶⁰ and bladder⁹⁶¹ cancers, as well as non-Hodgkin lymphoma.⁹⁶²

Overall, eating a more inflammatory diet was associated with 75 percent increased odds of having cancer and 67 percent increased risk of dying from cancer.⁹⁶³ Not surprisingly, those eating more *anti*-inflammatory diets appear to live longer lives.^{964,965,966,967} But how does the Dietary Inflammatory Index impact body weight?

Obesity and Inflammation: Cause or Consequence?

Pro-inflammatory diets are also associated with obesity, especially abdominal obesity.⁹⁶⁸ When researchers followed thousands of normal-weight adults over time, they found those eating more pro-inflammatory foods have higher annual weight gain and those on the most inflammatory diets have a 32 percent greater risk of becoming overweight or obese during about an eight-year period.⁹⁶⁹ The researchers were able to control for such nondietary factors as smoking and exercise—but is it possible that higher Dietary Inflammatory Index scores are just a reflection of a poor diet in general? The concept that diets with fewer fruits and vegetables and more meat and junk might lead to more weight gain isn't exactly revelatory. How do we know the connection has anything at all to do with inflammation?

Dozens of studies have shown that obesity is strongly associated with increased levels in the blood of inflammatory markers like C-reactive protein,⁹⁷⁰ but is that inflammation a cause or a consequence of obesity?

We used to think fatty tissue was just a passive depot for the storage of excess fat,⁹⁷¹ but we now know it actively secretes inflammatory chemicals. Fatty tissue can expand so quickly it may outpace its blood supply and become starved of oxygen.⁹⁷² (You can insert an electrode directly into an obese belly and measure how low the oxygen levels fall compared with healthy-weight individuals.⁹⁷³) This is thought to contribute to fat cell death, which draws out inflammatory cells like macrophages, a type of roaming white blood cell present in pus, to try to clean up the mess. If you take a belly biopsy of an obese individual, you can see that the fat is swarming with macrophages.⁹⁷⁴ The macrophages then appear to get stuck and fuse into giant cells, a hallmark of chronic inflammation seen in resistant infections like tuberculosis or around foreign bodies the body can't clear.⁹⁷⁵ All the while, inflammatory compounds spill out into general circulation.⁹⁷⁶

Obesity, then, appears to lead to systemic inflammation, rather than the other way around.^{977,978} And even if inflammation had no role in the cause of obesity, you'd still want any weight-loss diet to be anti-inflammatory to mediate the inflammatory consequences of the excess body fat. But there is a way inflammation seems to play a cause-and-effect role in the obesity epidemic: inflammation in our brains. To understand how inflammation in the brain can lead to obesity, we must first understand how our brains regulate our appetites.

Obesity is widely viewed as a neuroendocrine (nerve and hormone) disorder caused by damage to the appetite-regulating circuits in our brains.⁹⁷⁹ Wait— isn't it caused by indulgence in the cheap and easy overabundance of aggressively marketed fatty, sugary, high-calorie foods? Well, if that's all it was, wouldn't even more people be overweight? Maybe 90 percent instead of just 72 percent?⁹⁸⁰ The question that perhaps most intrigues obesity researchers is not *Why are so many people fat?* but rather, given how obesity-inducing our food system is, *Why isn't everyone fat?*⁹⁸¹

I know this is going to sound odd in a book about the obesity epidemic, but our bodies are actually remarkably good at regulating our weight. Think about it. We eat about a million calories a year, yet most of us only fluctuate by a few pounds. Without even thinking about it, our bodies maintain our energy balance with a precision exceeding 99.5 percent.⁹⁸² You couldn't even count calories that effectively. Literally. When put to the test, the calorie labeling on packaged foods was sometimes found to be so inaccurate that one investigation discovered up to a quarter of foods sampled failed to even comply with the 20 percent error allowed by the FDA.⁹⁸³ How do our bodies do better?

The master regulator of metabolism is the hypothalamus,⁹⁸⁴ an almond-sized part of our brains near eye level in the middle of our skulls. Just like your hypothalamus regulates body temperature by causing you to shiver when you get too cold and sweat when you get too hot, it also regulates body fat, causing you to eat more when you get too thin and less when you get too fat. It's our "satiety center," carefully controlling our appetites so we eat just the right amount over time and don't gain or lose too much weight. But how exactly does the hypothalamus know how fat we are?

Our fat cells release a hormone called *leptin*, from the Greek *leptos* for *thin*. The more fat we have on our bodies, the higher the levels of leptin in our blood. The hypothalamus uses leptin levels as our fat thermostat and downregulates our appetites when leptin levels get too high.

"Experimental Obesity in Man," a classic set of prisoner experiments published in the 1970s, showed how difficult it was to perturb this system of appetite regulation when it is working properly. Lean inmates in a Vermont prison were fed up to ten thousand calories a day in closely supervised meals with a goal of increasing their weights by up to 25 percent.⁹⁸⁵ This turned out to be surprisingly difficult. Most started dreading breakfast and sometimes involuntarily threw it up.⁹⁸⁶ Most powered through, though, and achieved the excess weight target. But as soon as they were released from the experiment, they tended to rapidly shed all those extra pounds and get back to around their original weights.⁹⁸⁷

This all makes sense based on what we now know about the leptin-hypothalamus fat thermostat. All that extra body fat led to extra leptin production, and in response, their hypothalami profoundly depressed their appetites until they got back down to baseline. When their fat volumes dropped back to normal, their leptin levels presumably dropped back to normal, too, and so it seems their hypothalami made their normal appetites return. How, then, do people become obese—and what does it have to do with inflammation?

Inflammatory Brain Damage as a Cause of Obesity

People can gain weight—and keep it on—when there is damage to this leptin-hypothalamus circuit. Extreme cases of so-called hypothalamic obesity date back to 1840, when an "uncommonly obese" woman was found on autopsy to have a tumor near her hypothalamus.⁹⁸⁸ Anything that harms the hypothalamus can cause obesity—head trauma, aneurysms, brain surgery.⁹⁸⁹ Once the damage occurs and that feedback loop is broken, the hypothalamus can no longer respond adequately to rising leptin warning signals. As a result, people can develop out-of-control appetites, even to the point of having to be locked up for stealing food.⁹⁹⁰

You can imagine how the same thing could happen if a baby were born with congenital leptin deficiency, a condition in which their fat cells couldn't produce leptin at all. Their hypothalamus would never get the too-much-fat signal to turn down their appetites—and indeed, such children eat constantly, tragically becoming so obese some can hardly walk, sometimes exceeding one hundred pounds by age four.⁹⁹¹

But inject these children with leptin, and the weight comes off. The first child this was tried on was a nine-year-old girl weighing more than two hundred pounds. Within days of the leptin administration, there was a marked change in her eating behavior. For the first time in her life, she felt satiated eating the same quantity of food as her siblings, in effect proving the importance of leptin in appetite regulation.⁹⁹²

Want to guess how eager the drug industry was to start injecting people with leptin as the next new miracle weight-loss cure? But remember: Obese individuals are already awash with excess leptin secreted by all their extra fat. The problem is that the leptin just isn't working.

An analogy can be made with diabetes. In type 1 diabetes, blood sugars get too high because people can't make enough insulin. Inject them with insulin, and their blood sugars come right back down. That's like the kids with the rare leptin birth defect: Their body weights get too high because they can't make enough leptin, but if you inject them with leptin, their body weights come right back down. In contrast, type 2 diabetics *can* make enough insulin, but the target tissues are resistant to the effects of the insulin. There's already enough insulin in the body—in fact, there's often excess insulin, as the pancreas tries to pump out more to overcome the resistance. The body just isn't responding properly.

Similarly, obesity is thought to be caused by leptin resistance. Overweight individuals produce enough leptin—excess leptin, actually—but the target tissue, the hypothalamus, is resistant to its effects. So what can we do about it? Well, what do we do to treat insulin resistance?

Broadly, there are two ways to approach type 2 diabetes: The traditional medical model tries to overwhelm the system by injecting even more insulin, whereas the lifestyle medicine model instead treats the cause, attempting to reverse the insulin resistance itself so the body's own natural feedback loop can start working again. Similarly with obesity, attempts have been made to try to overwhelm the system by injecting even more leptin, but why not instead treat the underlying problem by reversing the leptin resistance?⁹⁹³

Interestingly, insulin resistance and leptin resistance may share a common cause: lipotoxicity, from the Greek *lipos*, meaning *animal fat*. Lipotoxicity is caused by eating a diet high in calories with too much saturated fat and can result in inflammation.⁹⁹⁴

Out of the Frying Pan and Into the Fire

If you feed lab animals saturated fat, the fat crosses the blood-brain barrier and accumulates in the hypothalamus within hours, causing inflammation, leptin resistance, and overeating.⁹⁹⁵ You can re-create this scenario right in a petri dish. If you drip the main saturated fat from the American diet (found mostly in meat and dairy)⁹⁹⁶ onto hypothalamic neurons, inflammation can be turned on like a light switch.⁹⁹⁷ The original animal studies were done with lard-based diets, but butterfat seems to work just as well.⁹⁹⁸ The good news is that when the lab animals were switched back to eating their regular low-fat food, their hypothalamic inflammation disappeared.⁹⁹⁹

So what about in humans? Extrapolating data from lab animals is infamously fraught with difficulty,¹⁰⁰⁰ and obesity research is no exception.¹⁰⁰¹ For one, the diets between lab animals and humans are incomparable. Lard-based, high-fat rodent food may be around 60 percent fat.¹⁰⁰² But bacon is only about 40 percent lard,¹⁰⁰³ so you could eat a 100 percent bacon diet and still not get the kind of fat intake that the rodent was receiving.

Because of the difficulty of extrapolating from animals, we didn't know if the same kind of hypothalamic inflammation occurred in obese humans until researchers were able to use high-resolution MRI brain scans to put it to the test.¹⁰⁰⁴ Subsequent comparisons with brain slices obtained on autopsy confirmed that what researchers were seeing on the MRIs was indeed the same hallmarks of hypothalamic inflammation.¹⁰⁰⁵ The nerves were inflamed, but not destroyed, suggesting the whole process could be reversible. (No improvement in hypothalamic inflammation was seen about ten months after bariatric surgery,¹⁰⁰⁶ but this is perhaps because stomach stapling can force a change in diet quantity but not necessarily diet quality.)

Randomized crossover trials show that by covertly increasing saturated fat intake, you can reversibly induce negative changes in brain function, mood, inflammation, and resting metabolic rate, and even, apparently, undercut motivation to exercise.^{1007,1008} Study subjects become 12-15 percent less physically active on high-saturated fat diets compared to low-saturated fat diets.¹⁰⁰⁹ And note that researchers used a saturated *plant* fat—palm oil—found in some nondairy cheeses, vegan spreads, and other processed junk, so an anti-inflammatory diet is not just a move toward a more plant-based diet in general but specifically one centered around whole, unprocessed plant foods.

If Memory Serves

The hippocampus is the seat of memory in the brain. Structurally, it's composed of two upside-down, seahorse-shaped ridges nestled deep in the temporal lobes. In Alzheimer's, it's one of the first areas to be hit. If saturated fat-induced inflammatory damage to the metabolic center of the brain may be contributing to obesity, what might that same damage be doing to the memory center?

When lab animals are fed saturated fat (lard), neurons in their hippocampi exhibit stress within seventy-two hours.¹⁰¹⁰ Subsequent memory problems and obesity suggest a vicious cycle, where saturated fat harms the hippocampus, causing memory impairments that result in even more lard being eaten—it's as if they had forgotten how much they'd already had—and then goes on to cause more brain damage, cognitive dysfunction, and weight gain.¹⁰¹¹ This finding inspired human investigations. MRI imaging scans taken of people's brains approximately four years apart found that those eating junky, meat-centered diets experience a significant shrinkage of their hippocampi compared to those eating more healthful diets.¹⁰¹² Saturated fat consumption is also associated with accelerated cognitive decline, but you don't know if any of this is cause and effect until you put it to the test.¹⁰¹³

Researchers put people on a high-fat, ketogenic diet and confirmed a blunting of cognition, including impaired reaction times and attention, within seven days.¹⁰¹⁴ Another research team found that a high-fat diet impaired brain function in just five days: "Deficits were found in the speed of retrieval of information from memory, the ability to intensely focus attention, and performance of a complex higher order task involving working memory and attention."¹⁰¹⁵

Even one bad meal a day for four days can impair our brain function. Australian researchers randomized men and women to eat either a breakfast high in saturated fat and added sugars or a healthier breakfast for four consecutive days. That's all it took to cause a significant loss in hippocampus-dependent learning and memory. People were instructed to repeat a list of twelve words over and over, for example, and then try to recall them twenty minutes later. Most were able to remember about 90 percent of them. For those randomized to eat one fatty meal a day for four days, their recall dropped down to around 75 percent. Although the high-fat breakfasts also had added sugar, overall sugar intake didn't change over the four days or differ from the control group, but their intake of saturated fat was double.¹⁰¹⁶

The fatty breakfast group also appeared to suffer a hit to their *interoception*, the ability to perceive internal body states. In other words, they had to eat more food, about seventy calories' worth, to feel the same sensation of satiety and fullness. The impaired hunger sensitivity, combined with the poorer memory retention, would seem to be a setup for weight gain. The hippocampal injury should be reversible, though. The researchers suggest that the recovery period to repair the damage done by those four fatty meals may be as short as four to six weeks.¹⁰¹⁷

Even though overall sugar intake didn't change, the researchers suspect the breakfast "burst" of saturated fat and added sugar was the most plausible cause.¹⁰¹⁸ A single meal high in saturated fat (equivalent to a quarter-pound cheeseburger and large fries) has been shown to increase whole-body insulin resistance by 25 percent.¹⁰¹⁹ That, combined with the added sugars, could spike blood sugars high enough to contribute to the hippocampal dysfunction. As the accompanying medical journal editorial put it, a single load of saturated fat "packs a punch."¹⁰²⁰

By choosing to eat more anti-inflammatory foods and fewer pro-inflammatory foods, we may be able to both prevent and treat the damage to the appetite-regulating apparatus in our brains that can lead to—and sustain—obesity.

In the Dietary Inflammatory Index, the single most anti-inflammatory food is the spice turmeric, followed by ginger and garlic, and the most anti-inflammatory beverage is green or black tea. The two most anti-inflammatory food *components* are fiber and flavones.¹⁰²¹ Dietary fiber is found in all whole plant foods, but it is most concentrated in legumes, such as beans, split peas, chickpeas, and lentils.¹⁰²² Flavones are plant compounds concentrated in herbs, vegetables, and fruits,¹⁰²³ and the leading sources in the U.S. diet are parsley, bell peppers, celery, apples, and oranges.¹⁰²⁴ The most flavone-filled beverage is chamomile tea.¹⁰²⁵

The most pro-inflammatory food components are saturated fat and trans fat. Essentially, the top five sources of saturated fat in the United States are cheese, desserts like cake and ice cream, chicken, pork, and then burgers.¹⁰²⁶ Thankfully, with the ban on added trans fat, the only remaining sources in the food supply will be the small amounts found naturally in meat and dairy and created in the refining of vegetable oils.¹⁰²⁷

Ultimately, an anti-inflammatory diet in clinical practice first and foremost “focuses on eating whole, plant-based foods.”¹⁰²⁸ As I mentioned, not all plant-derived foods are anti-inflammatory (like the tropical oils), just as not all animal foods are pro-inflammatory. Omega-3 fatty acids found in fish, for example, score as an anti-inflammatory component in the Dietary Inflammatory Index.¹⁰²⁹ Though fish oil may not affect systemic inflammation in healthy individuals,¹⁰³⁰ it can reduce inflammatory markers in those with chronic disease.¹⁰³¹ Curiously, unlike plant-based omega-3 sources like nuts, fish consumption is not associated with lower inflammatory disease mortality.¹⁰³² Perhaps the benefits of the omega-3s are offset by the industrial toxins that now contaminate much of the aquatic food chain.¹⁰³³

CLEAN

Obesogenic Pollutants

The notion that we are being exposed to obesogenic pollutants—that is, obesity-generating chemicals—went from mere speculation in an alternative medicine journal in 2002¹⁰³⁴ to strong scientific plausibility within a decade.¹⁰³⁵ The supposition started out on pretty shaky ground, pointing out, for instance, that recent national surveys appear to show our weight exceeds what we report eating.¹⁰³⁶ Therefore, the argument went, something else must be going on beyond just calories in and calories out. But it is notoriously difficult to get an accurate calorie count from dietary recall surveys, especially from overweight individuals, who tend to underreport their intakes.¹⁰³⁷

Theoretically, though, the obesogen concept was not that much of a stretch. All sorts of synthetic chemicals cause obesity in humans: They’re called *medications*. Multiple classes of drugs are infamous for contributing to weight gain, such as certain types of antidepressants, antipsychotics, and diabetes medications.¹⁰³⁸ The animal agriculture industry has made fattening into a science, utilizing a whole array of chemicals, hormones, and pharmaceuticals to pack on the pounds.¹⁰³⁹ An analysis of chicken feathers found that the poultry industry appears to feed the birds everything from arsenic¹⁰⁴⁰ to Prozac.¹⁰⁴¹ (Poultry producers say feeding caffeine “keeps the chickens awake so that they eat more and grow faster.”¹⁰⁴²)

So what evidence do we have that chemicals are making *us* grow fatter too?

Early on, the purported link between chemical pollutants and obesity was based in part on the observation that the rise in chemical production seemed to coincide with the rise of the obesity epidemic.¹⁰⁴³ Yes, but how many other millions of changes have there been over the last half century? Why jump to pollution when there are so many other easier explanations, everything from couch potatoes to fried potatoes?

One clue that pollutants may be playing some role is that our pets are also getting fatter.¹⁰⁴⁴

Fido isn’t drinking more soda. Of course, the more *Seinfeld* reruns we watch, the less we may walk the dog, but what about our cats? Are we just giving them—and our kids—a few too many treats? That would seem a simpler explanation than imagining pervasive, obesity-causing chemicals building up in the pet and person food chains. It’s not just our kitties and kiddies, though. A remarkable paper was published in 2011 entitled “Canaries in

the Coal Mine: A Cross-Species Analysis of the Plurality of Obesity Epidemics.”¹⁰⁴⁵ It was a study of more than twenty thousand animals from twenty-four distinct populations, including feral animals, lab animals, and even urban and rural rats. The researchers found “large and sustained” increases in body weight nearly across the board, not just among pampered pets.

We’re all getting fatter. The odds that every single population studied would be getting heavier just by chance are around eight million to one. Given that evidence, it’s hard to blame our collective weight problem just on things like dwindling physical classes, the advent of video games, or junkier food. And our infants are heavier too. There’s been an alarming rise in obesity rates among young children under two years of age.¹⁰⁴⁶ It’s hard to argue that today’s six-month-olds are eating more or exercising less than they were in previous generations.

These are the kinds of data that piqued serious interest into the search for obesogenic chemicals, and to date, about twenty different purported obesogens have been found.¹⁰⁴⁷ The most well-studied thus far is a group of tin-based biocides known as *organotins*.¹⁰⁴⁸

The Case of the Sex-Change Paint

Organotins were used in “antifouling” paint applied to the outer hulls of ships and other submerged structures like fish farm cages and oil rigs to prevent barnacles from attaching. But once this chemical was being used widely, scientists began to notice that female sea snails started to grow penises.¹⁰⁴⁹ As a result of a variety of hormone-disrupting effects, organotins were banned from the maritime industry in 2008.¹⁰⁵⁰ Disrupting hormones isn’t the only thing these compounds do, though. Organotins also activate peroxisome proliferator-activated receptor gamma, or PPAR- γ , which is the master regulator of adipogenesis, the process of creating new fat cells (known as *adipocytes*).¹⁰⁵¹

Once activated, PPAR- γ recruits connective tissue stem cells to turn into new fat cells. PPAR- γ stimulation can also cause fat cells to swell up even larger with fat. In other words, contact with this chemical leads to more, and bigger, fat cells,¹⁰⁵² and exposure in the womb to organotins may permanently establish an elevated fat cell count throughout our lives.¹⁰⁵³

By the time we hit early adulthood, the total number of fat cells in our bodies remains fairly stable.¹⁰⁵⁴ When we gain or lose weight, we are pretty much just enlarging or shrinking our existing fat cells. Starting out with a higher number of fat cells or gaining more later in life may make it easier to put on pounds, harder to lose them, and more difficult to maintain weight loss.¹⁰⁵⁵

What’s more, each fat cell we make may be at the expense of one fewer bone, cartilage, or muscle cell.¹⁰⁵⁶ The connective tissue stem cells recruited by PPAR- γ to become fat cells could have otherwise become any of those other types of cells, so excess PPAR- γ activation could potentially set us up not only for obesity but also osteoporosis.¹⁰⁵⁷ The Swiss cheese-like holes in osteoporotic bone are often filled with fat.¹⁰⁵⁸ Perhaps this is why the PPAR- γ -activating diabetes drug rosiglitazone (sold as Avandia) not only causes weight gain as a side effect but appears to increase the risk of bone fractures as well.¹⁰⁵⁹

How are we exposed to PPAR- γ -activating organotin compounds? Mainly through food, especially from fish and other seafood.¹⁰⁶⁰ Even though organotins were banned on boats and other marine vessels years ago, they persist in our waterways, and contamination levels in fish fillets remain comparable to those obtained worldwide before the ban.¹⁰⁶¹ Some fish are worse than others. Halibut, swordfish, and canned tuna have been recorded as having the highest levels,¹⁰⁶² and a sampling of U.S. market-bought seafood found that farm-raised fish was generally worse than wild-caught.¹⁰⁶³

Are the contamination levels high enough to be of concern? Researchers calculated the “tolerable average residue levels” for tributyltin, a common organotin, in seafood products

around the world, defined as the levels in seafood tolerable for the average adult consumption pattern. Of the eighty-four U.S. seafood samples examined, seven products exceeded this level, or about 8 percent.¹⁰⁶⁴ Note this is for the average adult consumer, so the percentage would be higher in children or those who ate more seafood than average. The percentage violating the tolerable average dose exceeds 30 percent in Japan, for example, but that is because the Japanese tend to eat more seafood, not because their fish is any more contaminated.

Everybody's Plastic

Persistent pollutants have blanketed the world and now are found even in the Arctic, thousands of miles from known sources. Fortunately, many have been regulated strictly since the Stockholm Convention in 2004,¹⁰⁶⁵ but unfortunately, there continue to be hormone-disrupting chemicals that are underregulated or not regulated at all. DDT, the banned pesticide now found mostly in meat, particularly fish,¹⁰⁶⁶ is a “presumed” human obesogen¹⁰⁶⁷ responsible for perhaps thousands of annual childhood obesity cases.^{1068,1069,1070} Meanwhile, the number attributable to the plastics chemical bisphenol A (BPA) may be in the *tens* of thousands.¹⁰⁷¹

BPA was first developed more than a century ago as a synthetic estrogen.¹⁰⁷² It wasn't until the 1950s, however, that the manufacturing industry realized BPA could also be used to make polycarbonate plastic. Despite having long been recognized as having hormonal effects,¹⁰⁷³ BPA rapidly became one of the most widely used chemicals worldwide.¹⁰⁷⁴ It's currently one of the highest-volume chemicals produced globally, with more than six billion pounds made each year.¹⁰⁷⁵

In a petri dish, BPA was shown to accelerate the formation of new fat cells¹⁰⁷⁶ and increase fat accumulation within fat cells, but that was at doses many thousands of times the concentration found in most people's bloodstreams.¹⁰⁷⁷ Though more than 90 percent of Americans tested in a national survey had BPA circulating in their bodies,¹⁰⁷⁸ it was at concentrations down around 10 nM.¹⁰⁷⁹ In contrast, those early studies were using 25,000–80,000 nM. We knew there were estrogenic effects even at those low, real-world doses,¹⁰⁸⁰ but it wasn't discovered until recently—in part using fat samples taken from children¹⁰⁸¹ and adults¹⁰⁸² undergoing abdominal surgery—that fat cell formation could also be affected by BPA at as little as 1 nM.¹⁰⁸³ Even once metabolized by the liver, which destroys the estrogenic effects, BPA retains the ability to promote adipogenesis, the process of creating fat cells.^{1084,1085}

BPA exposure at all life stages tends to correlate with increased weight,¹⁰⁸⁶ and population studies in the United States, Canada, China, and South Korea have found it to be associated with various body fat measures.¹⁰⁸⁷ Six out of seven BPA studies on general obesity and five out of five studies on abdominal obesity have found a link. Putting together all the studies, those with the highest BPA levels had 67 percent greater odds of obesity compared to those with the lowest.¹⁰⁸⁸ In men, BPA may also be associated with lower lean body mass.¹⁰⁸⁹ Those in the highest quarter of BPA urine levels averaged about three pounds less lean mass than those in the lowest quarter, suggesting BPA may have negative effects on muscle as well. (BPA exposure is also associated with declining male sexual function, but that's a whole other book.¹⁰⁹⁰)

How can we stay away from BPA? A small amount of exposure comes from handling thermal paper, such as cash register receipts and printed tickets,¹⁰⁹¹ especially if our hands are greasy or wet after the application of lotion or sanitizer.¹⁰⁹² Ninety percent of exposure, however, appears to be from our diets.¹⁰⁹³ How can you tell? When people fast for a couple of days, their BPA levels drop as much as tenfold.¹⁰⁹⁴

Fasting isn't very sustainable, though. Researchers had families try a “fresh foods intervention,” where the families switched away from canned and processed foods. (Why

canned? BPA is used in the epoxy that lines most canned goods, since it costs companies about 2 cents more per can to use non-BPA material instead.¹⁰⁹⁵) Simply by avoiding canned and processed foods, the highest BPA levels dropped 76 percent within three days.¹⁰⁹⁶

Alternately, you can conduct the experiment by adding a serving of canned soup to people's daily diets. Compared to serving soup prepared with fresh ingredients, five days of a daily serving of canned soup led to a 1,000 percent rise in BPA levels in the urine.¹⁰⁹⁷ It could have been even worse had they used cans of condensed soup, which may have about 85 percent more BPA than cans of ready-to-serve soup. Otherwise, the highest BPA levels have been found in canned green beans and canned tuna.¹⁰⁹⁸ The only fresh food found contaminated with BPA in the United States was sliced turkey.¹⁰⁹⁹

Take-Home Tip: BPA is why I specify in *The How Not to Die Cookbook* to choose beans and tomato products in jars, aseptic packaging (Tetra Paks), or BPA-free cans. Eden Foods, for example, has a line of BPA-free canned beans. You can also BYOB: Boil Your Own Beans. It's cheaper, and they end up with a better texture. My favorite way is to use an electric pressure cooker (like an Instant Pot).

Phthalates are another class of plastics compounds associated with weight gain.¹¹⁰⁰ A European consensus panel of obesogen experts gave a 40–69 percent probability of phthalate exposure causing more than fifty thousand cases of obesity annually in older women.¹¹⁰¹ Rapid plunges in phthalate levels upon fasting implicated dietary sources,¹¹⁰² and significant drops within days of having people eat a vegetarian diet gave researchers a clue as to where to look.¹¹⁰³

Indeed, high concentrations of phthalates have been found consistently in some meats (particularly poultry), fats, and some dairy products.¹¹⁰⁴ The fact that egg consumption is also associated with elevated phthalate levels suggests that the chickens themselves are contaminated even before they're wrapped in plastic for sale.¹¹⁰⁵ The phthalates in dairy, though, appear to be from the plastic tubing in milking machines, as dairy from hand-milked cows can have ten times less.¹¹⁰⁶ Diets high in meat and dairy can sometimes contain up to four times the Environmental Protection Agency's recommended daily phthalate safety limit.¹¹⁰⁷

This is what makes population studies linking pollutants and obesity so difficult.¹¹⁰⁸ Phthalate levels just may be an indicator of fried chicken intake, and BPA levels a sign of SPAM consumption. Similarly, just as exposure to plastics chemicals may be an indicator of a diet bereft of fresh foods, DDT exposure may be a marker for the foods that frequently contain the highest levels of DDTs identified by the Endocrine Society: "meat, fish, poultry, eggs, cheese, butter and milk."¹¹⁰⁹ Pollutants like DDT are just one of many reasons why diets rich in those foods might be associated with obesity risk.

Take-Home Tip: BPA and phthalate metabolites are detectable in 95 percent of the U.S. adult population.¹¹¹⁰ BPA is already banned from baby bottles and sippy cups in the United States,¹¹¹¹ but for other plastic containers, keep an eye out for recycle codes 3 and 7, as those indicate items that are more likely to contain high levels of BPA.¹¹¹² Certain phthalate levels are now banned from toys for children,¹¹¹³ but not from "toys" for adults. Jelly-based sex toys are often made from a plasticized vinyl material packed with phthalates. Sticking to water-based lubricants may reduce phthalate transfer a hundredfold, but such adult toys may still have opposite the intended effect.¹¹¹⁴ Women with the highest levels of phthalates flowing through their bodies report more than twice the odds of lack of interest in sexual activity.¹¹¹⁵

Up in Smoke

In 2015, when meat was officially classified as a “known carcinogen” or a “probable carcinogen” depending on whether or not it was processed, the focus was on substances generated during cooking, curing, or smoking, rather than on pollutant contamination.¹¹¹⁶ Given this, we could just follow recommendations to keep cooking temperatures under 260°F, thereby avoiding broiling, roasting, pan-frying, or any other cooking method that causes a crust to form, and instead stick to boiling or microwaving to keep the outside “pale and soft.”¹¹¹⁷ But even just being around a barbecue may be hazardous, based on the recognition that light clothing probably provides little protection from gaseous carcinogens.¹¹¹⁸

Polycyclic aromatic hydrocarbons (PAHs), a class of combustion by-products found in cigarettes, car exhaust, and grilled meat,¹¹¹⁹ may explain why the Long Island Breast Cancer Study Project found a 47 percent increase in breast cancer risk among postmenopausal women with a high lifetime intake of grilled, barbecued, or smoked meats.¹¹²⁰ These contaminants may be more than just carcinogenic—they may be obesogenic as well. A nationwide study of thousands of young people found that the more children are exposed to PAHs, the fatter they tend to be. And prenatal exposure to these chemicals may cause a higher subsequent risk of childhood obesity.¹¹²¹

If you look at one of the most common of these toxins, smokers get about half their exposure from food and half from cigarettes. For nonsmokers, however, 99 percent may come from diet. The highest levels are found in meat, with pork apparently worse than beef.¹¹²² Even dark green leafy vegetables like kale can get contaminated by pollutants in the air, so don’t forage your dandelion greens next to the highway, and make sure to rinse your broad-leafed greens well under running water.¹¹²³

PAHs are fat-soluble, so absorption may be diminished with eating lower-fat foods,¹¹²⁴ but importantly, they don’t appear to build up in your body. Unlike persistent pollutants like PCBs, a particularly toxic class of man-made chemicals that may take fifty to seventy-five years to clear from the body after regular (even monthly) meals of farmed Atlantic salmon,¹¹²⁵ PAHs can pass in and out of you in a day. If you have people eat a meal of barbecued chicken, you can see a big spike in these chemicals in their systems—up to a hundredfold increase—but the body can detoxify most of them away within about twenty hours.¹¹²⁶ Rather than detoxing, though, perhaps it would be better not to “tox” in the first place—at least not on a daily basis.

Prepackaged Pollutants

Industrial chemical contaminants come prepackaged regardless of cooking method in “diary [*sic*] products, meat and fish.”¹¹²⁷ (Although dioxins are created when paper pulp is bleached, I have a feeling “diary” was an autocorrect error.) The Food and Drug Administration has regulations about toxic chemicals in the food supply, determining the “action levels” of contaminants above which foods must be removed from the market, but those levels tend to be far higher than the levels based on health standards set by the Centers for Disease Control and Prevention (CDC). For example, a glass of milk tainted with the amount of DDT permitted by FDA’s action level would expose a consumer to nearly ten times the daily exposure considered “safe” by the CDC, and a single serving of fish could be sold with fifty times the daily limit.¹¹²⁸ Presumably, the reason the commercial standards are so lax is because too much food would have to be pulled from the shelves.

The USDA determined that, based solely on dioxin levels, American children consuming average servings of meat, including poultry (which regularly contained the highest levels they found), could be ingesting in excess of the daily safety limit.¹¹²⁹ Taking all thirty-three chemical pollutants in meat shown to be potentially carcinogenic into account, some European toxicologists suggest limiting children’s consumption of beef, pork, and chicken to no more than five servings a *month*, an average of no more than one serving every six

days or so.¹¹³⁰ In Europe, lamb is the most contaminated and the recommendation calls for adults to eat no more than a single serving every four or five months.¹¹³¹

In the United States, if there was any standout, it would be chicken and PBDE flame-retardant chemicals—not only compared to other meats but also to other countries. U.S. chickens are about ten to twenty times more contaminated than chickens tested from other countries.¹¹³² Sadly, the newer flame-retardant chemicals introduced to replace the original PBDEs also¹¹³³ activate adipogenesis, diverting stem cell development away from bone building and toward the formation of fat.¹¹³⁴

Meat is certainly not the only source of flame-retardant exposure, though, as those eating vegetarian diets only have about 25 percent lower levels in their bloodstreams.¹¹³⁵ For other chemicals, meat may play a larger role. Studies dating back over thirty years looking at the pollutants in the breast milk of vegetarians have found the average vegetarian levels of some pollutants were only 1–2 percent as high as the national average.¹¹³⁶ For six out of seven pollutants reviewed, there wasn't even an overlap in the range of scores; the highest vegetarian value was lower than the lowest value obtained in the general population. This is presumed to be because these pollutants concentrate *up* the food chain, so by eating more from all the way *down* the food chain, those eating more plant foods may have an edge.¹¹³⁷

The problem with studies just comparing populations is that you can't single out the diet. Maybe vegetarians have other lifestyle behaviors that protect them. You don't know until you put it to the test by changing people's diets and seeing what happens. That's hard to do with persistent pollutants like PCBs, which may take literally decades to detoxify from the body, but we can get rid of heavy metals like mercury in a matter of months. And, indeed, within three months of the exclusion of eggs and meat, including poultry and fish, from people's diets, there was a significant drop in their levels of mercury, cadmium, and lead. Within just a few months of changing their diets, the levels of toxic heavy metals in their bodies dropped by up to about 30 percent.¹¹³⁸

What About Organic Meat?

What if we just stick to organic meat? Certified organic meat comes from livestock fed organically produced feed free of pesticides and animal by-products. Therefore, you would assume there would be less chemical residue accumulation, but there hadn't been any studies measuring the chemical contamination in organic meat until recently. Researchers acquired seventy-six samples of different kinds of meat, both organic and conventional, and quantified their levels of contamination with thirty-three different persistent toxic pollutants. No sample was completely free of industrial toxins, which is to be expected given how polluted our world has become. What was surprising, though, was how minimal the differences were between organically and conventionally produced meats. In some cases, organic was inexplicably worse. Whether choosing conventional or organic meat, the researchers concluded that the current pattern of meat consumption exceeded the maximum tolerable safety limits either way.¹¹³⁹

Given that 90 percent of persistent pollutant exposure comes from animal-derived foods,¹¹⁴⁰ it's no surprise that those eating more low-carbohydrate, high-protein-type diets have higher levels of pollutants circulating in their systems. This included PCBs 118 and 153, trans-nonachlor (a component of the banned pesticide chlordane), hexachlorobenzene (a banned fungicide), DDE (from DDT), mercury, and lead.¹¹⁴¹ Mediterranean diet scores were correlated with elevated levels of PCBs (118, 126, 153, and 209), trans-nonachlor, and mercury, presumably because of the focus on fish consumption.¹¹⁴²

Any increase in body fat caused by obesogenic chemicals could potentially serve as a reservoir for further chemical accumulation, possibly setting up a vicious cycle.¹¹⁴³ Our fat stores—like those of farm animals—harbor toxic pollutants. How do we know this? Because

we see a surge in these chemicals in people's bloodstreams as they lose weight.¹¹⁴⁴ After bariatric surgery, for example, certain pollutant levels can rise more than 300 percent.¹¹⁴⁵

The release of these compounds trapped in our body fat may then affect our metabolisms, slowing down the rate at which we burn calories during sleep, which could frustrate additional weight loss.¹¹⁴⁶ To help break this cycle, a reduction in animal fat is suggested to reduce further accumulation of pollutants, along with an increase in whole grains, as the fiber may help draw toxins out of the body.¹¹⁴⁷

What About Organic Produce?

A recent expert review on obesogens suggests that doctors can help patients reduce their exposure by advising them to choose organic fruits and vegetables “insofar as possible.”¹¹⁴⁸ What evidence is there that the pesticides used on produce may play a role in the obesity epidemic? Just as the link between asbestos and disease first became apparent when studying those with the greatest exposure—miners and shipbuilders—public health researchers set out to study more than eight thousand licensed pesticide applicators to see if there was any connection between crop pesticides and weight gain.¹¹⁴⁹ One pesticide stood out, atrazine, the weed killer commonly used in corn production that was found to induce complete feminization of frogs—as in total sex reversal, with male frogs ending up laying eggs.¹¹⁵⁰ Agricultural workers spraying lots of atrazine had about 50 percent greater odds of being overweight and obese.¹¹⁵¹

Just because levels in the field may predispose people to obesity doesn't mean levels in the grocery store are high enough to have any effect, though. To see if buying organic makes a difference, can't we just compare the body weights of those who choose organic to those who don't? A study of more than fifty thousand consumers did exactly that, and those who chose organic “most of the time” only had about half the obesity rates of those who “never” chose organic.¹¹⁵² Your critical thinking alarm bells should have started ringing instantly. Think of all the other attributes of organic shoppers. Indeed, those choosing organic were better educated and better off financially, both of which in and of themselves have been associated with lower obesity risk,^{1153,1154} and, more to the point, exercised more and had better diets. Those who chose organic ate more whole plant foods and less meat, dairy, and junk. No surprise they had a healthier weight.

The researchers controlled for each of these other factors, however, and still found dramatically lower obesity rates in “most of the time” organic consumers, though not necessarily in those who just chose organic “occasionally.”¹¹⁵⁵ Still, this was just a cross-sectional study, meaning a snapshot in time. Rather than conventional foods contributing to weight gain, maybe weight gain led people to throw up their hands and care less about how their food was grown or produced.

In 2017, we got a prospective study where people were followed over time. Sixty thousand French consumers were followed for about three years to see if those choosing organic gained less weight. After controlling for such factors as education, income, physical activity, and overall dietary quality, those who reportedly ate more organic foods were significantly less likely to become overweight or obese.¹¹⁵⁶ Note, though, that this was only for those choosing healthier diets in general. Eating organic Oreos and Pop-Tarts doesn't do your body any favors.

Take-Home Tip: Personally, I try to choose organic whenever I have the option, but I never let pesticide concerns prevent me or my family from indulging in as many fruits and vegetables as possible regardless of how they were grown.

Microplastics in Seafood

In 1869, a patent was taken out on a new substance to replace elephant ivory in the production of billiard balls, and the plastics industry was born.¹¹⁵⁷ What started as a conservation-minded measure has turned into an environmental calamity.¹¹⁵⁸ Trillions of little plastic particles now float on the surface of the sea.¹¹⁵⁹ Plastic objects like water bottles get worn down into tinier and tinier pieces, and plastic microbeads in personal care products like facial cleansers flow from our sinks down into the waterways. Up to ninety-four thousand microbeads are flushed down the drain in a single rinse.¹¹⁶⁰

The plastic then accumulates toxic compounds from the water and shuttles them, along with any chemicals originally in the plastic, into marine life, concentrating up the food chain and eventually ending up on our plates.¹¹⁶¹ This may explain how fresh cod can sometimes end up with higher BPA levels than canned tuna.¹¹⁶²

It is inevitable that we'll ingest at least some microplastics when we eat seafood, particularly when the entire animal is consumed, such as with sardines.¹¹⁶³ Researchers sampled twenty brands of canned sardines and sprats from thirteen countries over four continents and found plastic particles in about one in five.¹¹⁶⁴ They suggested the disparities may have been due to improper gutting in the contaminated samples, but in mammals, at least, ingested microplastics can get through the gut wall, circulate throughout the body, and even cross the placental barrier.¹¹⁶⁵

When researchers compared the level of microplastics in eviscerated flesh versus the guts of fish, the meat sometimes actually contained higher microplastics loads than the excised organs.¹¹⁶⁶ Some studies have detected microplastics in all fish muscle samples tested.¹¹⁶⁷ The average intake of microplastics from eating fish like flathead, grouper, shrimp scad, or barracuda may be in the hundreds per serving or in the dozens of plastic particles in a two-ounce, child-sized serving.¹¹⁶⁸ As the particles travel through our bodies, they may then release any absorbed pollutants or plastics additives—some of which may play a role in the obesity epidemic.¹¹⁶⁹ Because of this, some have suggested weekly servings of these kinds of fish may threaten the health of consumers, especially vulnerable groups, such as children and women who are pregnant or breastfeeding.¹¹⁷⁰

FOOD FOR THOUGHT

The obesogen field is still in its infancy but continues to gain scientific support.¹¹⁷¹ The American Medical Association, American Public Health Association, and the Endocrine Society, the oldest and largest association of hormone specialists, have all called for improved regulatory oversight of hormone-disrupting chemicals.¹¹⁷² We don't have to wait to make simple diet and lifestyle changes to reduce our exposure, though. We can make a difference now by prioritizing plant foods, opting for fresh or frozen vegetables over canned, and, if eating or drinking out of polycarbonate and PVC plastics, choosing not to microwave them, put them in the dishwasher, leave them in the sun or in a hot car, or use them once they're scratched,¹¹⁷³ as that can increase the release of the chemicals.

HIGH IN FIBER-RICH FOODS

Feeding Our Forgotten Organ

We used to think of food simply as a source of nutrients and energy, but we now know there are components in what we eat that can act as signaling molecules that bind to specific receptors within the body and trigger drug-like effects to regulate our metabolisms, among other things. Ironically, one of the food components that produces the most dramatic effects is something that initially appeared to be the most inert of dietary constituents: fiber.¹¹⁷⁴ In fact, telling people to increase their intakes of fiber-rich foods may actually be one of the single most effective pieces of advice for weight loss.

Fiber seems so, well, boring. By definition, fiber is indigestible. Since it can't be absorbed into the body, it just stays in our gut to bulk up our stool. This is not to belittle the importance of bowel regularity. If just half the adult population ate three additional grams of fiber a day—only a quarter cup of beans or a bowl of oatmeal—we could relieve enough constipation to save billions in medical costs a year.¹¹⁷⁵ But it's not as if we thought fiber really *did* anything beyond helping to keep us regular.

While it's true we can't technically digest fiber, that's only applicable to the part of us that's actually human. But most of the cells in our bodies are bacteria.¹¹⁷⁶ Our gut flora, which weigh more than one of our kidneys and are more metabolically active than our

livers,¹¹⁷⁷ have been called our “forgotten organ.”¹¹⁷⁸ And our good gut bacteria don’t just digest fiber—they thrive on it. Fiber is like comfort food for your colon. So we *can* digest fiber, just not without a little help from our little friends.

What do the bacteria do with the fiber? They make short-chain fatty acids (SCFAs) with the fiber that can then be absorbed from the colon into our bloodstreams, circulate throughout our bodies, and even end up in our brains.¹¹⁷⁹ In this way, these fiber-sourced SCFAs can potentially have wide-ranging effects on everything from immune function and inflammation¹¹⁸⁰ to mental health¹¹⁸¹—and, as you’ll see, may play a key role in regulating our appetites, metabolisms, and body fat.¹¹⁸²

Crowding Out Calories

The first major review, “Dietary Fiber and Weight Regulation,” included a dozen interventional studies in which people were randomized into higher-or lower-fiber diets. The additional consumption of fourteen grams of fiber a day led to an average weight loss of 1.9 kilograms over 3.8 months.¹¹⁸³ That’s only about a pound a month, but the weight loss was greater among those who needed it; overweight and obese study subjects lost triple the weight compared to lean individuals. How much is fourteen grams of fiber? Not much. Fourteen grams would barely bring the average American’s diet up to the recommended *minimum* average adequate daily fiber intake.¹¹⁸⁴

The increased fiber intake appeared to lead to about a 10 percent drop in daily caloric intake.¹¹⁸⁵ Why would more fiber mean fewer calories? Well, conventionally, fiber is considered to have zero calories, so it adds bulk to food without adding extra calories. To illustrate, let’s compare a food to its fiber-depleted equivalent. Consider a bottle of cold-pressed apple juice, which is basically an apple with its fiber removed. You could chug a regular 15.2-ounce bottle of juice in a matter of seconds, but to get the same number of calories, you would have to eat nearly five cups of apple slices.^{1186,1187} Which do you think would fill you up more? Obviously, the apple slices. But why?

First, you’d need to chew every apple slice. Fiber-rich foods require more chewing, slowing down eating rate, which itself can improve satiety.¹¹⁸⁸ This also allows for more secretion of saliva and stomach juices. In one study, researchers spread a barium paste onto slices of different kinds of bread and found that, upon x-ray, the stomach shadow was larger after eating whole-wheat compared to white bread, showing how much fuller you physically get.¹¹⁸⁹ So, in our cold-pressed apple juice versus apple slices scenario, we have the extra fluid secretion on top of the five cups of slices pushing on the walls of the stomach, which has nerves with stretch receptors that can send fullness signals directly to the brain.¹¹⁹⁰

One type of fiber in apples is pectin, the gelling agent used to make jams and jellies. Imagine how eating all those apples would not only add a lot of extra bulky volume but could start to form a gel to further slow the rate at which those five cups of slices left your stomach. This would keep you feeling fuller for longer compared to consuming the same number of apple calories in fiber-depleted juice form, which would pass right through you much more rapidly. Other gummy fibers like those found in oats can have the same gelling effect. Five grams of a highly gelling fiber can hold approximately one quart of water as it passes through the stomach and small intestine, so that’s like having an extra two pounds of zero-calorie food mass filling you up.¹¹⁹¹

Obviously, juice is going to drain out of your stomach faster than apples, but even the same volume of fiber-depleted solid food exits more quickly. In a study entitled “Gastric Emptying of a Solid Meal Is Accelerated by the Removal of Dietary Fibre Naturally Present in Food,” researchers compared how long it took for a meal that included higher-fiber foods—whole-wheat pasta with puréed fruits and vegetables—to leave the stomach compared to a meal with the same volume and same calories, but made from white pasta and fruit and

vegetable juices. The fiber-depleted meal was out of the stomach forty-five minutes earlier than the meal with the fiber intact.¹¹⁹²

It's Not the Calories You Eat but the Calories You Absorb

Now imagine what happens next: The apple juice would get rapidly absorbed as soon as it spilled out from the stomach into the small intestine and spike our blood sugars, whereas sugar trapped in the mass of apple slices would be absorbed more slowly along the length of the intestine. Our bodies can only absorb nutrients when they come in physical contact with our intestinal walls, so fiber, which never gets absorbed, can act as a carrier to dilute and even eliminate calories out the other end. Fiber doesn't just trap sugars; it can act as a fat¹¹⁹³ and starch-blocker¹¹⁹⁴ too. There are drugs on the market that can do this, but eating fiber-rich foods can do it more safely—and naturally.

What if you dipped those apple slices in peanut butter? Everything would get mixed together, and some of the peanut oil calories would make it all the way through the intestines, trapped in the middle of a gelled mass of apple fiber. In contrast, if you ate a spoonful of peanut butter and then washed it down with apple juice, the juice would get absorbed right off the bat, leaving the peanut butter to coat the walls of the intestine and all the calories to get absorbed. This has been demonstrated in experiments measuring fecal fat excretion dating back nearly a half century.

What happens if you feed people white bread with butter versus whole-wheat bread with butter, along with lots of fruits and vegetables, and measure how much butter comes out the other end? The higher-fiber whole-wheat group poops out more than twice as much fat as the white-bread group,¹¹⁹⁵ since some of the butter calories get trapped in all that fiber. Even if you just drink a third of a cup of oil on a high-fiber diet, you'd excrete twice as much fat as you would on a low-fiber diet.¹¹⁹⁶ The same goes for the calories of starch. Eat whole-grain bread as opposed to white bread, and stool analyses will find that you flush out nearly ten times as many carb calories.¹¹⁹⁷

It's not what you eat but what you absorb, so you can lose more weight on a high-fiber diet eating the exact same number of calories simply because some of those calories get trapped and never make it into your system. Those on a Standard American Diet lose about 5 percent of the calories they eat in their waste,¹¹⁹⁸ but a higher-fiber diet can double that.¹¹⁹⁹ It's not simply that the calories in high-fiber foods are less available. High-fiber foods trap calories across the board. So eat a Twinkie on a high-fiber diet and absorb fewer Twinkie calories! It's like every calorie label you read instantly gets discounted on a high-fiber diet.

We learn in school that a gram of protein has four calories, a gram of fat has nine calories, and a gram of carbs has four calories—but that's only on a typical, low-fiber diet. On a higher-fiber diet, up around the average of those eating completely plant-based diets,¹²⁰⁰ the effective calorie counts drop from 4-9-4 to around 3.5-8.7-3.8.¹²⁰¹ That may not seem like a lot, but if Americans just reached the minimum recommended fiber intake, that might decrease calorie absorption by more than one hundred calories a day,¹²⁰² which may be enough to prevent that average, gradual, annual weight gain most experience through middle age.¹²⁰³ Even a small, consistent change in daily calorie absorption could potentially have long-term significance for weight management.¹²⁰⁴

Putting On the Brakes

A review entitled "Food Fibre as an Obstacle to Energy Intake" summarized what I call the Four Ds by which dietary fiber results in reduced caloric intake:¹²⁰⁵ *dilution* of calories by expanding the volume of food, *distention* of the stomach through fluid absorption, *delay* in stomach emptying of the gelled mass, and *dumping* of calories by blocking the absorption

of other macronutrients, such as carbs and fat. That fourth *D* triggers a fifth phenomenon known as the *ileal brake*.

The ileum is the last part of the small intestine before it empties into the colon. When undigested calories are detected that far down our intestines, our bodies put the brakes on eating more by curbing our appetites. This can be shown experimentally. If you insert a nine-foot tube down people's throats and drip in protein, fat, or sugar, you can activate the ileal brake. Then, if you sit them down to an all-you-can-eat meal, they will eat at least one hundred fewer calories than those in the placebo group who had only gotten a squirt of water through the tube.¹²⁰⁶ Activating the ileal brake can make people feel full up to nearly two hundred calories earlier.

Ever since its discovery, the ileal brake has been considered a medical target for appetite control. So did doctors simply advise patients to eat lots of whole, unprocessed plant foods so that the fiber would drag calories down to activate the brake? Not quite. Instead, they developed the first major bariatric surgery, the jejunoileal bypass.

Fiber-depleted foods get absorbed quickly and never make it all the way down to the ileum, but instead of having people eat foods in their natural form, some doctors decided just to cut out the intervening twenty or so feet of intestine. By attaching the end of the ileum right up to within about eighteen inches of the stomach, the ileal brake is activated no matter what you eat. It's like your emergency brake is always on. You can still drive, but not as fast. So, with the jejunoileal bypass, you can still eat, but not as much because you're already feeling full.

More than twenty-five thousand patients underwent the procedure in the United States before it was realized that cutting out 90 percent of the intestines wasn't such a good idea. The jejunoileal bypass resulted in long-term progressive liver scarring in 38 percent of patients.¹²⁰⁷ That's nearly two out of every five patients. Though the surgical approach failed, the medical mind-set still prevails, with researchers teaming up with drug companies and the food industry to exploit the ileal brake for weight loss with "dietary encapsulation or slow release strategies,"¹²⁰⁸ failing to recognize that Mother Nature already designed a natural strategy in the form of fiber-rich food.

Intestinal Workout

There are many ways eating more fiber means eating fewer calories, but the "Dietary Fiber and Weight Regulation" review found that study subjects randomized to consume higher-fiber diets lost more weight even when caloric intake was fixed.¹²⁰⁹ Think about it: more weight loss even when prescribed the same number of calories. So if it wasn't the calories-in side of the equation, could it be the calories-out side? Normally, *calories out* means things like exercise, but, in the case of high-fiber diets, there are literally calories out—as in out the other end and flushed down the toilet. But the same-calorie, higher-fiber groups were losing more weight even after taking into account the excess calorie dumping. Where were the calories going?

To solve the mystery of the missing calories, researchers fed people different amounts of fiber and sealed them in an airtight chamber called a *whole-body calorimeter* to closely monitor their metabolic rates.¹²¹⁰ Those with more fiber in their systems burned more calories—even in their sleep. Though it was only about 2 percent more, that translated into about fifty more calories burned a day without getting out of bed. What was going on?

For people on long-term, fiber-rich diets, the researchers figured that all that fiber might bulk up their intestinal linings, which are highly metabolically active tissues. The gut may only represent 5 percent of body weight, but it might burn 25 percent of daily calories.¹²¹¹ Why were the research subjects spontaneously burning off more energy even while they were sleeping? It turns out all that extra fiber may be giving their gut a workout.

Our intestines are muscular tubes, so our small intestines are essentially twenty feet of muscle, which contract in waves to move food along. But fiber-depleted foods don't offer much resistance. Wonder Bread and apple juice get absorbed almost immediately without much effort. It's like pumping iron with barbells made out of Styrofoam.

Researchers had people swallow long strings of electrodes to measure the electrical activity of the muscular contractions of the intestines of those eating low-fiber meals versus high-fiber meals.¹²¹² Those eating more fiber sometimes not only had stronger, faster, and longer contractions, but they had also reduced the periods of intestinal inactivity. Turns out our gut can be sedentary too. But if you eat lots of fiber-rich foods, your gut could be exercising all night long while you sleep.

Discovering the Keys to Weight Loss

This laundry list of mechanisms for fiber-induced weight loss included the best explanations we had back in 2001 when the "Dietary Fiber and Weight Regulation" review was published, but that was two years before a discovery was to change our ideas about fiber forever.¹²¹³

Cells are the fundamental unit of life. We're composed of trillions of them,¹²¹⁴ and they communicate with each other through receptors on the cell surface. That's how many hormones work: Like a lock and key, hormones are signaling messengers, and each has a unique shape. When released into the bloodstream, they circulate throughout the body until they find a receptor they can fit into. Once the key is in the lock, a whole series of reactions can be turned on or off in the target cell. For example, cells in our adrenal glands release adrenaline when we get scared, and there are receptors on our hearts, called *beta receptors*, into which adrenaline fits that can trigger an increased heart rate. That's how beta-blocker drugs work to lower our heart rates—by gumming up this lock so adrenaline can no longer fit.

The largest family of cell receptors is known as *G protein-coupled receptors*. G proteins are molecular switches inside the cells that transmit the receptor signal.¹²¹⁵ More than one-third of the drugs currently on the market work by plugging into these receptors,¹²¹⁶ from antihistamines to heroin overdose drugs that block opioid receptors. We've discovered hundreds of different G protein-coupled receptors, but remarkably, we don't know what many of them do.¹²¹⁷ We have the lock, but we just don't know which key fits into them. Accordingly, these are called *orphan* receptors.

Two of these mystery receptors, known only as *G protein-coupled receptor #41* and *G protein-coupled receptor #43*, were found heavily expressed throughout the body in our gut, on our nerves, and in our immune, muscle, and fat cells.¹²¹⁸ We knew they must be vital, but we didn't know what activated them until 2003 when they were "deorphanized." (That's actually what scientists call it.) And the keys that fit into those important locks were the short-chain fatty acids that our gut bacteria make when we feed them fiber.¹²¹⁹

This may be how our gut bacteria communicate with us.¹²²⁰ Renamed *free fatty acid receptors*, their existence gives us crucial insight into how fiber could play such a critical role in so many of our chronic diseases.¹²²¹ They may explain why fiber is so anti-inflammatory.¹²²² So, for example, how can a single high-fiber meal improve lung function in asthmatics within a matter of hours? The fiber we eat is turned into SCFAs by our good gut bacteria, which then are absorbed into our bloodstreams, where they are thought to dock with these free fatty acid receptors found on inflammatory immune cells in our airways, turning them off.¹²²³

Hormones are defined as signaling messengers that are produced in one organ, circulate through the bloodstream, and have a regulatory effect on another organ. So these SCFAs could be considered hormones. It's just that the organs producing them are our microbiomes, the bacteria that populate our gut. They can't make these hormones without

fiber, though. Just like our bodies need iodine to make thyroid hormones and our thyroid function suffers when we eat iodine-deficient diets, our bodies need fiber to make short-chain fatty acids and can suffer the consequences if we eat fiber-deficient diets.

Hacking Hunger Hormones

Short-chain fatty acids also stimulate the production of leptin,¹²²⁴ the hormone produced by fat cells to tell our brains to trim us down. Leptin is an *anorectic* hormone, so called because it generates a loss of appetite and weight, but it does so over the long term. Leptin levels slowly rise as the volume of body fat gradually increases. In contrast, there are other anorectic hormones that work rapidly, signaling our brains on more of a meal-to-meal basis.¹²²⁵ Two of these short-term appetite suppressants are PYY and GLP-1, both of which are secreted by specialized *L cells* that line our colons (named for their release of large packets of hormones).¹²²⁶ Guess which receptors are crowded all over the surface of L cells? Free fatty acid receptors.¹²²⁷

Drip some SCFAs onto L cells, and they start churning out PYY and GLP-1. You can do this in a petri dish¹²²⁸ or in a person, either by infusing their rectums with an SCFA enema¹²²⁹ or the old-fashioned way of feeding people fiber¹²³⁰ or, even better, fiber-rich foods.¹²³¹ These hormones then get released into the bloodstream where they can shoot right up into the appetite center of the brain and turn down our cravings.¹²³²

The flip side to PYY and GLP-1 is ghrelin, the so-called hunger hormone. Ghrelin levels rise in our blood before a meal to stimulate our appetites and fall right down once we eat, before slowly building back up again to propel us once more to the fridge.¹²³³ But feed people twenty-four grams of fiber, and four hours later, ghrelin levels are suppressed as much as if they had just eaten five hundred calories' worth of food.¹²³⁴ Over the longer term, overweight eleven- and twelve-year-olds who had been randomized to increase fiber intake for sixteen weeks ended up eating hundreds of fewer calories at a buffet meal challenge compared to a placebo control group.¹²³⁵

One of the most fascinating studies that has been done in this area involves putting people into an fMRI machine that measures real-time brain activity. Subjects were shown a high-calorie food such as a donut, and the reward centers in their brains instantly lit up compared to when they were shown a low-calorie food like cucumber slices. What happens if you repeat the experiment, but this time, after secretly delivering SCFAs directly into their colons? The subjects reported the high-calorie foods seemed less appealing, and this was matched by decreased activity in some of the reward centers in their brains, whereas their brains continued to react about the same to the less-craveable foods.

The researchers figured this was due to PYY and GLP-1 secretion, but that wasn't the case: The effect was independent of hormone release. The researchers speculated that perhaps they had directly stimulated free fatty acid receptors on nerves in the gut that travel straight to the brain.¹²³⁶ Similar results were not found with psyllium supplements (like Metamucil),¹²³⁷ which makes sense since psyllium is nonfermentable, meaning our gut bacteria can't eat it—so although it can improve bowel regularity, it cannot be used to make the key ingredients for appetite suppression.¹²³⁸ Eat fiber-rich foods, though, and our good gut flora take the fiber we eat and churn out molecules that calm our cravings.

Putting Fiber to the Test

The evidence for the role of fiber in weight control started with so-called ecological studies.¹²³⁹ These involve comparing population averages, noting that populations with extraordinary fiber intakes tend to have negligible obesity rates. The problem with dealing with population averages is that we don't know if the individuals eating the higher-fiber diets are themselves necessarily the ones protected from obesity. In cross-sectional studies, you can confirm in both adults¹²⁴⁰ and children¹²⁴¹ that those who eat more fiber

are indeed significantly less likely to be obese. A problem with these types of studies, however, is that they represent only a snapshot in time, so you don't know which came first, the obesity or the poor eating habits.

This brings us to cohort studies, where individuals and their diets can be followed over time. A cohort study of overweight youth found that the amount of fiber in a single, half-cup, daily serving of beans over about a two-year period was associated with a “profound” 25 percent difference in abdominal obesity.¹²⁴² In about the same time frame, in middle-aged women, each two-gram increase in daily fiber was associated with a weight decrease of about a pound.¹²⁴³ The postpartum period places women at risk for retaining baby weight,¹²⁴⁴ and a study of hundreds of new moms followed for the first five months found that inadequate fiber intake during the postpartum period appeared to increase obesity risk by 24 percent. And the benefits of fiber are not limited to women.¹²⁴⁵ A cohort that included tens of thousands of men who were followed for years concluded that a daily ten-gram increase in fiber consumption might be expected to prevent about 10 percent of weight gain within the population.

Overall, the evidence is strong from these kinds of observational studies that “increasing consumption of dietary fiber with fruits, vegetables, whole grains, and legumes across the life cycle is a critical step in stemming the epidemic of obesity.”¹²⁴⁶ These studies can control for nondietary influences like physical activity by equipping people with gadgets to measure their movement, but there may be uncontrolled confounding dietary factors. Think about that list of high-fiber foods—fruits, vegetables, whole grains, and beans. Maybe fiber intake is just a marker for the intake of healthy foods. There are many reasons why eating whole plant foods could facilitate weight loss that have nothing to do with fiber. To know if there's a cause-and-effect relationship between fiber and weight loss, you need to put it to the test in interventional trials.

This is where rectal infusions come in handy.

In a randomized, double-blind, placebo-controlled crossover study, researchers showed that by infusing SCFAs into people's rectums, you can boost their metabolisms within thirty minutes.¹²⁴⁷ They used the amounts you'd expect to create yourself from eating a high-fiber diet. Not only did the subjects' resting metabolic rate go up (that is, the amount of calories burned just by being alive), but specifically, their fat oxidation jumped up, too, increasing the amount of fat they were burning by more than 25 percent.¹²⁴⁸ This translates into about an extra third of a pat of butter's worth of fat burned off their bodies within two hours of the infusion.¹²⁴⁹

Colonic catheters aside, you can feed people SCFAs directly and get the same little bump in resting metabolic rate and whole-body fat breakdown,¹²⁵⁰ in addition to decreasing appetite. So, again, fiber may work on both sides of the energy-balance equation.¹²⁵¹ But does that decreased appetite actually result in people eating less? Given the equivalent of about ninety grams of fiber worth of SCFAs, study subjects consumed about two hundred fewer calories at an all-you-can-eat meal.^{1252,1253}

Can't you just feed people some beans? Indeed you can. Researchers in Sweden fed people beans for dinner, and, by the next morning, after their friendly flora had also had a chance to feast, their satiety hormones like PYY were up, their hunger hormone ghrelin was down, and they reported feeling less hungry.¹²⁵⁴ The researchers didn't measure subsequent food intake, but a similar study with whole-grain rye for dinner led to a decreased food intake at lunch the next day. Those who had eaten the fiber-rich whole grain the night before felt fully satiated about one hundred calories sooner at a meal more than twelve hours later.¹²⁵⁵ So, by eating fiber-rich foods on a daily basis, you can set yourself up for success.

What About Fiber Supplements?

Reduced caloric intake at a single meal or even over the course of a whole day doesn't necessarily translate into long-term weight loss, though, as our bodies may find ways of compensating.¹²⁵⁶ Experimentally delivering SCFAs directly to the colon every day for months showed that it does reduce abdominal fat, liver fat, and overall weight gain,¹²⁵⁷ but what about getting SCFAs the old-fashioned way, by taking fiber by mouth?

To isolate out the effects of fiber, studies have tried using straight fiber supplements. A 2017 systematic review and meta-analysis compilation of a dozen randomized controlled trials of various fiber supplements versus placebo powders found that the groups taking the actual fiber lost an average of about five and a half pounds more than the control groups.¹²⁵⁸ These were studies ranging in duration from two to seventeen weeks, though there have been fiber supplementation trials that have lasted up to a year that have shown significantly superior weight changes in both young adolescents¹²⁵⁹ and adults.¹²⁶⁰

Many of the fiber supplement findings were inconsistent,¹²⁶¹ though, presumably because dozens of different isolated fiber types had been tested.¹²⁶² There are all sorts of newfangled fibers on the market with names like *IQP G-002AS*. (The *IQP* stands for *InQpharm*, the drug company that came up with it.¹²⁶³) After all, how much money can you make selling beans?

Real Fiber FTW

Using isolated fiber extracted from plants or made in a lab can be useful in experimentally proving fiber's effectiveness apart from all the other healthy components in whole foods, but, if anything, you might expect even greater benefits from getting fiber the way nature intended: by eating intact plant foods.¹²⁶⁴

Published in the prestigious *Annals of Internal Medicine*, a study entitled "Single-Component Versus Multicomponent Dietary Goals..." randomly assigned hundreds of people into one of two weight-loss regimens:¹²⁶⁵ One simply encouraged people to get at least thirty grams of fiber each day, which is about the recommended minimum adequate intake, and the other advised people to also follow the far more complex weight-loss program recommended by the American Heart Association. So, in addition to also hitting that thirty-grams-of-fiber target, study subjects in the second group were prescribed carefully calculated caloric intake goals and were told to switch from red meat to white, moderate their alcohol intakes, cut down on sugary beverages, and reduce sugar and sodium intake across the board.¹²⁶⁶

Even though both groups were told to reach the same fiber target, the group whose focus was solely on fiber intake ended up eating more than twice as much extra fiber as the multicomponent intervention and, surprisingly, similarly improved the quality of their diets. For example, the group focused only on fiber intake ended up reducing their saturated fat intakes as much as the group who was explicitly instructed to do so.¹²⁶⁷ Simply telling people to eat more whole plant foods seems to naturally crowd out some of the less healthy options by default. With similar dietary improvements, both groups lost similar amounts of weight,¹²⁶⁸ suggesting if you could give only one piece of weight-loss advice, eating more fiber might not be a bad choice. Of course, it only works if you actually do it.

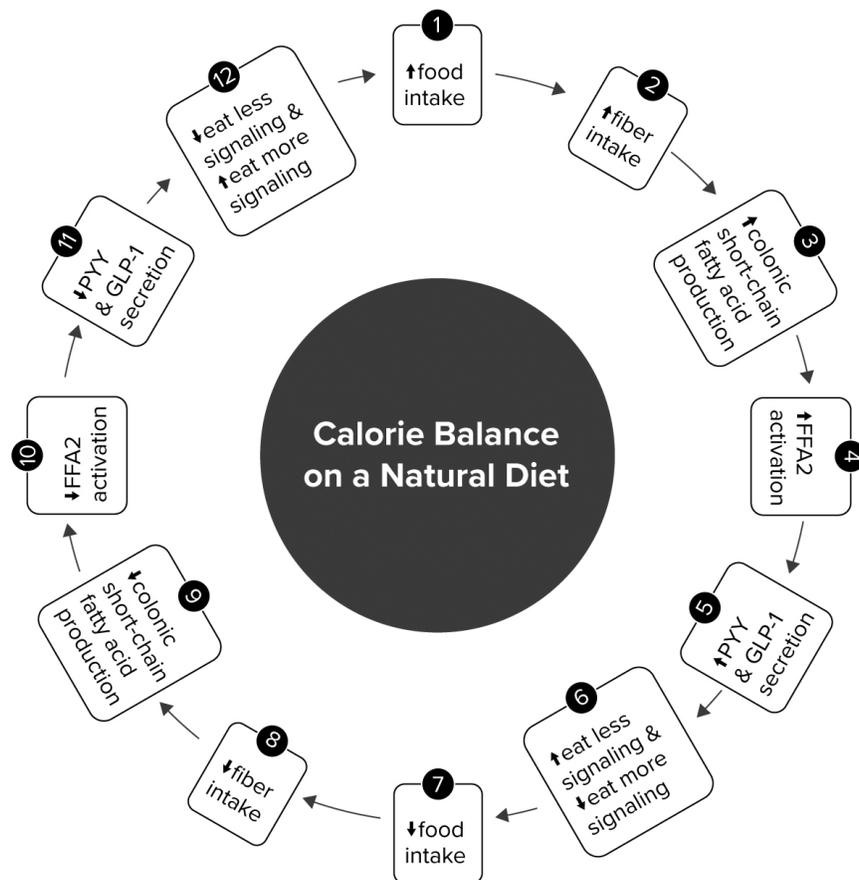
There was one study that reported favorable results when eating a low-carb diet compared to a "high-fiber" diet. But just how high was this so-called high-fiber diet? The subjects started out at a pitiful 17.4 grams of fiber a day. Sadly, that's about typical for the United States,¹²⁶⁹ but it's only about half the average recommended minimum daily intake of 31.5 grams.¹²⁷⁰ The low-carb study subjects started out at 17.4 grams a day and, on their "high-fiber" diets, shot up to ... 18.6 grams a day. Seriously. In no universe is that a high-fiber diet. Nevertheless, the low-carb study researchers used their findings to conclude "previous claims of the benefits of fiber for weight loss may have been overstated."¹²⁷¹

Eating the Way Nature Intended

Fewer than 3 percent of Americans reach even the recommended *minimum* daily adequate intake of fiber.¹²⁷² There's so much fuss about protein, but for that, the stats are reversed: More than 97 percent of Americans get enough protein, but more than 97 percent of Americans don't get enough fiber. Nearly everyone is suffering from a fiber-deficient diet, and that's just based on the wimpy federal recommendations of fourteen grams per thousand calories, which comes out to be about twenty-five grams per day for women and thirty-eight daily grams for men.¹²⁷³ That's a far cry from the hundred grams our bodies were designed to get,¹²⁷⁴ based on the diets of modern-day, isolated, hunter-gatherer tribes¹²⁷⁵ and an analysis of coprolites, human fossilized feces—paleopoo!¹²⁷⁶

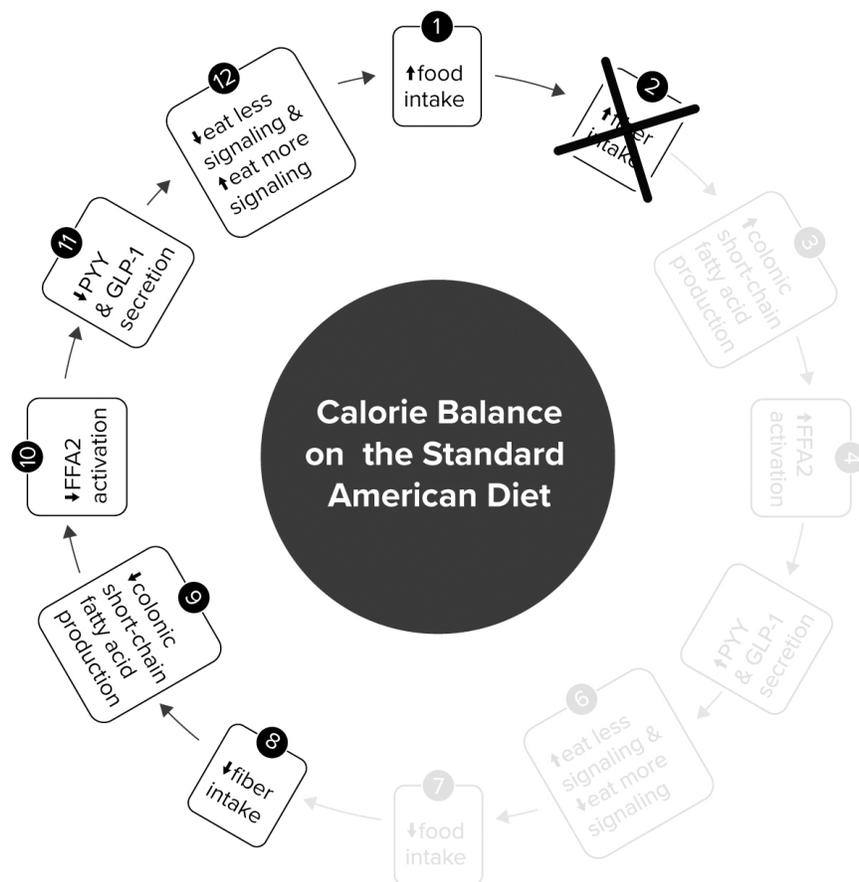
For perhaps more than 99 percent of our existence as a distinct species, the natural state of affairs was having our guts literally packed with fiber-filled foods all the time.¹²⁷⁷ Before the gristmills and certainly for the millions of years before the first stone tools and evidence of butchering, our physiology evolved eating huge amounts of unprocessed plants.¹²⁷⁸ That's the nutritional landscape upon which our bodies developed.

This could explain why our bodies centered this whole elaborate system of body fat regulation around short-chain fatty acids, the microbial by-product of fiber. Indeed, for most of our time on Earth, fiber equaled food.¹²⁷⁹ In fact, one of the theories used to explain the obesity epidemic is that the body's mechanisms for controlling appetite evolved to match our ancestral diet.¹²⁸⁰ It's like a classic negative feedback loop (adapted from Sleeth et al.).¹²⁸¹



Follow along in the diagram above, starting at the top (1). Imagine if we ate too much of the foods we were designed to eat. Since, essentially, food meant fiber, (2) our fiber intake would go up. The body would detect that change because of (3) all the extra SCFAs flooding the system, which would (4) activate the free fatty acid receptors all over the body, with direct effects on our fat cells and brains, and indirect effects by (5) stimulating the release of those anorectic hormones that (6) suppress our appetites. With fewer cravings and less hunger, our (7) food intake would drop, which is beneficial because, remember, we were (1) eating too much.

On our original, natural diet, a drop in food necessarily meant (8) a drop in fiber intake, which our bodies would pick up on, because, all of a sudden, there would be (9) less signaling by SCFAs and (10) less activation of those free fatty acid receptors, which means (11) less of those anorectic hormones circulating throughout our bodies, (12) perking up our appetites once again. That may be how our bodies were meant to work to keep our body weight stable.



Okay, but now, fast-forward past the Industrial Revolution and time-machine drop the human body into the middle of bologna-on-Wonder-Bread country. The figure above shows what happens when food doesn't equal high fiber anymore. When calories are divorced from fiber, we may just keep getting these signals to eat, eat, and eat some more. We're always hungry because our bodies aren't getting the signal that we've eaten enough, even though we're piling in the calories. If we haven't eaten our hundred grams of fiber for the day, our bodies may be like, *What? Are we starving here?*

Sadly, the average fiber intake in the United States has failed to improve in recent years despite ongoing public health messaging about its importance.¹²⁸² One problem may be

that people just don't know what fiber is. More than half of Americans surveyed think steak is a significant source of fiber.¹²⁸³ However, literally by definition, fiber is only found in plants.¹²⁸⁴ There is zero fiber in meat, dairy, or eggs and typically little or no fiber in junk food.

Therein lies the problem.

Ninety-six percent of Americans don't eat the minimum recommended daily amount of beans, 96 percent don't eat the measly minimum for greens, and 99 percent don't get enough whole grains.¹²⁸⁵ Nearly the entire U.S. population fails to eat enough whole plant foods—the *only* place fiber is naturally found in abundance. You know things are bad when french fries make it into the top ten sources of fiber in the American diet,¹²⁸⁶ and donuts, cookies, and cake come in at number thirteen. In comparison, sweet potatoes are down at number forty-seven. And what's the number-one source of fiber in the American diet? Ironically, it's white bread. Even though it's severely fiber-depleted, we eat so much of it and so few whole grains and beans that white bread is Americans' top fiber source.

You'd think the discovery of the free fatty acid receptor mechanism for appetite control would reignite the public health push to get us all to eat healthier food, but instead, Big Food and Big Pharma view it as an opportunity to market new products. Since "large amounts of dietary fibre (>30g/day)"—in other words, the recommended *minimum* adequate intake—"are required for these beneficial effects,"¹²⁸⁷ researchers conclude, "alternative ways of optimising colonic SCFA production may be needed."¹²⁸⁸ The measly minimum represents "unpalatably high levels,"¹²⁸⁹ according to these drug industry-funded researchers. Thus, there are calls for "pharmacological manipulation of appetite using a GPR43 agonist [stimulator]."¹²⁹⁰ Their conclusion is that "activation of colonic [free fatty acid receptor] FFA2 by ... pharmacological mimetics [mimickers] is a promising candidate in the fight against the current obesity onslaught."¹²⁹¹

Or we could just eat as nature intended.

FOOD FOR THOUGHT

What are the best sources of fiber? The American Medical Association published a patient summary about fiber-rich foods listing an array of whole, unrefined plant foods.¹²⁹² Those of us who may be a little smug about our hearty intake of fruits and vegetables need to realize that fruits and leafy veggies are the *poorest* whole-food sources of fiber. Why? Because they're 90 percent water. Root vegetables have about twice as much on a per-weight basis, but the fiber superstars are whole grains and legumes, which include dried or canned beans, split peas, chickpeas, and lentils.¹²⁹³

HIGH IN WATER-RICH FOODS

Mouthwatering

Like fiber, water adds bulk to foods without adding calories. A prune and a plum are pretty much the same—one just has more water. You could eat a whole handful of prunes as a snack, but the same number of plums would be an armload. In a famous experiment, dozens of common foods were scored for their ability to satiate the appetites of individuals for hours, and the characteristic most predictive of satiety in general was water content.¹²⁹⁴

Grapes, for example, have less fiber than bananas but were significantly more satiating—perhaps in part because of their greater water content.¹²⁹⁵ Apples and oranges, which have even higher water content, beat out both grapes and bananas, but researchers fed people up to twice as much to match them calorie for calorie. So, in effect, they found that four oranges were more satiating than two bananas, which seems kind of obvious, but the size difference is exactly the point. Because apples and oranges are about 85 percent water, you have to eat a lot more of them to get the same number of calories.¹²⁹⁶

People tend to eat a fairly consistent weight of food on a day-to-day basis, and serving weight is largely determined by water content.¹²⁹⁷ The more water-rich the food, the fewer calories are being taken in overall. Higher-volume foods also take longer to eat, which slows the rate of consumption and increases “oropharyngeal stimulation,”¹²⁹⁸ the sensation of food in our mouths and throats. The more we chew, taste, and feel food in our mouths, the more our brains get tipped off that we’re filling up. Stomach tube studies in which food bypasses the mouth show that the body has difficulty regulating appetite when we don’t experience those oral sensations.¹²⁹⁹

Which foods have the most water? On the next page, I’ve put together a ranking for you of the water content of common foods.¹³⁰⁰

As you can see, vegetables top the charts, with most being more than 90 percent water by weight, followed by most fruit coming in around the 80s. Starchier vegetables, whole grains, and canned beans are in the 70s, meaning about three-quarters of their weights are pure water. Pasta and most unprocessed meat, including seafood, fall down to the 60s. Most dried fruits, cheeses, and breads are in the 30s. Cake crumbles into the 20s, cookies into the teens, and candy and most common snack foods are all the way at the bottom with less than 9 percent water by weight. In general, when it comes to water-rich foods, most whole plant foods float up near the top, most animal foods fall somewhere in the middle, and most processed foods sink to the bottom.

Water Content of Foods

100–90%

asparagus, beets, bell peppers, broccoli, cabbage, cauliflower, celery, cucumber, grapefruit, green beans, greens, lettuce, melons, mushrooms, okra, onions, pumpkin, strawberries, summer squash, tomatoes, zucchini

79–70%

avocados, bananas, canned beans, corn, couscous, edamame, eggs, millet, oysters, pomegranates, potatoes, pudding, quinoa, rice, sweet potatoes

59–50%

cream cheese, frankfurters, tempeh

39–30%

bagels, bread, cheese, dried apples, dried apricots, figs, prunes

19–10%

brownies, cookies, energy bars, goji berries, jerky, raisins

89–80%

apples, apricots, artichokes, bean sprouts, brussels sprouts, carrots, cherries, grapes, jello, kiwifruit, mangoes, oatmeal, other berries, other citrus, pears, peas, pineapples, plums, tofu, winter squash, yogurt

69–60%

barley, beef, boiled beans, canned tuna, hummus, ice cream, lobster, lunch meat, pasta, pork, poultry, salmon

49–40%

cheesecake, french fries, sausage

29–20%

cake, croissants, dates, pepperoni

9–0%

breakfast cereals, candy bars, chocolate, crackers, nuts, oils, popcorn, potato chips, pretzels, seeds, tortilla chips

Trapped vs. Free Water

Can't you just drink a few glasses of water while you eat a steak and make up for the meat's low water content that way? If you drank ten gulps of water with every bite, wouldn't you end up with the same 95 percent water stomach contents you'd get eating, say, cucumbers and lettuce? This scheme works for fat cats—adding water to dry kibble can help our pet cats lose weight¹³⁰¹—but it doesn't seem to work for dogs.¹³⁰² So are we more like dogs or cats?

If you have people drink two glasses of water with a meal, their subjective feelings of hunger and satiety can be affected. This led researchers to suggest that drinking extra water could decrease food intake in a manner “far more simple and cheaper than installing an intragastric balloon.”¹³⁰³ Drinking water with meals would certainly be safer, but it doesn't appear to actually cut down on food intake.¹³⁰⁴ People tend to feel fuller when they drink water with a meal, but that doesn't appear to actually translate into eating less.¹³⁰⁵

Why does water *inside* a food reduce intake, but not water *alongside* a food? It all just ends up in the same place, right? What appears to be happening is a phenomenon known as *sieving*.¹³⁰⁶ When water is outside the food, the stomach simply siphons it off from the solid chunks and strains it right out, which leads to a rapid drop in stomach volume. On the other hand, when water is part of a food, it all forms a homogenous mass that more slowly empties from your stomach over time.¹³⁰⁷

If you give people a casserole for lunch, they eat the same amount whether or not they're also given a glass of water, about four hundred calories' worth. But if that same casserole and that same water are blended into a soup, they only eat three hundred calories' worth before feeling full.¹³⁰⁸ You can do real-time MRI scans of people's stomachs and witness the sieving process in action. A half hour after eating, the stomach volume remained 36 percent greater after eating the same meal in soup form.¹³⁰⁹ Blended together, the same meal components served as a soup left people significantly fuller even three hours later.¹³¹⁰

Even though the soup was puréed in a blender, its thickness from all the little suspended particles prevented the stomach from separating out the water and draining it off.¹³¹¹ It even works with thinner liquids.¹³¹² If you give people a milkshake followed by a glass of water, the body is able to layer out the water and empty the stomach twice as fast than if you had preblended in the water to make a more dilute, thinner shake. This helps explain observational data showing that, compared to water consumed separately, the intake of water in foods is more closely related to a slimmer waist.¹³¹³

Does Dried Fruit Make You Gain Weight?

Some dried fruit is as dry as beef jerky. Drying concentrates the calories. Compared to dried fruit, fresh fruit gives us more volume, more weight—more *food*—for the same number of calories.¹³¹⁴ Drying also concentrates the sugars, which could drive overeating. The raisin industry is quick to point out that raisins don't cause any more of a sugar spike than when consuming the same number of calories of grapes, but with grapes, that means eating about four times as much food.¹³¹⁵ On the other hand, in dried fruit, the fiber also gets more concentrated, which could potentially aid satiety. So which is it?

In population studies, those who eat dried fruit tend to be slimmer than those who don't,¹³¹⁶ but they also tend to eat better diets overall. This is one reason interventional studies are so important to prove whether there's a cause-and-effect relationship. Leave it to the California Raisin Marketing Board to dream up a study entitled “An After-School Snack of Raisins Lowers Cumulative Food Intake in Young Children.”¹³¹⁷ Sounds good, right? Well, what did they compare raisins to? Potato chips and chocolate chip cookies. They gave kids raisins, grapes, chips, or cookies and told them to eat as much as they wanted. Surprise, surprise, the kids ate less fruit and more junk. To be fair, I guess naming the paper “Kids Prefer Cookies” would not have garnered the same kind of sponsor approval.

Give people fresh fruit, and they end up eating less at subsequent meals. Give people strawberries, raspberries, blackberries, and blueberries, and they eat less pasta an hour later compared to those given the same number of calories in the form of gummy bears, which have about the same water content as raisins.¹³¹⁸ The same effect can be found with other kinds of fresh fruit,¹³¹⁹ and this can translate into greater weight loss. Give people apples or pears every day instead of the same calories in cookies, and they lose significantly more weight.¹³²⁰ The only way

to know if *water* content played the critical role, though, is if the researchers had included a third group in the study who had been given *dried* pears and apple rings.

There have been experiments directly comparing raisins to grapes. Although grapes appear to suppress appetite better than raisins,¹³²¹ raisins beat out grapes when it came to reducing pizza intake a half hour later. I know as parents there's a concern that if our kids eat snacks, it might spoil their dinners, but when the snacks are fruit and the meal is "pepperoni and 3 cheese pizza,"¹³²² perhaps the more we can ruin their appetites, the better.

Does the satiating effect of raisins translate into weight loss, though? Prunes can also cut down on appetite¹³²³ and subsequent meal intake,¹³²⁴ but feed people about nine prunes a day and they don't appear to lose any weight, at least in the short term (though their bowel habits did improve).¹³²⁵ Similarly, replacing about four hundred to five hundred calories of someone's diet with raisins every day may not lead to weight loss. However, you can imagine how adding the same caloric load in the form of grapes every day—four or five cups—might have more of an effect.¹³²⁶ Bottom line: Although eating dried apples,¹³²⁷ figs,¹³²⁸ dates,¹³²⁹ prunes,¹³³⁰ or raisins¹³³¹ may not lead to inordinate weight gain, they don't appear to actively promote weight loss. That makes fresh fruit the better choice.

FOOD FOR THOUGHT

Take a deep dive into the Water Content of Foods chart so your diet swims in water-rich vegetables and juicy fruit (though not the gum!).

LOW GLYCEMIC LOAD

Chew on This

One of the major dietary shifts from the ancient to the modern world has been the increased consumption of fiber-depleted processed carbohydrates—sugars and starches.¹³³² The impact of carbs on the body depends on their source. Kidney beans and jelly beans are both rich in carbs but can have diametrically different impacts on our bodies. Bread made from the exact same ingredients as pasta causes nearly twice the blood sugar spike, leading to nearly three times the insulin release as the same number of carbs consumed in noodle form.¹³³³ That's because bread is filled with tiny bubbles, allowing digestive enzymes easy access to more surface area to more rapidly digest starch into sugars compared to pasta, which is more compact. The more solid nature of pasta forces the enzymes to have to work their way in from the edges, slowing the rate at which pasta can be broken down.

You can try this experiment at home: Take a bite of a piece of bread, and chew, chew, and chew some more without swallowing. Gradually, that piece of bread will taste sweeter and sweeter, thanks to the starch-digesting enzyme in our saliva. Next, try it with cooked spaghetti. Sore jaw alert! It may take two hours of chewing pasta to get the same sweetness in your mouth that you'd get from chewing bread for only ten minutes. You probably won't want to try it with the whole intact grain—wheat berries—because it might take all day.¹³³⁴

Why do we care how quickly carbohydrates are digested? Because it can affect our appetites, our metabolic rates, and how much fat we burn.

You can measure the impact different carbohydrate-rich foods have by feeding people a certain amount and seeing what happens to their blood sugar levels over the next few hours. Then you can compare the size of the blood sugar bump from the carbs in bread form to the same number of carbs in pasta form, or fruit form—or cotton candy form, for that matter. This is how the glycemic index of foods is generally calculated. Then, based on the number of carbs per serving, we can come up with the glycemic load of a food. The higher the glycemic load, the higher our blood sugars tend to spike when we eat them. A breakdown of some common sweet and starchy foods appears [here](#).¹³³⁵

Glycemic Load Per Serving

Low ≤ 10	Medium 11–19	High ≥ 20
beans chickpeas & split peas fruit lentils whole-grain bread	oatmeal spaghetti brown rice sweet potato white bread	corn flakes & rice krispies dates white rice white potato raisins

Lighten Your Load

If you feed people two types of meals matched for calories, nutrition, and taste, but one has a high glycemic load and the other low, what happens when you put them in a brain scanner? The high-glycemic-load meal causes significantly greater activation in the regions of the brain associated with reward and craving, along with increased hunger four hours later.¹³³⁶ This may help explain why most of the top dozen problematic foods identified in a study entitled “Which Foods May Be Addictive?” were high-glycemic-load foods. (I expand on this study in the Low in Addictive Foods section.) Rather than the *quantity* of refined carbs, such as white flour and sugar, it was the speed at which they were absorbed in the system that was more predictive of being “addictive.”¹³³⁷

What do you think happened when kids ate Corn Flakes, Coco Pops, or Rice Krispies for breakfast versus a lower-glycemic-load food like oatmeal with a spoonful of sugar? After the high-glycemic breakfast, the kids went on to eat more of a buffet-style lunch than when they had started their day eating about the same number of calories of the lower-glycemic breakfast. Even with the extra sugar added to their oatmeal, they ended up eating about one hundred fewer calories of the all-you-can-eat lunch, compared with after the high-glycemic breakfast.¹³³⁸ In this case, the difference in fiber intake also could have played a role, but in general, these types of short-term satiety studies have shown that lower-glycemic carbohydrates may make one feel fuller longer.¹³³⁹

Beyond appetite regulation, lower-glycemic-load foods can also cause you to burn more fat. If you feed people a low-glycemic meal (All-Bran cereal and fruit) and put them on a treadmill three hours later, they burn more fat than they would after having eaten the same number of calories of a high-glycemic meal (for example, Corn Flakes and white bread).¹³⁴⁰ This enhanced fat loss can occur not only during brisk walking¹³⁴¹ or running¹³⁴² but can happen even when doing nothing.

One of the reasons it’s so hard to maintain weight loss is that our bodies try to defend themselves against losing fat by slowing down our resting metabolic rates, the number of calories our bodies burn every hour just by existing.¹³⁴³ That’s one of the reasons weight loss can stall on a diet. But put people on a low-glycemic-load diet, and metabolic rate doesn’t slow down as much—their metabolisms slow by 96 calories a day after losing about twenty pounds, compared to a metabolism that is 176 calories slower on a higher-glycemic-load diet.¹³⁴⁴ An 80-calorie-a-day difference might not seem like a lot, but those calories are burned automatically without an ounce of additional effort on our parts. Eighty calories is about how much we’d burn walking an extra mile a day (or eating about two fewer bites of a donut).

This process can work the other way too. If you overfeed people on a high-glycemic diet, then they store more fat than those eating the same number of calories of a low-glycemic diet. If you eat 50 percent more calories than needed, you add about a quarter pound of pure fat to your body each day on a high-glycemic diet. However, if you eat the same number of extra calories on a low-glycemic diet, you gain about 40 percent less,¹³⁴⁵ which comes out to a difference of about a pound of fat a week while eating the same number of calories.

Putting Lower-Glycemic Eating to the Test

Between the satiating power and metabolic benefits of low-glycemic foods, it's no wonder that those randomized to be given lower, rather than higher, glycemic meals appear to lose more body fat.^{1346,1347} What did surprise me was how underwhelming the evidence was for significant or long-term weight loss with low-glycemic-load interventions. A review prepared by the Cochrane Collaboration, historically considered to be the evidence-based gold standard, concluded that "lowering the glycaemic load of the diet appears to be an effective method of promoting weight loss" but only found the benefit to be a few extra pounds of weight loss after weeks or months on lower-glycemic-load diets.¹³⁴⁸

The DIOGENES trial is held up by advocates of lower-glycemic eating as evidence of its efficacy.¹³⁴⁹ Hundreds of overweight individuals were advised to eat either higher- or lower-glycemic index diets after losing an average of twenty-four pounds to see who could keep off the weight better. Those on lower-glycemic diets regained less weight at six months compared to those on the high-glycemic-index diet, but it was only two pounds less,¹³⁵⁰ and the benefit appeared to effectively vanish by the one-year mark.¹³⁵¹ In retrospect, this is unsurprising given how unsuccessful they were at convincing people to change their eating habits.

Anytime findings in controlled feeding studies don't seem to translate into real-world results, the first question you always have to ask is: *Did the subjects actually follow the prescribed diet?* In a controlled setting like in that metabolic rate study, the glycemic load can be dropped 70 percent, from a total daily glycemic load of 287 down to 82. In the case of the DIOGENES trial, where people were randomized not to different diets but to different dietary *recommendations*, the difference in daily glycemic loads between the "high" glycemic group and the "low" glycemic group differed by less than 3 percent.¹³⁵² No wonder the demonstrated benefits were slim to none. Foods only work if you eat them.

Even in the most successful studies, it's hard to separate out the specific effects of the glycemic change. Many high-glycemic foods are highly processed and fiber-depleted, so when you swap them for low-glycemic foods like beans and fruit, you're doing more than just changing the glycemic load. The big drop in glycemic load in the metabolic rate study was accompanied by a similar-sized boost in fiber intake—so how do we know it was the glycemic load and not the fiber?¹³⁵³ That's the problem with diet studies: It's hard to change just one thing. With drug trials, it's easy—just give the drug or a sugar pill and if there's a change, you know it was the drug that caused it. If only we could stuff the change in glycemic load into a pill. Well, it turns out we can.

Acarbose is a drug that partially blocks our sugar- and starch-digesting enzymes in the digestive tract, slowing their absorption into the body.¹³⁵⁴ When taking the drug with a meal, you can effectively transform a high-glycemic meal into a low-glycemic meal without changing the foods at all.¹³⁵⁵ Weight-loss trials with acarbose offer the strongest case that simply lowering dietary glycemic load may indeed be beneficial for weight management.^{1356,1357}

As you can see in the Glycemic Load Per Serving chart, the simplest way to stick to a lower-glycemic diet is to try to stick to foods that were grown, not made. If you are going to eat high-glycemic foods, though, there are ways to help blunt the blood sugar spikes. I explore a few options in part IV, where I cover a series of weight-loss boosters, including the use of vinegar in the Amping AMPK section and choosing intact grains over whole ones in the Wall Off Your Calories section.

You can also eat berries with your meals, which can act as starch blockers by inhibiting the enzyme that digests starch.¹³⁵⁸ This slows the absorption of blood sugars into your system. So, if you are going to sit down to a high-glycemic breakfast, put a raspberry spread on your toast, add strawberries on your cornflakes, or make your pancakes blueberry, for example, to help mediate the glycemic rush.

Some starch is naturally resistant to digestion. Prior to the discovery of this “resistant starch” in 1982, we thought all starch could be broken down by the enzymes in our small intestines.¹³⁵⁹ Now we know there are indeed starches that resist digestion, which not only lowers their glycemic impact but, since they make their way down to our large intestines, can act as prebiotics to feed our good bacteria, just like fiber does. (Probiotics are live bacteria; prebiotics are the fuel that feeds them.) Resistant starch is found naturally in many common foods, including beans, grains, vegetables, seeds, and some nuts—but in small quantities, just a few percent of the total.¹³⁶⁰ There are ways, though, to get more resistant starch into your diet.

When regular starches are cooked and then cooled, some of the starch recrystallizes into resistant starch. For this reason, pasta salad can be a bit healthier than hot pasta, and potato salad sometimes healthier than a baked potato. But the effect isn’t huge. The resistant starch goes from about 3 percent up to 4 percent. So rather than relying on cold starches, the best source of resistant starch is legumes—beans, split peas, chickpeas, and lentils—which start out at 4-5 percent and then go up from there.¹³⁶¹

LOW IN ADDED FAT

The Fat Wars

Dueling *Time* magazine covers, one depicting an egg-and-bacon frowny face and another exhorting people to eat butter, exemplify the two battlefronts in the contentious issue of dietary fat’s role in disease. On one side, all sources of fat are villainized, while on the other, lard is lauded. As is so often the case with fervent partisan positions, both could stand a dose of science.

A common trope of the pro-fat faction is that the obesity epidemic was fueled by government calls to reduce fat intake. This presupposes the American public actually followed that advice. In fact, fat intake has not fallen; it’s gone from an estimated average of 743 daily calories of fat in the 1970s to 747 in the latest national survey.¹³⁶² The availability of added fats and oils rose more than 50 percent, from 52.5 pounds per person in 1970 to 82.2 in 2010.¹³⁶³ America presumably got fat because we ate more of everything—more carbs, more protein, and more fat.¹³⁶⁴ We now eat about 500 more calories every day and gained about an extra 500-calories-a-day’s worth of weight.¹³⁶⁵ So there’s no great mystery there.

The percentage of calories from fat decreased from about 37 percent to 34 percent, but that’s just because the increase in carbs and protein exceeded the increase in fat. At no time in recent history has America eaten a low-fat diet.¹³⁶⁶ The pro-fat faction is right about one thing, though: The food industry’s response to the call to reduce fat may have made things worse.

The low-fat diet recommendation, as proposed in the original *Dietary Goals for the United States*, was intended, for example, to “decrease consumption of meat”¹³⁶⁷ and increase consumption of naturally low-fat foods, such as fruits, vegetables, and whole grains.¹³⁶⁸ But how much money can be made on millet? Not nearly as much as bastardized “low-fat” junk foods. Enter SnackWell’s Fat-Free Devil’s Food Cookie Cakes.

The packaged-food industry is happy to hop on any bandwagon and sell us any kind of junk food we want: low-fat junk, low-carb junk, gluten-free organic junk, and even, ironically, processed paleo junk. But low-fat doesn’t necessarily mean low-calorie.¹³⁶⁹ A systematic comparison of different foods and their low-fat versions found that items with reduced-fat claims tend to have more sugar.¹³⁷⁰ Instead, we can dismount the processed food industry’s sugar-fat seesaw by opting for whole, natural foods.

Researchers have shown that overfeeding people with either fat or sugar can cause the same weight gain.¹³⁷¹ The debate is often framed as fat versus carbs, but health-wise, the term *carbs* is practically meaningless, as it could refer to black beans or Blow Pops. If, for weight loss, you replace fatty foods in people's diets with sugary foods, nothing happens, but if you replace fatty foods with starchy foods, they lose weight.¹³⁷² Presumably, this is because the researchers started feeding people more real food (as inferred by increased fiber intake), rather than just processed foods with either added fats or added sugar.

The Halo Effect

Akin to the way people evidently tend to start doing more laundry when they get energy-efficient washing machines and thereby undercut their savings,¹³⁷³ low-fat claims can lead consumers to eat larger portions and take in more calories.¹³⁷⁴ When M&M's candies were labeled as "low-fat," for example, overweight study participants ate 47 percent more of them.¹³⁷⁵ Consumers tend to overgeneralize specific claims and arrive at overreaching conclusions. Many people see the words *low fat* and assume that means the product is healthy overall.

Taken from the social psychology literature, the halo effect theory helps explain these types of leaps. Positive personality traits, for example, are inexplicably attributed to people who are more physically attractive.¹³⁷⁶ Cereals use this ploy all the time with nutrient-specific claims like "good source of vitamin D." Lucky Charms can produce a positive "health halo" impression to distract the purchaser from the incongruity of feeding their children multicolored marshmallows for breakfast.

Deliberately distracting attention away from negative qualities or the overall vacuity of nutritional content has a name: *nutri-washing*.¹³⁷⁷ Ironically, cereal boxes bearing low-calorie claims have been found to have *more* calories on average than those not asserting to be low-calorie, so nutrient claims can be misleading even when understood correctly.¹³⁷⁸

Food, not nutrients, is the fundamental unit in nutrition.¹³⁷⁹ The *source* of fat is likely more important than the *amount* of fat. And let's not forget that the healthiest foods don't have any nutrition labeling on them at all. In the grocery store, you're more likely to see "healthy" claims adorn Apple Jacks than apples.¹³⁸⁰

What Do Losers Eat?

To bolster their position, low-fat diet proponents often point to the National Weight Control Registry. The largest study of those who have successfully lost weight,¹³⁸¹ the registry followed thousands of individuals who on average reportedly lost sixty-nine pounds and kept it off for more than six years.¹³⁸² The hope of the study was to identify behaviors associated with the most successful losers. What were their secrets?

Most reported being physically active (primarily walking)¹³⁸³ and weighing themselves at least a few times a week.¹³⁸⁴ In terms of diet, at both time of entry into the registry and after ten years of successful weight maintenance, they were said to have "low calorie and fat intake." However, only a third of the participants ate what you might consider truly low-fat diets (no more than 20 percent of their calories from fat).¹³⁸⁵ In general, though, they did eat relatively low fat, coming in at 26 percent calories from fat¹³⁸⁶ compared to the current national average of 34 percent.¹³⁸⁷

Although the average registrant dropped from severely obese (BMI 35) to normal weight (BMI 24) and kept off the weight for years, several hundred of the participants began adding back some of the weight at follow-up. This offered the researchers an opportunity to study the factors associated with the flip side of the coin, weight gain, and the same finding arose: Those who started gaining back the weight were significantly more likely to report an increase in fat intake.¹³⁸⁸

Together, the National Weight Control Registry studies provide suggestive evidence that lower-fat diets may help with weight loss and maintenance, but because it's not a random sample, the findings can't be generalized to the entire population.¹³⁸⁹ Maybe those on lower-fat diets are just more likely to submit their medical records and apply for a spot on the registry. You don't know until you put low-fat diets to the test.

Is Fat Fattening?

A review of "low-fat" diets for "long-term" weight loss found they resulted in about twelve pounds greater weight loss compared to people's usual diets.¹³⁹⁰ Why the quotation marks? The tested diets were rarely low in fat in actuality, and just a single year counts as "long-term" in many weight-loss research circles.

A major limitation of such studies is that the control groups often don't receive the same amount of attentiveness as the group given the diet being tested.¹³⁹¹ Any intervention that focuses greater attention on food intake and dietary instruction, regardless of the specifics, may facilitate weight loss. Simply being in an obesity study and knowing you have to go in and get weighed regularly can motivate people to watch what they eat and cause them to lose weight even if they're in the control group and not told to do anything.

There have been low-fat studies that weren't about weight loss at all and instead aimed to reduce cancer or cardiovascular disease risk. A compilation of thirty-two such randomized controlled trials involving more than fifty thousand participants found that dietary fat reduction was consistently shown to induce body fat reduction even when that wasn't the intention of the intervention.¹³⁹² That's more promising, but there were often other lifestyle changes as well, such as exercising or quitting smoking, so you can't separate out the effects of the dietary component.¹³⁹³ What's more, at least five long-term weight-loss trials failed to show low-fat diets offer the same or superior weight loss compared to other diets,¹³⁹⁴ adding to the debate. But what were these researchers considering "low-fat"?

A Big Fat Low-Fat Fail?

To define *low fat*, you first need to figure out what a normal-fat diet is. Not surprisingly, the "normal" intake of dietary fat varies widely by cultural cuisine around the world, from 6 percent of calories on the traditional Okinawan diet¹³⁹⁵ to 66 percent among indigenous Arctic people.¹³⁹⁶ But what's normal for us as a species?

For millions of years, we may have evolved getting approximately 10 percent of our calories from fat.¹³⁹⁷ There was no butter or oil, nuts were trapped inside hard shells, and animals hadn't yet been bred to be extra juicy. The flesh of some wild game, like moose and elk, is less than 2 percent fat by weight and less than 15 percent calories from fat.¹³⁹⁸ Even the "lean" ground beef of today can have nearly half of its calories from fat.¹³⁹⁹ What about "extra lean"? That comes in at 28 percent fat calories,¹⁴⁰⁰ which is about double that of the extra, extra, *extra* lean meat of many wild animals eaten by our ancestors.

Some low-fat proponents have used our evolutionary legacy to support their case. After all, the argument goes, what's the ideal fuel for a motor? The fuel it was designed and built for.¹⁴⁰¹ Our metabolic physiology was essentially genetically programmed by our ancestral fat intake, but just because 10 percent fat may be normal doesn't mean it's best. Natural selection is more about getting us to reproductive age intact than it is about optimal health and longevity. So while we may not be able to use our prehistoric diets to argue for the ideal, we can use them to define normalcy for our species.

It's been argued that for about 99.8 percent of our time on Earth, it was virtually impossible for us to regularly consume more than 15 percent of calories as fat.¹⁴⁰² If it's the case that 10 percent is a normal fat intake for humans, less than 10 percent could be

defined as low-fat. Given that context, let's review the five studies I could find that purported to show "low-fat" diets failed.

One study published in *The New England Journal of Medicine* claimed to put people on a low-fat diet, but their fat intakes didn't budge significantly, drifting only from 31 percent fat to 30 percent fat.¹⁴⁰³ The "low-fat" groups in three other studies also ended up at 30 percent fat, far from actually being low in fat.^{1404,1405,1406} A study in Tehran did claim that a 30 percent fat group beat out a 20 percent fat group for weight loss, but the lower-fat group had zero change in fiber intake and no significant change in protein, saturated fat, or cholesterol consumption.¹⁴⁰⁷ To get a bump in fiber-depleted carb intake without adding fruits, vegetables, whole grains, or beans, or without removing meat and dairy would presumably mean giving people the Iranian equivalent of SnackWell's. Regardless, even 20 percent fat may be high by evolutionary standards.

So if 10 percent of calories from fat is normal for us as a species and less than that can be considered to be low-fat, why are these studies of so-called low-fat diets allowing double and even triple that? You can't tell if a low-fat diet works unless you test a diet that's actually low in fat.

You Can't Win If You Don't Play

If you put people on a specific diet and nothing happens, then either the diet didn't work or the people didn't follow it. Adherence to prescribed diets in weight-loss studies is poor even when researchers provide all the meals¹⁴⁰⁸ and truly abysmal when the subjects are left to fend for themselves.¹⁴⁰⁹ Just as medications never work if you don't take them, diets don't work if you don't eat them.

The accompanying editorial to a meta-analysis of "low-fat" weight-loss studies that showed little to no benefit was entitled "Prescribing Low-Fat Diets: Useless for Long-Term Weight Loss?"¹⁴¹⁰—with the key word *prescribing*. One could imagine a similar editorial called "Prescribing Smoking Cessation: Useless for Preventing Lung Cancer?" because the failure rate of physician advice to quit smoking is 98 percent.¹⁴¹¹ It's not that quitting smoking doesn't help; it's just that people often don't comply. If smokers are able to stop, they can see dramatic improvement in their health, but it may take them an average of thirty attempts to quit before they're successful and stop lighting up.¹⁴¹² Even with a dismal 2 percent success rate, we physicians are still urged to advise our patients to stop smoking because we know it works if they actually do it. Is that the same with low-fat diets? You don't know until you put *actual* low-fat diets to the test.

In a remarkable study out of Hawaii that I detail further [here](#) and [here](#), subjects achieved seventeen pounds of weight loss in twenty-one days eating unlimited quantities of fruits, vegetables, whole grains, and beans.¹⁴¹³ That diet was 7 percent fat, similar to the traditional Okinawan diet. But what about longer term? Some of the heart disease reversal studies got people's diets down to 10 percent of fat or less, which can lead unintentionally to a sixteen-pound weight loss in three months.¹⁴¹⁴

In the famous Lifestyle Heart Trial, Dr. Dean Ornish motivated people to reduce their fat intakes to 6 percent with a diet centered on whole plant foods for a year.¹⁴¹⁵ The participants were also told to exercise, but they failed to become any more significantly active than the control group. Even though weight loss wasn't the intention of the study and people could eat as much as they wanted, by the end of the year, those randomized to the low-fat lifestyle intervention got a twenty-four-pound weight loss as a side benefit to reversing their heart disease. At five years, their fat intakes were still low at 9 percent and they had sustained a thirteen-pound weight loss.¹⁴¹⁶

The Leaking of Alli's (Orlistat's) Spotty Record

Like studies involving changes in glycemic index, low-fat interventions involve myriad dietary changes, such as changes in meat, junk food, and fiber content. With so many factors, how do you know what role the change in fat itself played? You may remember that in the case of the glycemic index, there was a starch- and sugar-blocking drug that could effectively change the glycemic index of a meal without actually altering the meal itself, which allows us to isolate the effect. Well, there's a fat-blocking drug too.

Orlistat inhibits the enzyme in your intestines that digests fat and can effectively block the absorption of up to 30 percent of the fat you eat.¹⁴¹⁷ Researchers were able to track people on similar diets, with half on the drug and the other half on a placebo, to see if reducing the absorption of fat in our bodies really does lead independently to weight loss. So does it work? Yes,¹⁴¹⁸ but it may result in only about a half pound of weight loss a month.¹⁴¹⁹ But half a pound is still half a pound. Orlistat's serious potential side effects like severe acute kidney¹⁴²⁰ and liver¹⁴²¹ failure are rare, so why aren't more people taking the drug?

As I mentioned before, orlistat—sold as Alli—causes “unpleasant symptoms such as anal leakage.”¹⁴²² Well, the fat that doesn't get absorbed has to go somewhere. For the oily discharge, the drug company apparently prefers the term *fecal spotting over anal leakage*,¹⁴²³ but soiled clothes by any other name would smell as (not so) sweet.

The drug company's website offered some helpful tips, such as “it's probably a smart idea to wear dark pants, and bring a change of clothes with you to work.”¹⁴²⁴

How did this drug even get approved? A Freedom of Information Act inquiry unearthed more than a thousand adverse events the drug company effectively hid from regulators.¹⁴²⁵ Ironically, though, the “highly visual side effects” actually may have facilitated weight loss by steering users away from fattier foods.¹⁴²⁶

So how many people actually stick with the drug? Those seeking weight loss are often willing to go to extremes—even major surgery—to lose weight by any means necessary. But crapping your pants at work? The percentage of people still on the drug after two years was found to be only 2 percent.¹⁴²⁷

The More the Merrier

Is it possible to lower fat intake yet still achieve weight loss even when there is no restriction on portion sizes, no conscious effort to cut calories, and unlimited opportunities to eat? Yes. People lose weight on low-fat diets not because they are eating less but because they are eating more. In the Hawaii study, the subjects lost seventeen pounds in three weeks because their caloric intakes dropped 40 percent. If you were to do that with caloric restriction, you'd have to cut the amount of food you ate nearly in half, but the Hawaiians ate *more* food—in excess of four pounds of food a day.¹⁴²⁸ Natural, low-fat foods tend to be so calorie dilute—that is, have so few calories per bite—that eating the same amount of food inevitably leads to fewer calories. The same, of course, cannot be said of fat-free cookies.

This calorie-density mechanism of low-fat-diet weight loss was illustrated by an elegant study from my medical alma mater, Tufts. Research subjects were switched from a more conventional diet of 35 percent calories from fat down to a diet getting only 15 percent of its calories from fat, but they were forced to eat so much food that they didn't lose any weight. Their weights were monitored closely, and if they started to lose weight, they were made to eat more food. The subjects had to eat more than five pounds of food a day to maintain their weights and “frequently complained of abdominal fullness.” Then, after five or six weeks, they were kept on the same 15 percent fat diet but were allowed to eat however much they wanted, the amount of food with which they were comfortable. Over the next ten to twelve weeks, they lost an average of eight pounds. They weren't told to purposely lose weight. They just couldn't help it.¹⁴²⁹

Normally on a diet, if quantity limits are suddenly removed, you gain weight. But on a low-enough-fat diet, even when most people can eat as much as they want, they lose weight. It doesn't happen for everybody, though. One guy in the Tufts study actually gained weight in the free-feeding phase, and another, who must have gotten used to eating that much more food, stayed the same. But the other twenty-seven out of twenty-nine participants lost weight, one as much as twenty-nine pounds, all eating *ad libitum*, which is Latin for *at one's pleasure*. That's where the term *ad lib* comes from. In acting, it means going off script. In nutrition research, it means eating without limits on quantity.

It isn't hard to imagine how *ad libitum* diets might be superior for long-term weight maintenance. To test this, researchers had people lose twenty-eight pounds through a combination of drugs and severe caloric restriction. They then randomized the subjects to

an ad libitum low-fat diet or a food exchange-based calorie-counting system to restrict caloric intake to see which group was better able to keep off the weight. One year later, the weight loss was three times higher in the ad libitum group, and they were about 50 percent more likely to maintain a substantial portion of their initial lost weights.¹⁴³⁰ In the short term, most people can force themselves to cut down on the amount of food they eat, but for lifelong weight loss, eating as much as you want may be more sustainable.

Too Little, Too Late

Give people all-you-can-eat buffets of lower-fat foods, and they end up eating hundreds of fewer calories a day than if the buffets contained similar foods containing more fat.¹⁴³¹ Depending on the fat content of the food, this can then translate into weight loss (at 15–20 percent fat) or weight gain (at 45–50 percent fat).¹⁴³² Researchers offered people essentially the same foods, but with some slight tweaks, such as more or less oil, butterfat, or margarine slipped in. The foods evidently looked and tasted about the same, so people ate about the same amount and spontaneously lost or gained weight depending on the fat content. This is the passive consumption I explore [here](#), an artifact of calorie density.¹⁴³³ It's not the fat per se but rather the consequent increase in calories per mouthful because fat can sneak lots of calories into a relatively small space.¹⁴³⁴ However, there may actually be a difference in the appetite feedback loop between fat calories and carb calories.

If I hooked you up to an IV and, unbeknownst to you, dripped 1,300 calories of sugar into your veins, studies show your body somehow “tastes” how sweet your blood has become, does the math, and turns down your appetite so much that you spontaneously eat about 1,100 fewer calories that day.¹⁴³⁵ That's a huge drop in intake, but your body sensed all those extra calories in your system and made you that much less hungry to compensate. Genius!

But if I repeat the experiment with fat, we get a different result. Have 1,300 calories of fat secretly infused into your veins, and your body knows something is going on but doesn't quite get the same picture as it did when you got those extra calories from sugar. So you only end up compensating by eating about 500 fewer calories that day.¹⁴³⁶ Your body just doesn't seem to register fat calories as well as sugar calories. You can demonstrate this with food too.

If you give people a breakfast of yogurt with a few hundred extra calories of sugar mixed in, they eat significantly less of a meal offered ninety minutes later than they do when their morning yogurt doesn't have the added sugar. Not enough to account for all the extra sugar, mind you, but at least their bodies are trying to compensate. But when they're given the same number of extra calories in fat rather than sugar, there is no effect on subsequent meal intake; in fact, they eat a little more.¹⁴³⁷ The fat just didn't seem to induce the same braking effect on their appetites, or at least not in time.

So perhaps our bodies aren't so smart after all? They can only be as smart in the context in which they were designed. Snake a tube down someone's throat and secretly squirt some fat straight into their intestines, and their hunger can be slashed abruptly.¹⁴³⁸ Our bodies successfully sense the fat in our intestines and turn down our appetites. The problem is it happens too late. By the time high-fat foods make it through our stomachs and hit our intestines, we're usually already done eating. So what good are our bodies' detection mechanisms? Well, what kinds of high-fat foods were around during the millions of years our whole system was first evolving? Nuts. How fast can you eat walnuts in a shell? Even with a nutcracker in hand, it's slow going. So, in a natural context, our bodies can pick up on the fact we just stumbled on some nuts and make sure we don't overeat, but by the time our bodies sense we just ate that fat-infused yogurt or a donut, it's too late. We've already swallowed the last bite.

Dumping More Calories

So far, we've only talked about the calories-in side of the equation—how higher fat intakes can unintentionally lead to higher caloric intakes. When you think of calories out, expending energy, you likely think exercise, but the majority of the calories most of us burn is just from existing. That's what's called the *resting metabolic rate*, how many calories we burn every hour just to keep our hearts pumping and everything working. For most people, that's around 65 percent of the calories we burn every day.¹⁴³⁹ Another 25 percent is from movement, and the final 10 percent is the *thermic effect of food*, meaning the calories it takes for us to digest what we consume. Interestingly, what we eat not only constitutes calories in but also can affect all three of these dimensions of calories out.

Eat a low-fat diet (11 percent calories from fat), and you burn more calories in your sleep than when on a high-fat diet (58 percent).¹⁴⁴⁰ The difference could be as much as sixty-five calories a night, though measurements in this study were taken during overfeeding, which would be expected to exaggerate the effect. People on lower-fat diets may inexplicably start to move more too. Those randomized to a 20 percent fat diet started exercising more, expending eighty-three more calories a day on physical activity, whereas the group randomized to the 40 percent fat group started expending fifty-nine *fewer* calories a day.¹⁴⁴¹ Between them, that's a difference of about a two-mile walk a day.¹⁴⁴² This may help explain why those on the higher-fat diet lost significantly more *lean* body mass, down three pounds in six months compared to a gain in lean mass in the lower-fat group.¹⁴⁴³

At rest, we burn about one calorie a minute, which is comparable to the heat produced by a seventy-five-watt light bulb. After meals, that bulb burns a little brighter to handle what we just ate.¹⁴⁴⁴ Fat also appears to be absorbed more efficiently from the digestive tract, meaning it takes fewer calories to process it.¹⁴⁴⁵ A *really* low-fat diet (3 percent of calories from fat) costs about 65 percent more calories to digest than a high-fat diet (40 percent fat), so, in effect, you're doing more work just by eating low-fat, though the benefit may only come out to be about forty calories a day.¹⁴⁴⁶

In addition to the three primary components of calories out, there's actually a fourth component, and it's much more literal: the calories we poop out. Those eating low-fat appear to flush more calories down the toilet. Overeating on an 11-percent-calories-from-fat diet led to 620 more calories down the toilet every week than a same-calorie diet containing 58 percent calories from fat.¹⁴⁴⁷ That's nearly 2,500 fewer calories a month available for building up fat. Though calories in is the more important side of the equation, all these little benefits on the other side may add up to greater weight loss over time.

The Fat You Eat Is the Fat You Bear

In the Vermont prison studies I mentioned earlier where lean “volunteers” were overfed to study experimental obesity, the researchers made an important discovery: They learned how difficult it is to get people to gain weight on purpose—unless you feed them lots of fat. To get prisoners to gain thirty pounds on a mixed diet, it took about 140,000 excess calories per a certain body surface area. To get the same thirty-pound weight gain just by adding fat to their diets, all the researchers had to do was feed the prisoners as few as 40,000 extra calories.¹⁴⁴⁸ When the extra calories were in the form of straight fat, it took as many as 100,000 fewer calories to gain the same amount of weight. Why? Isn't a calorie a calorie? Why are our bodies so much more efficient at storing *fat* calories?

The reason our bodies so easily store fat as fat is because it's already fat. Our bodies can turn protein or carbs into fat, but it's costly. To store one hundred calories of dietary fat as body fat, it only takes three calories of energy, but converting one hundred calories of dietary carbs into fat for storage takes twenty-three calories.¹⁴⁴⁹ So, if your body wanted to store the fat from one hundred pats of butter, it would have to essentially burn three pats

to make it happen, so you'd end up only storing ninety-seven pats. But in order to store one hundred sugar cubes as fat, the conversion process alone would burn up nearly a quarter of them. This is why our bodies would rather burn carbs and store fat instead of the other way around. Simply stated, fat may be more fattening.¹⁴⁵⁰

When we eat a meal, most of the fat is deposited directly as fat on our bodies, whereas a large proportion of the carbs get stored in our muscles for quick energy.¹⁴⁵¹ A study on children found that a high-fat meal deposited nine times more fat onto their bodies than the same number of calories of a low-fat meal.¹⁴⁵² Where exactly does the fat go? Researchers at the Mayo Clinic tagged the fat in a meal with special isotopes to track its movement throughout the body. They had research subjects eat the tagged fat and then, twenty-four hours later, brought them into the operating room and took fat biopsies from their thighs, belly flab, and deep within their abdomens. Of the fat in the meal they could account for, about 45 percent was burned right off the bat, but most of the fat consumed was simply directed right into their fat stores. The researchers found that about 50 percent went straight into belly flab, 40 percent to their thighs, and most of the remaining went into visceral fat, the fat that's buried around our major organs.¹⁴⁵³ Under normal circumstances, less than 1 percent of ingested carbohydrates suffers the same fate based on similar studies of isotope-labeled sugar.¹⁴⁵⁴

Low-fat proponents often point out this fact, that making significant amounts of new fat from scratch from ingested carbs only occurs with "massive overfeeding"¹⁴⁵⁵ of, for example, a "diet consisted of candy."¹⁴⁵⁶ If you feed people an extra thousand calories of sugar a day, the equivalent of up to eleven bags of cotton candy,¹⁴⁵⁷ they do gain about four pounds in three weeks,¹⁴⁵⁸ but most of the extra carb calories end up being burned off as excess heat.¹⁴⁵⁹ If, however, you added an extra thousand calories of fat, like a stick or so of butter every day or a half cup of oil, most of that would be directly socked away and stored for a rainy day.¹⁴⁶⁰

Under more normal circumstances, even if less than 1 percent of the carbs in a meal end up as fat, that doesn't mean that carbs can't be fattening. Normally, our bodies burn fat around the clock at, interestingly, about the rate at which a candle burns. (Candles, after all, used to be made from animal fat.¹⁴⁶¹) Carbohydrates are the body's preferred fuel, so when we eat them, our bodies switch from burning fat to burning carbs, effectively snuffing out the candle for a few hours. So, while we can certainly gain weight from eating carbs, it's more from sparing our own fat from being used, rather than adding more fat directly.¹⁴⁶²

Is All Fat Just as Fattening?

If you were surprised to learn that, in some ways, fat calories are handled differently by the body from how carbohydrate calories are, you may be *really* surprised by the data suggesting that some types of fat calories are more fattening than others. I certainly was. There have long been studies linking greater saturated fat intake specifically with greater weight gain,¹⁴⁶³ but I always assumed it was just because it was a marker for poorer diets and lifestyles in general. After all, the top five sources of saturated fat in the United States are essentially cheese, desserts like cake and ice cream, chicken, pork, and then burgers.¹⁴⁶⁴

Interventional studies started to make things more interesting. If you switch people from a 38-percent-calories-from-fat diet down to a 28-percent-calories-from-fat diet, they lose body fat. Nothing too surprising there. But if you switch people from a 38-percent-fat diet of mostly saturated fat to a 38-percent-fat diet of mostly monounsaturated fat, like that of a more Mediterranean diet, they *also* lose body fat.¹⁴⁶⁵ The same number of calories and the same amount of fat—but a different type of fat—meant a different degree of weight loss.

One way researchers have switched people from a diet rich in saturated fat to a more Mediterranean diet is to swap out some meat and dairy for nuts and avocados. In this way, they would be eating the same amount of fat and calories, but suddenly, they'd also be eating significantly more fiber.¹⁴⁶⁶ In that case, when they lose more weight, how do you know it was the change in fat quality rather than the change in fiber quantity?

To determine if there's really a difference between fats, researchers designed a study where people ate essentially the same foods—different only by the kind of fat. They baked scones. Half were made with sunflower oil, and the other half with butter. The liver fat in the sunflower scone eaters went down, while the liver fat in the butter scone eaters went up.¹⁴⁶⁷

Is it possible it was less unsaturated fat versus saturated fat, and more plant fat versus animal fat? Dietary cholesterol may be one of the main factors associated with liver injury and the development of nonalcoholic fatty liver disease,¹⁴⁶⁸ which helps explain why those who eat even just a few eggs a week were found to have more than triple the odds of fatty liver disease.¹⁴⁶⁹ So how could you separate out that factor?

Researchers designed a study where people ate essentially the same foods, but, this time, different only by saturated versus unsaturated fat. Instead of scones, this time they baked muffins. Half were made with sunflower oil, and the other half with palm oil, a fat that is saturated, but, like all plant fats, free of cholesterol. Not only did the palm oil muffins result in significantly greater liver and total body fat, they produced twice as much visceral fat, the particularly harmful fat wrapped around our internal organs.¹⁴⁷⁰ On the saturated-fat diet, they also gained four times as much fat as lean tissue.¹⁴⁷¹ So saturated plant fats like coconut oil not only join animal fats in increasing heart disease risk¹⁴⁷² but may also play a role in the obesity epidemic.

One reason saturated fats may be more fattening is that they appear more likely to be stored immediately rather than burned. This was found in comparisons to both monounsaturated fats (in a match between olive oil and cream)¹⁴⁷³ and polyunsaturated fats (in a match between mostly safflower oil and lard).¹⁴⁷⁴ Oleic acid, the primary monounsaturated fat found in olives, nuts, and avocados, is burned promptly about 20 percent more readily than palmitic acid,¹⁴⁷⁵ the predominant saturated fat in the American diet, which is sourced mainly from meat and dairy.¹⁴⁷⁶ You can drip palmitic acid on muscle cells in a petri dish and openly demonstrate the suppression of fat utilization.¹⁴⁷⁷ But this difference is too small to account for the pounds of extra weight lost when these fats are switched in randomized controlled studies.

In the five hours following a breakfast with about four teaspoons of olive oil, research subjects burned about sixteen grams of fat.¹⁴⁷⁸ In the same five-hour period after eating essentially the same breakfast, but with the olive oil replaced with butterfat, only about thirteen grams of fat were burned. A pound of fat is 454 grams, so even if you burned 3 more grams of fat at every single meal, at the end of the month, you might only end up about a half pound lighter. But in a study where saturated fat was swapped for the same amount of mostly olive oil, people lost five pounds of fat in a month.¹⁴⁷⁹ Something else has to be going on.

Remember that thermic effect of food, the amount of energy spent digesting, absorbing, and storing a meal? Well, it apparently costs 28 percent more calories to process a meal containing walnuts and 23 percent more calories to process a meal containing olive oil than it does to process a meal with the same number of calories and fat but in the form of cheese and butter.¹⁴⁸⁰ That sounds like a lot, but our bodies are so efficient either way that it doesn't add up to much—maybe as few as twenty or so calories a day.¹⁴⁸¹ A similar increase of a few calories a day in resting metabolic rate has been noted in a trial comparing hazelnut oil to palm oil,¹⁴⁸² but, again, there appears to be a missing piece.

What About Virgin Coconut Oil?

Coconut oil, one of the latest internet sensations, is touted as a weight-loss “miracle” that “ACTUALLY Burns BELLY Fat!”¹⁴⁸³ If rats are given purified, medium-chain fatty acids, one component of coconut oil, they end up eating less food¹⁴⁸⁴—but does the same apply to people?

An open-label pilot study was published that suggested coconut oil could facilitate weight loss.¹⁴⁸⁵ “Open label”? That just means the participants knew what they were eating. They didn’t use any kind of placebo control. In fact, there was no control group at all. We’ve talked about the well-recognized effect in dietary studies where just being in a weight-loss study and under observation tends to lead to a reduction in caloric intake—because you know the researchers are looking over your shoulder and are going to put you on a scale.¹⁴⁸⁶ So you can’t tell from that kind of study what role—if any—the coconut oil played.

Enter a non-open-label study. When researchers pitted virgin coconut oil against a placebo control, the coconut oil did worse. Not only was there no difference in fat burning, the study subjects ended up hungrier after the coconut oil meal. Coconut oil was less satiating than the same number of calories of a control oil.¹⁴⁸⁷ It turns out coconut oil is just as fattening as other oils in terms of total, belly, or butt/thigh fat and may have adverse metabolic effects.¹⁴⁸⁸ Give people two tablespoons of coconut oil a day, and, compared to two tablespoons of soybean oil, no significant¹⁴⁸⁹ effect on weight or waistlines was found. What did happen, though, was a worsening of insulin resistance in the coconut oil group (despite being instructed to increase fruits and vegetables, cut down on sugars and animal fat, and exercise three hours a week).¹⁴⁹⁰ Coconut oil hawkers claim coconut oil is special because it contains medium-chain triglycerides, but MCTs only make up about 10 percent of the product.¹⁴⁹¹ Cholesterol-raising saturated fats like those found in beef tallow make up the bulk of coconut oil.¹⁴⁹²

If no benefit to coconut oil for obesity over placebo has ever been demonstrated, how can coconut oil proponents get away with saying otherwise? They often cite studies of Pacific Islanders who were slimmer eating their more traditional, coconut-based diets than those now eating more modernized diets with fewer coconut products.¹⁴⁹³ Guess what they were eating instead? “The modern dietary pattern [was] primarily characterized by high intake of sausage and eggs and processed foods.”¹⁴⁹⁴

Solving the Mystery of the Missing Calories

How can people lose five pounds of body fat in a month eating the same number of calories? Well, if calories in are the same, then it must be calories out. If you remember, there are four main components to calories out: resting metabolic rate, physical activity, the thermic effect of food, and fecal losses. We already determined the differences in resting metabolic rate and the thermic effect are insufficient, and there does not appear to be a difference in fecal losses between saturated and unsaturated fats.¹⁴⁹⁵ That just leaves one other outlet: exercise.

How could a different type of fat make people exercise more? Early studies offered a clue. Those randomized to meals with fat from olives, nuts, and avocados tended to feel significantly “more energetic” than those getting the same amount of fat from meat and dairy, suggesting the weight loss they experienced could have been “enhanced by subtle, unconscious, increases in physical activity.”¹⁴⁹⁶ You don’t know, of course, until you put it to the test.

Twenty-nine people were covertly randomized to one of two diets that appeared identical but featured different oil blends, one with palm oil and one with hazelnut oil. Same calories, same amount of fat, same diets, but the palm oil group was secretly slipped saturated fat in place of monounsaturated fat. Researchers then attached activity monitors on all the subjects to objectively measure how much they were moving. The study found that 90 percent of the subjects inexplicably ramped up their exercise when they were unwittingly eating the low-saturated-fat diet, increasing their activity levels 12–15 percent on average. The researchers concluded that a high intake of saturated fat “might dampen motivation for physical activity.”¹⁴⁹⁷

FOOD FOR THOUGHT

The take-home message is to cut down on fatty meats and dairy, fried foods, greasy snacks like corn chips, and added oils.

At first I was skeptical of oil-free cooking. So many of the dishes I made growing up started with sautéing garlic and onions, and how could you possibly bake without fat?

I was delighted to discover that cooking without oil is surprisingly easy. To keep foods from sticking in the pan, you can sauté in wine, sherry, broth, vinegar, or just plain water. The trick is to just use a little liquid at a time. I use dried mushrooms a lot and always make it a habit to save the soaking liquid. I find porcini mushrooms produce an especially rich, dark, savory broth that's perfect for my garlic and onions, and the added umami flavor makes it even easier to leave the salt out completely.

For baking, I've successfully substituted a variety of healthy whole foods in place of oil. Ground flaxseeds blended with water, applesauce, mashed bananas or avocado, soaked prune purée, and even canned pumpkin can provide a similar moistness. Vegetables roast just fine without added oil. I use a silicone baking sheet, but I hear parchment paper works as well. That's how I make my purple sweet potato fries. I spritz the wedges in apple cider or malt vinegar and dredge in coarse blue cornmeal seasoned with sage and smoked paprika. Now I'm getting hungry!

LOW IN ADDED SUGAR

Sugar Daddy

A founding member of Harvard's nutrition department recalled that the "meat, milk and egg producers were very upset"¹⁴⁹⁸ by the original *Dietary Goals for the United States*—and they weren't the only ones. The *Dietary Goals* encapsulate healthy eating advice from the federal government, and they named names when it came to foods Americans should cut down on. The president of the National Cattlemen's Beef Association explained that his industry "reacted rather violently" because "if these 'Dietary Goals' are moved forward and promoted in the present form ... entire sectors of the food industry—meat, dairy, sugar, and others—may be so severely damaged that ... recovery may be out of reach."¹⁴⁹⁹

Critics suggested the adoption of the *Dietary Goals* would be costly for taxpayers too. Because of more expensive groceries? No. Because "health care expenditures increase if the lifespan is prolonged." It's like when people quit smoking: "The increase in the expected lifespan would simultaneously increase the cost of care of old people."¹⁵⁰⁰ In other words, if people eat more healthfully and stop smoking, there may be more seniors, some of whom might need our care.

The president of the International Sugar Research Foundation called the report "unfortunate and ill-advised" and evidently part of an "emotional anti-sucrose [anti-table-sugar] tidal wave." As immortalized in the official record, he said: "Simply stated, people like sweet things, and apparently the [Senate] Committee believes that people should be deprived of what they like. There is a puritanical streak in certain Americans that leads them to become 'do-gooders.'"¹⁵⁰¹

By the time the World Health Organization (WHO) attempted to release a similar report decades later, Big Sugar had graduated from name-calling to flexing its political muscle. The WHO report, entitled *Diet, Nutrition and the Prevention of Chronic Disease*, contained six fateful words: "limit the intake of free sugars" (meaning added sugars). Within days, the sugar industry led a vicious attack, culminating in a threat to get Congress to withdraw U.S. funding to the World Health Organization entirely¹⁵⁰²—all because of those six words.

The threat from the sugar industry was described by WHO insiders as worse than any pressure they had ever gotten from the tobacco lobby.¹⁵⁰³ As revealed in an internal memo, the U.S. government apparently had a list of demands from Big Sugar that included the removal of all references to the science that WHO experts had compiled on the matter, as well as the call for the "deletion of all references to fat, oils, sugar and salt."¹⁵⁰⁴ In the United States, the food industry, like Big Tobacco before it, has had a corrosive effect on global public health efforts. When asked why Michelle Obama's childhood obesity programs in the United States should not be modeled around the world, a U.S. official responded that they might harm American exports.¹⁵⁰⁵

Sugarcoated Science

At least a dozen interventional studies document adverse metabolic effects of consuming added sugars, though this may be due largely to the accompanying weight gain spurred by sugar consumption.¹⁵⁰⁶ This has led sugar industry spokespersons, like the head of the World Sugar Research Organisation, to say things like “overconsumption of anything is harmful, including of water and air.”¹⁵⁰⁷ Yes, he compared the overconsumption of sugar to breathing too much.

This is a throwback to the well-worn tobacco industry script: They’re simply providing choices; they don’t condone the overuse of their products; and, if people fall ill after consuming it, the victims can only blame themselves.¹⁵⁰⁸ The reason this is disingenuous, of course, is that the tobacco industry works day and night to make their products as addictive as possible, just as the manufacturers of ultraprocessed foods like sugary breakfast cereals engineer their products to be as hyperpalatable as possible to maximize consumption.¹⁵⁰⁹

Why won’t cereal manufacturers reduce the amount of sugar in their products? A number of explanations have been offered, such as “a product with semi-addictive properties may be a safe way to ensure long-term revenues.... Another possibility is that selling cereals high in sugar is a smart technique to sell expansively a cheap commodity product—*sugar*.”¹⁵¹⁰ Ultraprocessed foods like breakfast cereals¹⁵¹¹ tend to have the highest profit margins.¹⁵¹² Remarkably, the cost of *packaging* may outweigh the cost of *ingredients* in a cereal box by more than ten to one.¹⁵¹³

Denying evidence that sugars are harmful to health seems always to have been at the heart of the sugar industry’s defense.¹⁵¹⁴ When the evidence is undeniable, though—like the link between sugar and cavities¹⁵¹⁵—the industry switches from denial to deflection, such as trying to refocus attention away from restricting intake to finding a vaccine against tooth decay. We seem to have reached a similar point with obesity, as the Sugar Bureau again dodges denial and rushes to deflect. It commissioned research suggesting losing weight was useless for extending life among “healthy” obese individuals¹⁵¹⁶—a stance strongly contradicted by hundreds of studies across four continents involving more than ten million participants.¹⁵¹⁷

The Bitter with the Sweet

The obesity epidemic may just be the tip of the iceberg in terms of excess body fat.¹⁵¹⁸ As I noted in the Causes section, more than 90 percent of adults and greater than two-thirds of the children in the United States are estimated to be “overfat”—that is, having excess body fat sufficient to impair health. This can occur even in people of normal weight (often due to excess abdominal fat). Added sugars have been blamed in part for this overfat epidemic.¹⁵¹⁹

A century ago, sugar was heralded as one of the cheapest sources of calories in the diet.¹⁵²⁰ Just ten cents’ worth of sugar could furnish thousands of calories. Sugar pushers bristled at the term *empty calories*,¹⁵²¹ asserting that the calories in sugar were “not empty but full of energy”—in other words, full of calories, of which we now get too many. The excess body weight of the U.S. population corresponds to about 350–500 excess daily calories on average,¹⁵²² which just so happens to be how many calories, on average, Americans failing to stay under the suggested sugar limits of the U.S. Dietary Guidelines get in added sugars every day.¹⁵²³ Maybe that’s a good place to start cutting calories?

Even the most die-hard sugar defenders—researchers who rely in part on sugary food and beverage industry funding for their livelihoods—agree that not only is it considered indisputable that sugars contribute to obesity but that it is “also undisputable that sugar reduction ... should be part of any weight loss program.”¹⁵²⁴ And that came from someone who was reportedly paid \$40,000 a month by the high-fructose corn syrup industry on top of the \$10 million it paid for his research.¹⁵²⁵ Of all sources of calories to limit, a “reduction

in consumption of added sugars should head the list because they provide no essential nutrients,"¹⁵²⁶ said researchers funded by the Dr Pepper Snapple Group and the Coca-Cola Company, including Richard Kahn, infamous for signing a million-dollar sponsorship deal with the world's largest candy company when he was chief science officer at the American Diabetes Association.

Not surprisingly, randomized controlled trials show that increasing sugar intake increases caloric intake,¹⁵²⁷ which leads to body weight gain in adults, while sugar reduction leads to body weight loss in children.¹⁵²⁸ When researchers randomized individuals to either increase or decrease their intakes of table sugar, the added-sugar group gained about three and a half pounds over ten weeks, whereas the reduced-sugar group lost about two and a half pounds.¹⁵²⁹ A systematic review and meta-analysis of all such ad libitum diet studies—that is, real-life studies where sugar levels are changed but people can otherwise eat whatever they want—found that reduced intake of dietary sugars resulted in a decrease in body weight, whereas increased sugar intake resulted in a comparable increase in weight. The researchers concluded that “considering the rapid weight gain that occurs after an increased intake of sugars,” it seems reasonable to advise people to cut down.¹⁵³⁰

Findings from observational studies have been more ambiguous, though, with an association found between obesity and sweetened beverage intake, but failing to show consistent correlations with sugary foods.¹⁵³¹ Most such studies rely on self-reported data, however, and obese people tend to underreport consumption of sugar-rich foods, *fudging* their data, if you will. Researchers can, however, measure trace sucrose levels in the urine to get an objective measure of actual sugar intake while excluding contributions from other sweeteners, such as high-fructose corn syrup. Using this method, researchers discovered that sugar intake is indeed not only associated with greater odds of obesity and greater waist size in snapshot-in-time cross-sectional studies but also in a prospective cohort study over time.¹⁵³² Using urinary sucrose as the measure of sucrose intake, those in the highest versus the lowest fifth for table sugar intake had more than 50 percent greater odds of being overweight or obese.¹⁵³³

Not Sweet Nothings

On April Fools' Day 1998, the FDA announced its approval of the artificial sweetener sucralose,¹⁵³⁴ sold as Splenda, aka 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside.¹⁵³⁵ Despite its scary-sounding chemical name, the worst thing about it seemed to be that it was a rare migraine trigger in susceptible individuals,¹⁵³⁶ to which the manufacturer of sucralose responded that you have to weigh whatever risk there may be against the “broader benefits,” such as “helping to mitigate the health risks associated with the national epidemic of obesity.”¹⁵³⁷

How's that going?

Large-scale population studies have found that the consumption of artificial sweeteners, particularly in diet sodas, is associated with increased weight gain and abdominal fat over time.¹⁵³⁸ Now, the obvious explanation for this finding would be reverse causation: Instead of drinking more diet soda leading to obesity, it would make more sense that obesity leads to drinking more diet soda. But even when researchers controlled for preexisting differences in body fat, they still found evidence of increased obesity risk.¹⁵³⁹

However, not all reviews of the science concluded there was a link between artificial sweeteners and weight gain. Can you guess which ones? An analysis of industry bias found that reviews funded by the food industry were seventeen times less likely to suggest unfavorable effects, and in nearly half of the sponsored reviews, the authors failed to even disclose their conflicts of interest.¹⁵⁴⁰ That's even worse than the sugar industry, whose studies were “only” five times as likely to question the link between sugar-sweetened beverages and obesity.¹⁵⁴¹ You don't really know, though, until you put them to the test.

Ironically, many of the interventional studies on artificial sweeteners and weight gain were executed by animal agribusiness, feeding them to farm animals to fatten them faster.¹⁵⁴² (Is there anything they won't feed to chickens?) Animal agriculture has been feeding artificial sweeteners to farm animals since the 1950s,¹⁵⁴³ boasting their addition “increases ... body weight gain and ... optimizes return on investment.”¹⁵⁴⁴ What about in people?

If you give obese individuals the amount of sucralose found in a can of diet soda, for example, they get significantly higher blood sugar and insulin spikes in response to a sugar challenge, suggesting sucralose is not just an inert substance.¹⁵⁴⁵ The Splenda company emphasizes that sucralose is hardly even absorbed into the body and

ends up in the colon to be eliminated.¹⁵⁴⁶ Therein may lie the problem.¹⁵⁴⁷ The adverse metabolic effects of artificial sweeteners correlate with “pronounced” changes in the microbiome that occur within a week of daily consumption.¹⁵⁴⁸

The good news is that after stopping artificial sweeteners, your original balance of gut bacteria can be restored within a matter of weeks.¹⁵⁴⁹ The problem is that we may be exposed without even knowing it. Nearly half of study participants randomized to avoid sucralose, for example, still turned up positive, thought to be due to exposure from nondietary sources, such as toothpaste and mouthwash.¹⁵⁵⁰

Another way artificial sweeteners can lead to metabolic disturbance is via the disconnect that develops between the amount of sweetness the brain tastes on the tongue and how much blood sugar actually ends up reaching the brain. Your brain may end up feeling cheated by the artificial sweeteners, figuring you have to consume more and more sweetness in order to get enough calories.¹⁵⁵¹ For example, researchers slipped people either Sprite, Sprite Zero (a no-calorie, artificially sweetened Sprite), or unsweetened, carbonated lemon-lime water, and then, later on, offered them a choice: They could have M&M’s, spring water, or sugar-free gum. Guess who picked the M&M’s? Those who drank the artificially sweetened soda were nearly three times more likely to take the candy than either those who had consumed the sugar-sweetened soda or the unsweetened drink.¹⁵⁵² So it wasn’t a matter of sweet versus nonsweet or even calories versus no calories. There appeared to be something about noncaloric sweeteners that tricks the brain into wanting more junk.

The same researchers performed another study in which everyone was given Oreos and then asked how satisfied the cookies made them feel. Again, those who had drunk the artificially sweetened Sprite Zero reported feeling less satisfied after eating the Oreos than either the subjects who had had normal Sprite or sparkling water. These results are consistent with brain imaging studies demonstrating that regular consumption of artificial sweeteners can alter the reward pathways responsible for the pleasurable response to food.¹⁵⁵³

What about the natural, plant-based sweeteners derived from stevia and monk fruit? Researchers randomized people to drink a beverage sweetened with sugar, aspartame, monk fruit, or stevia. Blood sugars were measured over twenty-four hours, and surprisingly, there was no significant difference found among any of the four groups.¹⁵⁵⁴

Wait a second. The sugar group was given sixteen spoonfuls of sugar, the amount in a twenty-ounce bottle of Coke, so the other three groups consumed sixteen fewer spoonfuls of sugar—yet all four groups still had the same average blood sugars? How is that possible? Table sugar causes a big blood sugar spike. Drink that bottle of sugar water with its twenty sugar cubes’ worth of sugar, and your blood sugars jump forty points over the next hour. In contrast, after drinking a beverage sweetened with aspartame, monk fruit, or stevia, nothing happens to blood sugars, which is what we would expect. These are noncaloric sweeteners. Since they have no calories, isn’t it just like drinking water? How could our daily blood sugar values average out the same? The only way that could happen is if the noncalorie sweeteners somehow made our blood sugar spikes worse later in the day—and that’s exactly what happened. In the group who drank the aspartame-sweetened beverage, even though their blood sugars didn’t rise at the time, they shot up higher an hour later in response to lunch, as if they had just consumed a bottle of soda.¹⁵⁵⁵

That was for an artificial sweetener, though. What about the natural sweeteners, stevia and monk fruit? The same thing happened. The same exaggerated blood sugar spike to a regular meal occurred an hour later. So that’s how it all equals out in terms of average blood sugars even though, in these three noncaloric sweetener groups, the subjects took in sixteen fewer spoonfuls of sugar. This is at least partly because they ate more. After drinking a Diet Coke, you’re more likely to eat more at your next meal than you would if you had drunk a regular Coke. In fact, you’d eat so much more that the calories “saved” from replacing sugar with noncaloric sweeteners would be fully compensated at subsequent meals, resulting in no difference in total daily caloric intake. It’s as if the zero-calorie sweetener groups—whether sweetened artificially or naturally—had chugged a bottle of sugary soda. So, when it comes to caloric intake, blood sugars, or insulin spikes, all the other sweeteners appeared just as bad as straight sugar.¹⁵⁵⁶

Do we have direct evidence that diet beverages can adversely impact body weight? Yes. If you swap out diet beverages for water, there theoretically should be no difference in weight control since they both provide zero calories, right? Well, when researchers put it to the test, overweight and obese individuals on a diet randomized to replace diet beverages with water lost significantly more weight, about 15 percent more over six months.^{1557,1558}

The researchers who demonstrated artificial sweeteners can disrupt our microbiomes and metabolisms recognized the irony of their findings. Though these food additives were introduced to reduce caloric intake and counter the obesity epidemic, they noted their findings suggest artificial sweeteners may have instead “directly contributed to enhancing the exact epidemic that they themselves were intended to fight.”¹⁵⁵⁹

Long in the (Sweet) Tooth

The industry is quick to point out that a calorie is a calorie, and an excess of calories from Coca-Cola would cause no more weight gain than the same excess of calories from carrots.¹⁵⁶⁰ While this may be true in a tightly controlled laboratory setting,¹⁵⁶¹ it doesn’t take into account the appetite-enhancing effects of sugar.¹⁵⁶² Remember the experiment where children were alternately offered high- or lower-sugar cereals? As I mentioned [here](#), surprisingly, Cheerios has a similar number of calories to Froot Loops (104 calories per cup¹⁵⁶³ versus 110,¹⁵⁶⁴ respectively). Had the kids eaten more Cheerios than Froot Loops, they could have gotten more calories, but the opposite happened. On average, the children

poured and ate 77 percent more of the sugary cereals. So even with comparable calorie counts per serving, sugary cereals may end up nearly doubling caloric intake.¹⁵⁶⁵

Millions of years of evolution have genetically hardwired us with both an innate liking of the sweet taste of ripe fruit ¹⁵⁶⁶ and a sugar-induced subversion of some of our satiety mechanisms.¹⁵⁶⁷ When we eat, desire for salty, fatty, and savory tastes diminishes as we slake our hunger, whereas our desire for sweetness is maintained.¹⁵⁶⁸ This makes sense. Because fruit is sporadic and seasonal, an overfeeding response upon discovering a berry bush would have triggered our hunter-gatherer ancestors to eat as much as possible to store energy for later.¹⁵⁶⁹ This may explain why we seem to grow a “second stomach” when it comes to dessert. Children may be especially vulnerable since they have a stronger preference for sweet foods than adults,¹⁵⁷⁰ and repeated exposures to sugary foods may accustom young children to a lifelong habit of consuming overly sweet foods.¹⁵⁷¹

In recent years, much has been learned about the reinforcing effects of sugar and how it can promote overeating.¹⁵⁷² Evidence supports the thinking that we don’t just overeat sugar because we like its sweet taste.¹⁵⁷³ As I note in the Low in Addictive Foods section, innovations in brain scanning technology have shown that the pleasure-generating reward circuitry in our brains overlaps with the neurocircuitry that mediates the addictive properties of drugs like alcohol and opioids. Sugar consumption has also been shown to inhibit anxiety-induced cortisol (stress hormone) secretion, helping to explain why many “comfort foods” are high in sugar and also why excessive sugar consumption may be such a difficult habit to break.¹⁵⁷⁴

How Much Is Too Much?

At the time of the American Revolution, we consumed about an estimated four pounds of sugar per person per year.¹⁵⁷⁵ Now, we may each average more than fifty pounds annually.¹⁵⁷⁶ That’s the equivalent of about seventeen teaspoons of added sugars every day.

The excessive consumption of added sugar is a systemic problem that extends far beyond just a small group of individuals making poor dietary choices.¹⁵⁷⁷ In the United States, individuals in every single age bracket exceed the U.S. Dietary Guidelines’ recommended limit of no more than 10 percent of calories from added sugars. The average American exceeds the guideline by more than 30 percent,¹⁵⁷⁸ and adolescents exceed it by 60 percent.¹⁵⁷⁹

Though the Sugar Association describes the maximum limit as “extremely low,”¹⁵⁸⁰ let’s not forget that there is no dietary requirement for added sugars at all.¹⁵⁸¹ The American Heart Association went further, recommending that most American women should get no more than 100 calories per day from added sugars and most American men no more than 150.¹⁵⁸² This comes out to be about 6 percent of calories,¹⁵⁸³ with recommendations for some demographics falling as low as 3 percent.¹⁵⁸⁴ Currently, approximately nine out of ten Americans are exceeding these recommendations.¹⁵⁸⁵

In 2017, the American Heart Association released its guidelines for children, recommending they get no more than 100 calories of added sugars per day (and none for those under age two).¹⁵⁸⁶ For a teenager expending 2,500 calories a day, that represents a limit of fewer than 5 percent of calories from added sugars. Sugary breakfast cereals alone violate these limits in up to 30 percent of toddlers.¹⁵⁸⁷ An average serving¹⁵⁸⁸ of every single one of the top ten breakfast cereals marketed to children would take up more than half the daily sugar limit,^{1589,1590} and there are nearly one hundred cereals on the market for which a single serving would push kids up and over the limit.¹⁵⁹¹

The United States is one of at least sixty-five countries that have implemented dietary guidelines or public health policies to curb sugar consumption.¹⁵⁹² In the United Kingdom, the Scientific Advisory Committee on Nutrition made recommendations to reduce calories

from added sugars down to 5 percent,¹⁵⁹³ consonant with the American Heart Association and the latest conditional recommendation from the World Health Organization,¹⁵⁹⁴ whose policy-making process is protected from industry influence.¹⁵⁹⁵ That means a single can of soda could easily take us over the top for the day.¹⁵⁹⁶

FOOD FOR THOUGHT

Note that none of these recommendations to cut down on added sugars applies to fruit. As you'll read in the Rich in Fruits and Vegetables section, fruit can actually facilitate weight loss. If you randomize people to a diet low in all sugars, even the naturally occurring sugars in fruit, they do worse than those randomized to just cut down added sugars. Those who retained fruit in their diets lost nearly 50 percent more weight.¹⁵⁹⁷

For those of you who have a sweet tooth like I do, all hope is not lost. The same palate-changing effects on your taste thermostat found after cutting down on salt and fat also work with cutting down on sugar. Put people on a sugar-free challenge for two weeks, removing all added sugars and artificial sweeteners, and by the end of the trial, up to 95 percent said "sweet foods and drinks tasted sweeter or too sweet, and ... said moving forward they would use less or even no sugar."¹⁵⁹⁸ Most stopped craving sugar within the first week.

LOW IN ADDICTIVE FOODS

Gut Instincts

Food tastes good for the same reason sex feels good. We wouldn't last very long as a species without both. Without pleasure centers and reward pathways in our brains incentivizing our efforts, we might not have sufficient drive to seek out either. Hunting and gathering take a lot of work. No surprise, then, that our appetites and food cravings are governed in part by the "feel good" messengers in our brains: dopamine (the "reward hormone"), serotonin (the "happiness hormone"), oxytocin (the "love hormone"),¹⁵⁹⁹ endorphins (our own body's natural opioids), and endocannabinoids (our bodies' natural cannabis compounds—think of the "munchies" effect).¹⁶⁰⁰

Dopamine release is such an important motivator of food intake that animals genetically engineered to be unable to make dopamine simply starve themselves to death.¹⁶⁰¹ Food just doesn't seem to do much for them. Too much dopamine release, however, may lead to overeating.

Hijacking Our Natural Drives

Not all foods are equally rewarding. If you perform PET scans of people's brains after they eat different meals, you can show that dopamine release is greatest in response to foods people like the most,¹⁶⁰² which tend to be foods high in salt, sugar, and fat. We evolved for millions of years in an environment where sodium was scarce, so a taste for saltiness used to give us a survival advantage. Calories were sometimes scarce, too, but we didn't need nutrition labels to tell us which foods had more energy. Our taste for sweetness led us to ripe fruit, and our taste for fat drew us to nuts and seeds. Simple survival skills we developed over millions of years. The food industry, however, has hijacked these natural drives and turned them against us.

Ever find yourself eating even when you're no longer hungry and then continuing to eat even when you know you should stop? Taste engineers manipulate the salt, sugar, and fat contents of foods to achieve what's referred to in the industry as the *bliss point*, the peak of craveability.¹⁶⁰³ These days, food is designed so we "can't eat just one." Hyperpalatable foods can overstimulate our reward pathways, not only overriding our normal satiety signals but potentially our better judgment as well.¹⁶⁰⁴

Brain areas activated just by the *smell* of foods like potato chips, ice cream, roast beef, and cake are similar to those activated by addictive substances like alcohol.¹⁶⁰⁵ Drugs,

whether illicit or legal, may in effect be co-opting brain circuitry originally designed for seeking healthy foods. The reason we may be so vulnerable to such compulsions is that our brains are just not designed to cope with omnipresent access to drugs, video games, pornography, and snack foods.¹⁶⁰⁶

There's been an exponential increase in scientific publications on food addiction in recent years,¹⁶⁰⁷ spurred by a study entitled "Intense Sweetness Surpasses Cocaine Reward."¹⁶⁰⁸ Researchers found that when rats were allowed to choose between sugar-sweetened water or intravenous cocaine, nine out of ten chose the sweet taste over one of our most addictive drugs.

People have been chewing coca leaves for at least eight thousand years ¹⁶⁰⁹ as a mild stimulant without any evidence of addiction, but when certain components in the plant were isolated and concentrated into cocaine, it became a different story.¹⁶¹⁰ Just like with many drugs of abuse, salt, sugar, and fat are substances found in nature, but they exist naturally in much smaller concentrations and may only become problematic when extracted and concentrated by modern industrial processes.¹⁶¹¹ Only when the coca leaf is processed into a concentrated form for rapid delivery, such as cocaine and crack, does it become highly addictive. Similarly, the sugarcane stem has been chewed for its pleasant taste for ages,¹⁶¹² but it only presents a disproportionate reward signal once highly refined into added sugars¹⁶¹³ with the potential to override our self-control mechanisms and, thus, lead to analogous addictive-type behaviors.¹⁶¹⁴ From the medical journal *Current Drug Abuse Reviews*:

*First, highly processed foods and drugs of abuse are both capable of triggering cravings. Second, consumption of highly processed foods and drugs of abuse can both be associated with compulsive overuse in the face of severe negative consequences. And finally, in some individuals there is evidence of chronic relapse and an inability to cut down consumption of both substances.*¹⁶¹⁵

Certainly, there are lots of people who eat sweet, salty, and greasy foods yet don't exhibit addictive eating behaviors, but the same is true of addictive drugs. Only about one in seven people who try cocaine goes on to develop a cocaine addiction.¹⁶¹⁶ Some have contended that food addiction cannot exist because we *have* to eat, but that's like arguing alcoholism can't exist because we *have* to drink.¹⁶¹⁷ Yes, we have to drink, but we don't have to drink alcohol. Yes, we have to breathe, but we don't have to breathe tobacco. And yes, we have to eat, but we don't have to eat junk.

The Frosting Effect

The brain-imaging evidence supporting the concept of food addiction is bolstered by data from pharmaceutical trials that manipulate reward pathways. When researchers gave people the opiate-blocking drug naltrexone (similar to the drug Narcan used to reverse opioid overdoses),¹⁶¹⁸ the research subjects rated sweets as not tasting as good¹⁶¹⁹ and were found to consume fewer cookies.¹⁶²⁰ Narcan itself reduces the consumption of chocolate cookies, but not an unprocessed, whole-food source of sugar (orange fruit segments).¹⁶²¹ Given over a period of days, opiate blockers can decrease the calories consumed at all-you-can-eat meals by obese individuals by 30 percent.¹⁶²²

These Narcan-type studies suggest sugar consumption causes the release of endorphins.¹⁶²³ This would explain the more than one hundred randomized controlled studies on the pain-relieving effects of a little sugar water for infants undergoing painful procedures such as vaccinations¹⁶²⁴ (though it was not found effective enough for the pain of circumcision).¹⁶²⁵

Fat appears to have a similar effect on the brain as sugar. Feed people yogurt packed with butterfat, and within thirty minutes, they exhibit similar brain activity changes ¹⁶²⁶ to those who had just drunk straight sugar water.¹⁶²⁷ In the largest study of food addiction to date, involving more than one hundred thousand women from the Harvard Nurses' Health Study, greasy foods—hamburgers, french fries, and pizza—were the types of fare most linked to food addictions.¹⁶²⁸

So which is worse: fat or sugar? The answer is *both*. As it turns out, opiate-blocking drugs work best not for sugary foods like jelly beans but for foods that combine sugar and fat.¹⁶²⁹ The combination of sugar with fat creates a “hedonic synergy.”¹⁶³⁰ Think ice cream, candy bars, and donuts. Few folks may sit down to enjoy a bowl of straight sugar or a tub of shortening, but put them together and you have frosting! The sugar can act as a vehicle for fat intake and vice versa. Obese compared to lean individuals have similar pleasure responses to sugar solutions like Kool-Aid, but appear to have a heightened response to sweet foods that are also rich in fat.¹⁶³¹ The “sweet tooth” link to obesity may be more of a “sweet-fat tooth.”¹⁶³² If you follow people's chosen diets, the best predictor of overeating and weight gain in children, adolescents,¹⁶³³ and adults may be the selection of high-fat, high-sugar foods.¹⁶³⁴

In nature, while there are foods that contain sugar (like fruit) and foods that contain fat (like nuts), sugar and fat rarely occur in the same food naturally.¹⁶³⁵ There is one, and it's the most natural food of all. Can you think of it? *Breast milk*. Maybe that's why high-fat, high-sugar foods are so addictive. We wouldn't last long as a species if babies didn't crave breast milk. Some have speculated that much of the success of both low-fat and low-carb diets may be from the elimination of these high-fat, high-sugar mixtures that we're programmed to crave.¹⁶³⁶

It's All in the Process

Why don't we crave trail mix as much?¹⁶³⁷ That's about as sugary and fatty as natural foods get. The key appears to lie in the processing, which increases the dose and speed of absorption of the sugar and fat. Hard liquor is more addictive than beer because of the dose, and crack is more addictive than cocaine because of the speed of absorption. Food processing can increase both simultaneously, delivering high loads of concentrated sugar and fat, while, at the same time, stripping away fiber, protein, and water to maximize the rate of absorption.¹⁶³⁸

In the landmark study published in 2015 entitled “Which Foods May Be Addictive?” that I mentioned in the Low Glycemic Load section, dozens of foods were ranked based on reports of problematic, addictive-type behaviors from hundreds of individuals. The two most troublesome were high-fat, high-sugar combos: chocolate and ice cream. Most at the top of the list were high in fat, but every single one of the top fifteen was a processed food. In contrast, all the foods least likely to be associated with addictive behaviors were unprocessed. The bottom ten least-addictive foods were strawberries, apples, corn, salmon, bananas, carrots, brown rice, cucumbers, broccoli, and beans.¹⁶³⁹

This was finally put to the test for weight control in 2019. Study subjects were presented with the same amounts of calories, salt, sugar, fat, carbs, protein, and fiber in processed versus unprocessed forms, such as a breakfast of cereal and a muffin versus oatmeal with fruit and nuts. Over a two-week period, those randomized to eat the processed foods gained two pounds, whereas those randomized to unprocessed foods lost two pounds. The researchers concluded that “limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment.”¹⁶⁴⁰

Processed food manufacturers may also insert flavor-enhancing additives like sodium to further manipulate the reward value,¹⁶⁴¹ reminiscent of tobacco industry additives to enhance nicotine delivery and flavor¹⁶⁴²—including added fat, sugar, and salt.¹⁶⁴³ One of the

dietary changes noted during opioid detox is an increase in salted foods, perhaps to tap into the same reward pathways.¹⁶⁴⁴ In one sense, we have no control over most of the sodium we're exposed to since more than two-thirds of sodium intake comes not from the saltshaker at home but from salt added to packaged foods and dishes in restaurants.¹⁶⁴⁵ In another sense, however, most of us actually have total control, as we can choose to buy fewer processed foods and eat out less.

Eaten Away

The eating habits of Americans have been described as “eat[ing] breakfast in their cars, lunch at their desks and chicken from a bucket.”¹⁶⁴⁶ Most of us eat out at least three times a week¹⁶⁴⁷ and average an extra two hundred or so calories on the days we do, all while taking in less nutrition.¹⁶⁴⁸ The blood levels of nearly all examined micronutrients were lower among those who ate more meals out, largely reflecting a drop in the consumption of plant foods.¹⁶⁴⁹ This may be a particular problem at fast-food restaurants. A modern-day case of scurvy was even diagnosed in someone on a “strict fast food diet.”¹⁶⁵⁰

Little has changed in recent years to improve the quality of fast-food restaurant menus. (The one exception is the removal of partially hydrogenated oils, thanks to the trans fat ban, but not all trans fat has gone away—cheeseburgers are now worse offenders than fries, due to the inherent trans fat in meat and dairy.¹⁶⁵¹) Those who eat out more often in general tend to be at greater risk of becoming overweight or obese, and this appears to particularly be the case for fast food.¹⁶⁵² People who eat more fast food also tend to eat more unhealthfully in general, though—more meat, white bread, and sweets—so rather than fast food leading to bad eating habits, bad eating habits may lead people to fast food.¹⁶⁵³

An estimated three-quarters of adolescents eat fast food on a weekly basis, a dramatic rise over the last fifty years.¹⁶⁵⁴ What role might this play in the obesity epidemic? Teens were seated in a food court and allowed to eat as much as they wanted of a typical fast-food meal. If you assume three meals a day and a couple of snacks, you would want to stay under about 30 percent of your daily energy requirements in any one meal, which, in the case of these teens, came out to be just under 800 or so calories. Fast food, however, is so high in calorie density, so high in fat and sugar, and so low in fiber that they ended up eating an average of 1,652 calories at that one meal.¹⁶⁵⁵

Is it just the supersized portions and rapid eating rate intrinsic to the fast-food business model? The same researchers set up another experiment in which they portioned out a fast-food meal of chicken nuggets, french fries, and cola into smaller servings presented at fifteen-minute intervals to prevent gorging. It didn't work. In the end, the teens ended up eating the same amount, basically filling their stomachs to physical capacity.¹⁶⁵⁶

The industry spends nearly \$2 billion marketing these kinds of foods to children and adolescents.¹⁶⁵⁷ Maybe the nutrition profession would be more vocal in their disapproval if they stopped allowing their conferences to be sponsored by the likes of McDonald's and Coca-Cola.¹⁶⁵⁸ Just a thought.

Buzzkill

Fast-food meals frequently contribute a fourth addictive factor to the salt, sugar, and fat trifecta by adding caffeinated drinks. In response to a proposal to ban the use of caffeine as a food additive, soda manufacturers claimed it was not used to make their products more addictive but rather as a “flavoring agent.”¹⁶⁵⁹ When put to the test, though, even highly trained subjects could not detect a difference in taste between soda with and without caffeine.¹⁶⁶⁰ Given that, the more plausible explanation is that caffeine is added to produce physical dependence, which in turn encourages repeat purchases by consumers, many of whom are children.¹⁶⁶¹

Caffeine has a well-known reinforcing effect. It creates a Pavlovian connection between whatever behaviors the body associates with it, from experimentally conditioning one's choice of color-coded capsules¹⁶⁶² to changing flavor preferences.¹⁶⁶³ No wonder the food industry started adding caffeine not just to soda but to everything from ice cream and candy bars to beef jerky and potato chips.¹⁶⁶⁴ Even bottled water and instant oatmeal have been spiked.¹⁶⁶⁵

The phenomenon of caffeine reinforcing whatever behaviors we're up to when we're exposed to it brings up an interesting point: Caffeine is a problem when it's used by the soda industry to hook our kids on liquid candy, but anything that gets people to eat more oatmeal could flip the whole risk-versus-benefit equation. It makes me think we should start drinking our green tea with broccoli. Maybe that will get us to start craving greens!

Change Your Palate's Palette

The obesity epidemic has been blamed on the abundance of "palatable hyper-caloric" foods¹⁶⁶⁶—in other words, high-calorie foods that taste good. After all, as one medical journal editorial put it, "Yummy food is made from fat and sugar."¹⁶⁶⁷ So is the answer to just not eat anything tasty? No. As I detail in the conclusion of *How Not to Die*, you can actually change your taste buds and end up with the best of both worlds: tastes great *and* more filling.

One pharmacology journal review concluded that we "need to find ways to restrain compulsive intake of palatable food."¹⁶⁶⁸ It suggests opiate-blocking drugs, but you can imagine jaw-wiring or stomach-stapling would have the same desired effect. The underlying assumption is that palatable food equals unhealthy food, which is only true because the food industry has so deadened our palates with hypersalty, hypersweet, hyperfatty foods. The ripest peach in the world may taste sour after a bowl of Froot Loops. The good news is that studies show the more we eat healthy foods, the more we come to like them.¹⁶⁶⁹

The original taste-changing studies were done on salt reduction. Switch people to a low-salt diet, and everything may taste like cardboard at first.¹⁶⁷⁰ You can imagine the study subjects thinking they could never live like that. But then it happened. Over the ensuing weeks, they liked the taste of salt-free soup more and more, and the taste of salty soup less and less. Our tastes physically change. Let them salt their own soup to taste, and they added less and less the longer they were on the low-salt diet and began to prefer it that way. By the end, soup tasted just as salty with half the salt. The longer we eat healthier foods, the better they taste.

Surprisingly, we can change our sixth sense too. You've probably heard of the five basic tastes: sweet, sour, bitter, salty, and savory. It turns out there are indications our taste buds can register the taste of fat as well.¹⁶⁷¹ This may help explain why people on low-fat diets start liking low-fat foods more and high-fat foods less.¹⁶⁷² The less fat we eat, the more sensitive to fat our tongues appear to become, which may translate into people spontaneously reducing their intakes of butter, meat, dairy, and eggs.¹⁶⁷³ Salt may override this effect,¹⁶⁷⁴ though, so it may be important to cut down on both simultaneously.

It's all about resetting our taste thermostats. The average life span of a taste bud cell may only be about 250 hours.¹⁶⁷⁵ That means each of our taste buds could get replaced every ten days or so. This makes sense since they are constantly being assaulted by everything from burning-hot liquids to normal everyday abrasion by our teeth, food, and the roofs of our mouths. Though much of the change in taste perceptions is presumably higher up in our brains, it may be helpful to reflect that our taste buds are basically reborn anew every few weeks, giving us another chance for a fresh start.

FOOD FOR THOUGHT

There have been times when someone happens to see me eating something simple like a sweet potato, and they look at me as if I'm some type of ascetic monk. "Good for you," they might say, "but I could never eat that way." They think I'm living a life of deprivation. Far from it. They don't understand that a sweet potato really tastes good to me (and with a little sprinkle of cinnamon, it tastes even better!). Natural foods as grown can be delicious, but only after you've escaped the numbing shackles of industry manipulations to deaden your senses. I realize the thought of eventually savoring something like corn on the cob without butter or salt may sound ridiculous to some. You won't believe it until you try it out for yourself: Cut out processed foods for a few weeks, and you'll be amazed how good healthy can taste.

LOW IN CALORIE DENSITY

Solving the Mystery of the Obesity Epidemic

One of the key questions we've been trying to address is: *What's behind the explosion in obesity rates over the last few decades in the United States?* Well, we know that if we're to believe the food industry, the blame falls on our inactivity. Remember those leaked internal emails that evidently showed that Coca-Cola spent more than a million dollars covertly creating the Global Energy Balance Network to emphasize exercise over consumption to "serve as a 'weapon' to 'change the conversation' about obesity in its 'war' with public health"?¹⁶⁷⁶ But as I covered [here](#), if anything, physical activity may have actually even gone *up* since the 1980s.¹⁶⁷⁷ There's little mystery as to the primary cause of the obesity epidemic: We're consuming more calories.¹⁶⁷⁸

It's hard to track actual food consumption on a population scale, but you can monitor the food supply and how much is produced per person, taking into account imports and exports, as well as adjusting for food spoilage and waste. When you look at the number of calories produced per capita in the 1970s compared to the 2000s, the difference is more than enough to explain the obesity epidemic.¹⁶⁷⁹

Based on how many more calories kids appear to be eating these days, we'd expect them to weigh an average of about nine pounds more now than back when they were riding Big Wheels and banana-seat bikes, and that's exactly the case. The numbers add up. The prediction based solely on estimated increased caloric intake matches perfectly with how much heavier our children have become.¹⁶⁸⁰

Grown-ups have grown bigger too. Given the greater number of calories U.S. adults appear to be eating nowadays, we'd expect to weigh an average of about twenty-four pounds more than we did back in the 1970s, but we're actually only about nineteen pounds heavier.¹⁶⁸¹ So we're not as fat as one might expect based on increased calorie availability estimates, but this may be due in part to us wasting a greater proportion of food these days.¹⁶⁸² Regardless, the increase in calories we consume could easily account for our expanding waistlines.

To return to the average body weight of the 1970s, American children would need to eat about 350 fewer calories each day, which is about a can of soda and a small order of fries, and adults would need to cut back about a Big Mac's worth, which is about 500 calories (or take a brisk, daily two-hour walk).¹⁶⁸³

Was America Supersized?

Just because we're eating more calories doesn't necessarily mean we're eating more food. The calories in what we're eating these days may just be more concentrated. Theoretically, the estimated 20 percent more calories we're getting now could simply mean we're getting an average of 20 percent more calories per bite.

Portion sizes have gone up, though. From the 1970s to the 1990s, the average cheeseburger went from 5.8 to 7.3 ounces, the average portion size of salty snacks grew from 1.0 to 1.6 ounces, and the average soft drink increased from about 13 to nearly 20 fluid ounces.¹⁶⁸⁴ What's more, larger portions do seem to translate into larger intake, even if we don't take that last bite or final sip—so size does matter. Give moviegoers popcorn in a bucket, and they eat about 50 percent more than when they're served the same popcorn in a smaller (but still excessively sized) box.¹⁶⁸⁵ In a candy experiment, people given one-pound bags of M&M's reportedly ate 120 candies while watching a video compared to those given a half-pound bag who only ate 63.¹⁶⁸⁶

On a population scale, the increased portion sizes, along with increased eating frequency throughout the day, do appear to account for most of the national increase in caloric intake.¹⁶⁸⁷ On an individual basis, however, calorie concentration can trump portion size.¹⁶⁸⁸ Decrease by 33 percent the *size* of an extra-large serving of pasta, and people eat about 10 percent less, but decrease by 33 percent the calorie *concentration* of the sauce for a broccoli, cauliflower, and tomato purée by replacing some of the cream and cheese, and the decrease in calorie consumption is nearly three times greater.¹⁶⁸⁹

Obese individuals don't necessarily eat a greater weight of food, but the foods they choose do tend to have more calories per mouthful.¹⁶⁹⁰ So excess intake may have more to do with food quality than quantity. Overeating may be less about consuming an abnormal amount of food and more about consuming an abnormal type of food: meals that are unnaturally dense in calories.

How Many Calories Can You Stomach?

Our stomachs are only so big. Once we fill them up, stretch receptors in our stomach walls tell us when we've had enough. Given this limit, if you wanted to gain weight, how could you do it? Well, you could eat more frequently. Alternatively, you could increase the number of calories in each stomach-load by changing what you eat—that is, by changing calorie density, the number of calories for a given weight or volume of food.

Some foods have more calories per cup, per pound, per mouthful than others. Oil, for example, has a high calorie density, which means it has a high calorie concentration with lots of calories packed in a small space. Drizzling just one tablespoon of oil on a dish adds 120 calories.¹⁶⁹¹ For those same 120 calories, you could eat about two cups of blackberries, a food with a low calorie density.¹⁶⁹² You could swig down that spoonful of oil and not even feel a difference in your stomach, but eating a couple of cups of berries could start to fill you up.

A handful of jelly beans has about sixteen times more calories than a handful of cherry tomatoes.^{1693,1694} So for the same number of calories, you could eat that one handful of jelly beans or about four cups of cherry tomatoes. A large serving of french fries is about the same size and weight as a baked potato but has about four times more calories.^{1695,1696} So for the same number of calories, you could have that single serving of fries or around four baked potatoes. Which do you think would be more filling?

The average human stomach can expand to fit about a quart of food,¹⁶⁹⁷ which is around four cups. A single stomachful of strawberry ice cream, about two pints, could max out our caloric intake for an entire day.¹⁶⁹⁸ What if you wanted to get those same two thousand or so calories from strawberries themselves? You'd have to eat forty-four cups of berries.¹⁶⁹⁹ That's eleven stomachfuls. As delicious as strawberries are, I don't think I could fill my stomach to bursting eleven times in a day. Some foods are just impossible to overeat. They are so low in calorie density that you just couldn't physically eat a big enough quantity to maintain your weight.

On the next page is an infographic of how many stomachfuls of food you would need to eat in a day to get two thousand calories.

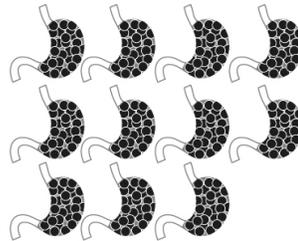
Zucchini is even less calorie dense than broccoli. You could eat 100 cups of sliced zucchini a day and still lose weight.¹⁷⁰⁰ The calories in cucumbers are so dilute you'd have to eat more than 150 cups a day to gain weight¹⁷⁰¹ and more than 250 cups of chopped kale.¹⁷⁰² You just couldn't do it. That's the magic of nonstarchy vegetables and fruit. You could be filled to the brim with fresh fruit three times a day and still lose weight because they're mostly water and air. An apple, for example, is 85 percent water by weight and 20 percent air by volume (which is why you can bob for them on Halloween).¹⁷⁰³

At the other extreme, there are pure fats like butter and oil that are so calorically dense you could exceed your total calorie input for the day filling up your stomach only a quarter of the way just once. So, hundreds of cups of vegetables or a single stick of butter? Hopefully no one is eating butter by the stick—this is just to illustrate how leaning toward the lower-calorie-density foods on average could enable you to eat the same amount of food, or even more, and still lose weight.

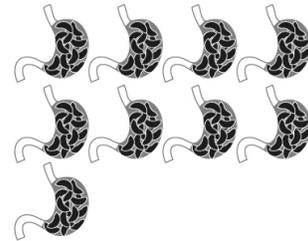
Stomachfuls to Fit 2,000 Calories



chopped broccoli



watermelon balls



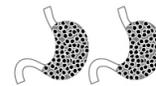
apple slices



sweet potato cubes



oatmeal



chickpeas



eggs



tuna



chicken



cashews



cheese



m&m's



cookies



butter

On average, those who eat low-energy-density diets consume hundreds of fewer calories, yet they eat significantly more food, about three-quarters of a pound more a day.¹⁷⁰⁴ Most weight-loss diets focus on decreasing portion size, but we know “eat less” approaches can leave people feeling hungry and unsatisfied.¹⁷⁰⁵ Shifting the emphasis from

restriction to positive “eat more” messaging of increasing intake of healthy, low-energy-density foods may offer a more promising strategy.¹⁷⁰⁶

Apes vs. Twinkies

It’s ironic that the method used to achieve rapid weight gain in malnourished children—frequent, high-calorie-density meals—has become the de facto norm for many children (and adults) today.¹⁷⁰⁷ In the study about fast food that I explored in the Low in Addictive Foods section, the teens, when presented with an unlimited fast-food lunch, piled in an average of 1,652 calories in just one meal.¹⁷⁰⁸ The propensity to overeat isn’t limited to fast food, of course, but even if you stuffed yourself to the brim with foods low on the calorie density scale—like vegetables, fruits, whole grains, and beans—you wouldn’t reach anywhere near that caloric load.

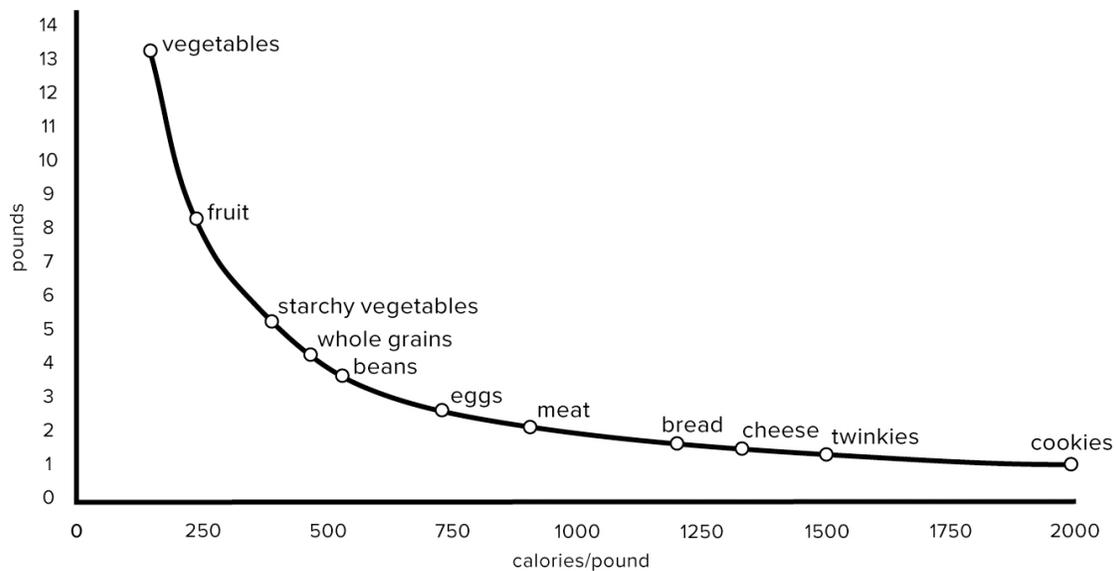
Fast food averages about 1,200 calories per pound,¹⁷⁰⁹ whereas traditional African diets, which more closely represent the likely diet of our ancient ancestors, average fewer than 500 calories per pound.¹⁷¹⁰ So the biological mechanisms our bodies use to regulate our weight likely evolved in the context of eating at least four or five pounds of food a day. That may be the more natural amount of food to eat. If your body is counting on eating five pounds of food but you max out with the same number of calories eating just two pounds of modern convenience food, what do you think happens? It’s no wonder we overeat—our bodies are expecting three more pounds of food! Our bodies just weren’t designed to handle such calorie-concentrated diets.

It makes evolutionary sense that we crave calorically dense foods. Put kids in a brain scanner, and you can see greater reward center activation when they view pictures of foods with higher calorie density.¹⁷¹¹ We’ve been hardwired by eons of periodic scarcity to seek out the greatest caloric bang for our foraging buck.¹⁷¹² In a primitive setting, that motivation would drive us toward picking the ripest fruits and digging up the starchiest roots, but now, that same biological drive compels us toward processed junk heaviest in added sugars and fats.

Traditional grain-based diets represent what we’ve been eating for thousands of years before the Industrial Age, but if you go back millions of years to the dawn of humanity, we likely ate more like contemporary great apes, with whom our DNA still differs at most by only a few percent. This means a diet centered around leafy vegetables, shoots, roots, berries and other fruits, seeds, and nuts.¹⁷¹³ Researchers at the University of Toronto decided to try putting people on just such an ape diet. Even after including higher-calorie-density foods like nuts, research subjects had to eat twelve pounds of food a day to maintain their weights.¹⁷¹⁴ So it seems very likely our appetite control mechanisms evolved eating massive quantities of food. Our bodies never expected to meet a Twinkie.

How much food does it take to reach 2,000 calories at different caloric densities? As you can see in the graph below, you would need to eat eight pounds of food a day on a low-calorie-density diet of 250 calories per pound, whereas on a high-calorie-density diet, you’d have to restrict yourself to eating four times less food.

What happens when you go back for seconds? On a low-calorie-density diet, an extra helping might only add a few dozen calories, whereas, at the higher end, the same helping could add hundreds. A second serving of concentrated-calorie foods a few times a week could translate into tens of thousands of excess calories a year.



Seventeen Pounds in Twenty-One Days

Given that on a day-to-day basis, we tend to eat a similar amount of food,¹⁷¹⁵ it would make sense that if there were fewer calories in the same mass of food, you'd take in fewer calories and lose more weight. Studies in which foods are covertly passed into people's stomachs through a tube have confirmed that the stomach registers volume much more than it does calories in terms of appetite and subsequent food intake.¹⁷¹⁶ Researchers were able to cut people's caloric intake nearly in half, from 3,000 daily calories down to 1,570, without cutting portions—just by substituting less-calorie-dense foods.¹⁷¹⁷ They replaced meats and sugary foods with lots of fruits, vegetables, whole grains, and beans. Despite the sudden slashing of their caloric intakes almost in half, the research subjects reported equal satiety and enjoyment.

So do people who eat higher-calorie-density diets gain more weight? Apparently so. There is "strong and consistent evidence" that those consuming a diet higher in calorie density do tend to gain weight, while those eating diets lower in calorie density improve both weight loss and weight maintenance.¹⁷¹⁸ We can't be sure this is due to calorie density itself, though, since calorie-dilute foods tend to be healthier¹⁷¹⁹ in a variety of ways—for example, less processed, more fiber.

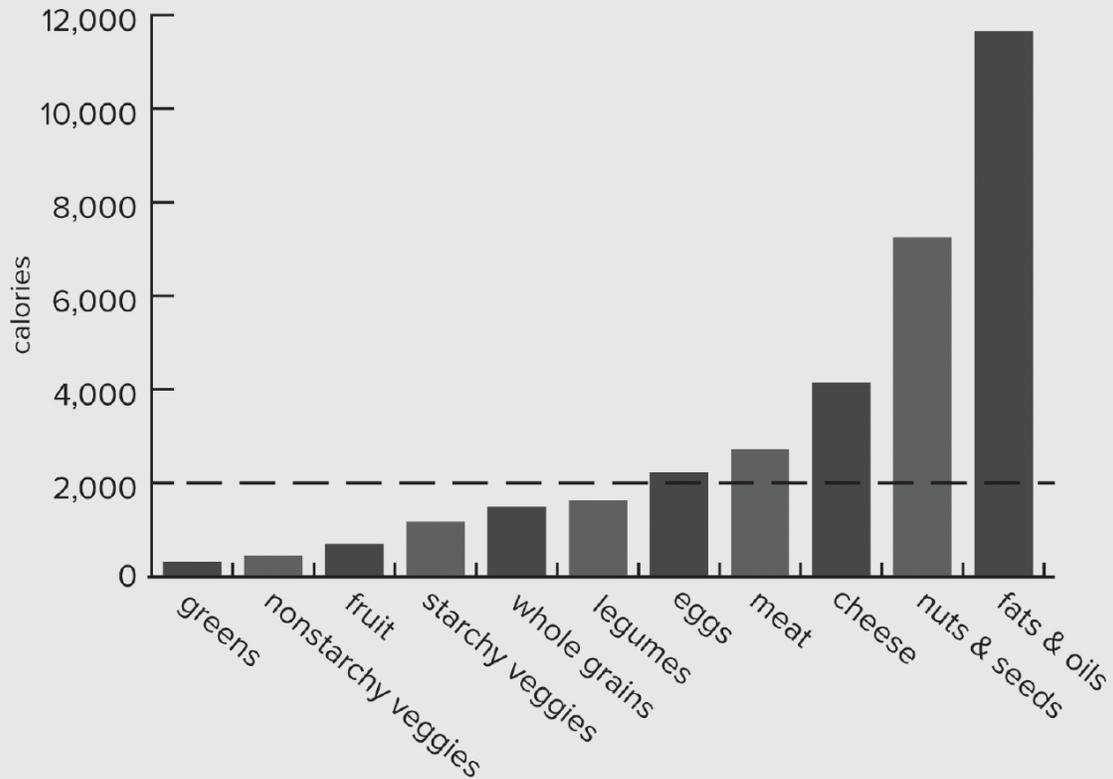
Low-calorie-density diets offer the best of both worlds: higher dietary quality and better weight loss.

Portion-controlled diets, often incorporating liquid meal replacements, can be effective in the short term¹⁷²⁰ but may increase the risk of binge-eating episodes¹⁷²¹ and may actually be counterproductive in the long run. Individuals randomized to a few months of lifestyle education and SlimFast meal replacements actually did significantly worse years later than the group who had just gotten the education.¹⁷²² The thinking is that the motivation to learn and implement healthy eating strategies was undermined by the reliance on meal replacements as a convenient crutch. What if instead of having people eat *less* food overall, you have them eat *more* calorically dilute foods?

Before spam was unwanted email cluttering our in-boxes, it was SPAM, a processed canned meat product popular in Hawaii. Researchers in Hawaii tried putting people on a traditional, pre-SPAM, Hawaiian diet with all the plant foods they could eat.¹⁷²³ The study subjects lost an average of seventeen pounds in just twenty-one days. Caloric intake dropped by 40 percent, but not because they were eating less food. The subjects lost seventeen pounds in three weeks eating *more* food, in excess of four pounds of food a day.

Calories in Three Pounds of Food

Americans appear to average about three pounds of food a day.¹⁷²⁴ How many calories would that add up to if you chose to get your three pounds from the following foods?



Chewing the Fat

If you lower the calorie density of your diet, you could keep eating the same amount of food yet lose weight. If you lower it enough, you could eat even more food than usual and still shed pounds. So how can you decrease the density? A quick look at the two extremes of the Calories in Three Pounds of Food graph should make apparent two methods: abandon added fats and add abandoned vegetables.

As we saw in the Low in Added Fat section, covertly put people on a relatively low-fat diet (20 percent calories from fat), and they tend to lose body fat every day even though they can eat as much as they want. If you then give those same people the same meals, but this time sneakily add in enough extra fats and oils to change it to a high-fat diet (60 percent of calories from fat), they gain body fat every day.¹⁷²⁵ Because people randomized to consume higher-fat diets tend to consume more calories, the term *high-fat hyperphagia* was coined, implying that fat somehow made people eat more, but that wasn't the case. Instead, those secretly switched from low-fat to high-fat diets simply continued to eat nearly the same amount of food no matter the fat content. All that extra fat just spiked the calorie density, so all of a sudden, eating the same amount of food meant inadvertently eating a lot more calories.

What About Olive Oil?

Second only to animal fats, such as lard, tallow, fish oil, bacon grease, and chicken fat, vegetable oil tends to be the most calorie-dense food,¹⁷²⁶ more so even than butter, which is about 16 percent water by weight.¹⁷²⁷ What about olive oil? In many cases, Mediterranean dietary patterns have been found to beat out other diets for weight loss,¹⁷²⁸ and in the context of a truly Mediterranean diet, olive oil has not been found to be associated with significant weight gain. But how the olive oil is being used may make the difference. In the Mediterranean, olive oil is often used to dress beans, vegetables, and salads, so olive oil consumption can be an indicator of a healthier, more traditional diet.¹⁷²⁹ In a more modern context, just adding olive oil to food is associated with increased obesity risk,¹⁷³⁰ so weight loss on a Mediterranean diet may be in spite of, not because of, the olive oil.¹⁷³¹

The study subjects were men with big appetites who were already eating about four pounds of food a day. The high-fat diet was so calorie dense that they would have had to have eaten around six pounds a day of the lower-fat meals to cause the same kind of weight gain. Since the subjects didn't even notice the difference between the two diet phases, those who were started on the high-fat diet ate the same four pounds of the lower-fat meals after being switched, so they went from gaining weight to losing weight without even realizing it.¹⁷³² That's why manipulating added fat content can be so powerful.

But if you feed people higher- or lower-fat diets with the same calorie density (by diluting the high-fat meals with water, for example), the high-fat hyperphagia effect disappears. So it isn't the fat per se. With more than twice the calories as carbs or protein, fat is just so calorie dense that it can slip in more calories per bite. So the phenomenon was renamed *passive overconsumption*, which you may remember from the Causes section. Fat doesn't drive us to overeat. Unintentionally, we just may eat more calories without even knowing it.¹⁷³³

A paper in the journal *Public Health Nutrition* entitled "Two Important Exceptions to the Relationship Between Energy Density and Fat Content" added important caveats.¹⁷³⁴ Processed foods with reduced fat claims on the front of their packaging are often so packed with sugar that they may have the same number of calories per serving as a higher fat product. SnackWell's fat-free cookies, for example, at 1,700 calories per pound¹⁷³⁵ are as calorie dense as a cheese danish.¹⁷³⁶

The other exception noted was that vegetables are so calorie dilute that even high-fat veggie dishes like buttered broccoli tend to be less calorically dense overall than most of what people are eating.¹⁷³⁷

This brings up the second strategy for lowering dietary calorie density: instead of sneaking out fat, sneak in vegetables.

Souped-Up Weight Loss

If the water content of vegetables is their secret to low-calorie density, what about taking that to its logical conclusion and feeding people liquids, as in soup? Soup consumers tend to have slimmer waists and lower body weight, perhaps as a consequence of the lower average calorie density of their diets, but they also tend to exhibit other healthy eating behaviors, such as eating more greens and beans.¹⁷³⁸ You don't know if it's the soup itself unless you put it to the test.

In a study funded by Campbell's—who else?—people on calorie-restricted diets were randomized to eat either two servings of soup a day or two dry snacks like crackers or pretzels with the same number of calories as the soup servings. After one year, the soup group lost 50 percent more weight, about fifteen pounds compared to around ten pounds.¹⁷³⁹ Of course, their sodium intakes went up—even "low sodium" Campbell's soup may exceed by more than 250 percent my one-to-one sodium-per-calorie ratio recommendation I detailed in *How Not to Die*.¹⁷⁴⁰ So I encourage everyone to look for no-salt-added soup varieties or make your own. For more on soup, check out the Wall Off Your Calories section.

Dangling a Carrot

The biggest influence on calorie density is not fat but water content.¹⁷⁴¹ Since water adds weight and bulk without adding calories, the most calorie-dense foods and the most calorie-dense diets tend to be those that are dry.¹⁷⁴² Some vegetables, on the other hand,

are more than 95 percent water, and, as we saw in the High in Water-Rich Foods section, it's not just iceberg lettuce. Bamboo shoots, bean sprouts, cucumbers, celery, turnips, cooked napa cabbage, bok choy, summer squash, and zucchini may top out at 95 percent water.¹⁷⁴³ They're basically water in vegetable form. A big bowl of water-rich vegetables is practically just a big bowl of trapped water.

The effect on calorie density is so dramatic, the food industry wants in on the action. In a research paper entitled "Food Nanotechnology: Water Is the Key to Lowering the Energy Density of Processed Foods," one researcher proposed "structuring a solid processed food similar to a celery stalk using self-assembled, water-filled, edible nanocells or nanotubes."¹⁷⁴⁴ No need, as Mother Nature has already done it for us.

If piling on vegetables causes protests at the dinner table, *hidden* vegetables can be used to covertly decrease calorie density, just as hidden fat can be used to covertly increase it. In a famous Penn State study, broccoli, cauliflower, tomatoes, squash, and zucchini were added secretly to familiar entrées, while the dishes' appearance, flavor, and texture were maintained (by puréeing vegetables into pasta sauce, for example).¹⁷⁴⁵ The kids in the study were none the wiser and ate the same amount of food, thereby taking in significantly fewer calories and significantly more vegetables. Win-win!

Surreptitiously slipping veggies to unsuspecting kids shouldn't be the only way to get them to eat them, though. The researchers stress the importance of using several approaches, including repeated exposure to originally disliked whole vegetables, which has been shown to improve acceptance over time.¹⁷⁴⁶ Taste familiarity is an important determinant of children's food preferences. The more they are exposed to the taste, the more likely it is they'll eat them.¹⁷⁴⁷ So the best way to get kids to eat their vegetables is to have them actually eat their vegetables so they can develop a lifelong appreciation.¹⁷⁴⁸ Covertly incorporating vegetables can be one strategy, but they're not going to be living at home forever, and we want to leave them with a legacy of overtly healthy habits too.

The same vegetable sneak-attack strategy has been used successfully in adults.¹⁷⁴⁹ In fact, study subjects actually preferred some of the "vegetable-enhanced" meals to their non-veggie-fortified options. What's more, even though they ate bigger portions of the meals with added vegetables, they still took in fewer calories.

Again, that's the beauty of calorie density. The subjects were awarded the twin benefit of eating a pound of vegetables a day and consuming 350 fewer calories. More food, fewer calories. Keep that up and over time, you could lose thirty-five pounds just like that.¹⁷⁵⁰

What may be an even more effective weight-loss strategy than just adding calorie-dilute veggies is a combination approach. Those randomized to receive advice about reducing fat intake lost more weight than those just told to eat more fruits and vegetables, but those instructed to do both—lower their fat consumption while increasing their fruit and veggie intakes—did the best, losing seventeen pounds and maintaining that reduction for the whole year.¹⁷⁵¹ Yes, simply adding vegetables—whether covertly or overtly, like adding chopped greens to rice—can decrease calorie density, caloric intake, and hunger,¹⁷⁵² but simultaneously adding vegetables while removing fat can attack the problem from both sides. For example, adding puréed broccoli and cauliflower in place of some of the cheese in a pasta sauce successfully decreased calorie density by 25 percent, leading to a full 25 percent reduction in caloric intake in children, 79 percent of whom rated the less cheesy, vegetable-heavier version as tasting the same or better.¹⁷⁵³

Mushrooming Weight Loss

Mushrooms are a great way to swap out calories and swap in flavor. They only have about one hundred calories per pound,¹⁷⁵⁴ so incorporating them into our meals can certainly lower calorie density, but it's their savory umami flavor that develops particularly well during cooking that makes them an ideal meat replacer. Studies show substituting mushrooms for meat can cut meal calories in half without compromising palatability or satiety. This led

researchers to suggest that even just making one such swap a week could result in more than five pounds of weight loss in a year.¹⁷⁵⁵

In another study, Johns Hopkins researchers randomized overweight individuals into one of two groups: those instructed to follow the USDA Food Guide Pyramid-based diet prescription, or another told to adhere to the same diet prescription but to also incorporate mushrooms instead of meat into meals three times a week. A year later, not only did the mushroom group have better metabolic markers and less inflammation (which you would expect from any sort of meat reduction), but they also achieved a significant loss in weight of seven pounds at six months and kept it off for the rest of the year.¹⁷⁵⁶ Pass the portobello burgers!

Out of Thin Air

Pop Quiz: Aside from fiber and water, what other food component has zero calories? Hint: Maybe I should have called this a *Popcorn* Quiz. Air. Air has zero calories. A cup of corn kernels has four times more calories than a cup of popped corn kernels,^{1757,1758} despite having more water. That may be one reason popcorn is more filling than potato chips. Six cups of popcorn was found to be more satiating than about the same weight of potato chips (one cup), though in this case the difference in fat content also affected the calorie density.¹⁷⁵⁹ To control for both water and fat content, researchers decided to study cheese puffs.

Researchers compared Crunchy Cheetos to Cheetos Puffs. Though both have the same number of calories per pound, the Puffs have fewer calories per volume because they've been puffed up with air. Study subjects were offered a big bowl of each, and, although they consumed nearly 75 percent greater volume of the Puffs, they still ended up taking in about 20 percent fewer calories, presumably because the Puffs had so many fewer calories per cup due to the added air.¹⁷⁶⁰ Of course, neither cheesy snack food is a good choice, as they both exceed 2,500 calories per pound, worse even than straight-up cheese.^{1761,1762}

The Cheetos study wasn't perfect. The two types of Cheetos differed in their ingredients, which could have affected the results. To see if food volume independently affects intake, an ingeniously simple experiment was devised: Researchers crushed up some Wheaties. Reducing the flake size reduced the volume, so they could feed people the identical food, differing not by calories per pound but by calories per cup. The study subjects poured themselves less of the crushed Wheaties, sensing it was denser, but not enough to avoid pouring themselves 34 percent more calories.¹⁷⁶³ So it seems volume really does appear to make a difference.

Since we tend to consistently eat both a certain weight and volume of food,¹⁷⁶⁴ eating foods higher in both water and air (and therefore lower in calorie density) may facilitate weight loss—which brings us to fruit.

Bearing Fruit

One of the reasons bananas are so light is that 20 percent of their volume is straight-up air.¹⁷⁶⁵ Because most of the rest of a banana is water, 85 percent of a banana is calorie-free. Fruits even higher in water content—like apples and pears—are more than 90 percent calorie-free. So what would happen if you had people add fresh fruit to their regular diets?

In a study out of Brazil, people were randomized to eat three apples or three pears a day as snacks between meals on top of whatever else they were eating. Fruit is low in calories, but not calorie-free, so if they're adding foods to their diets, won't they gain weight? No, they actually *lost* a couple of pounds. Could that weight loss simply be due to all the additional fiber they were getting from the apples and pears? Enter the cookie group. The study subjects were randomized to three apples, three pears, or three oatmeal cookies with enough oats in them to have about the same amount of fiber as the fruit. So all three groups added about the same number of calories and same amount of fiber. Unlike the fruit, however, adding oatmeal cookies to the diet did *not* lead to weight loss, despite the added fiber. No shocker there. Because of its water content, the fruit was five times

heavier, so it offered five times as much food as the cookies. Cookies are so calorie dense that you can add hundreds of calories without feeling much of a difference, whereas people appeared to unconsciously compensate for all the extra bulk from the fruit by eating less of everything else and lost weight as a result.¹⁷⁶⁶

When three methods of lowering calorie density were compared—covertly manipulating fat levels by removing butter and oil, adding diced or puréed fruits and vegetables, or adding water—decreasing fat seemed to work best in terms of decreasing overall daily calorie consumption. However, this may have been complicated by the fact that the entrées with the added fruits, vegetables, and water were rated moister and were associated with faster eating rates compared to the reduced-fat entrées. The bottom line is that a combination of approaches might work best, like replacing oil with applesauce when baking, achieving both a fat reduction and a fruit enhancement.¹⁷⁶⁷

If researchers with no culinary training can covertly reduce calorie counts without anyone noticing, why can't chefs? Nearly all chefs surveyed, 93 percent, thought the calories in menu items could indeed be reduced by up to 25 percent without customers noticing. So why don't they? The greatest barrier they identified was "low consumer demand."¹⁷⁶⁸

Are Nuts the Exception?

Nuts have a high calorie density. At the same time, nuts are one of the few foods that, on their own, may literally add years to your life.¹⁷⁶⁹ Not only may they slow the aging process itself,¹⁷⁷⁰ but an ounce a day, which is just about a handful or a quarter cup, may also reduce the risk of dying from heart disease, stroke, cancer, respiratory disease, diabetes, and infections¹⁷⁷¹—more than half of our top ten killers. So it comes as no surprise that nut consumption is associated with lower risk of dying prematurely across the board. As the title of a recent editorial in the *Journal of the American College of Cardiology* put it: "Eat Nuts, Live Longer."¹⁷⁷²

On a global scale, inadequate nut consumption (under twenty grams a day) may be responsible for millions of deaths,¹⁷⁷³ but what does that mean on a personal level? Studies have found, for example, that those eating nuts just twice a week or more appear to cut their mortality risk in half compared to those who almost never eat nuts.¹⁷⁷⁴ You could flip that around and suggest that not eating nuts doubles your chances of dying prematurely. Is that really true, though? Yes and no.

There are many potentially confounding factors, such as those who consume nuts tend to smoke less, exercise more, and eat less meat and more fruits and vegetables, but the mortality benefits appear to persist even after controlling for these factors.¹⁷⁷⁵ Even if we knew for certain it was cause and effect, it's important to understand what halving our mortality risk really means.

As a healthy, middle-aged person, our risk of dying over the next ten years may only be about 2 percent, a one-in-fifty chance of dying over the next decade, but that's if we don't eat nuts.¹⁷⁷⁶ If we do eat them, our risk of dying may drop to 1 percent. So, yes, technically, we just cut our risk in half by going from 2 percent to 1 percent, but, at the same time, we really only cut our *absolute* risk of dying by a single percentage point. That may not sound as impressive, but to me, dying at such a relatively young age seems such a tragedy that it would be worth making lifestyle changes to drive down that risk as low as possible, especially when one such strategy is a simple, delicious dietary tweak.

Given the purported mortality benefits of eating nuts and despite their high calorie density, it would seem worthwhile to include them in our regular diets by consciously substituting them in place of the same number of calories from other foods. Thankfully, our bodies appear to do it for us automatically.¹⁷⁷⁷ Nuts appear to be so satiating that if you give people a midmorning snack of almonds, not only do they subsequently eat less at lunch, they eat less at dinner, too, spontaneously accounting for the extra almond calories.

This explains how you can make thirty thousand calories "vanish" into thin air. Those randomized to add servings of almonds,¹⁷⁷⁸ pistachios,¹⁷⁷⁹ hazelnuts,¹⁷⁸⁰ or walnuts¹⁷⁸¹ to their daily diets for months didn't gain a single pound on average. In the Nuts and Seeds chapter in *How Not to Die*, I cataloged the factors beyond appetite suppression thought responsible for this vanishing act. A new one to add to the list arose from a randomized, double-blind, placebo-controlled brain scan study out of Harvard. The researcher's "fruit smoothie delivery system" involved identically tasting, fat- and calorie-matched smoothies made either with walnuts or with oil and walnut flavoring.¹⁷⁸² The brain scans showed that those unknowingly consuming the real walnuts exhibited increased activation of a part of their brains thought to involve the ability to control cravings. There's just something in nuts that appears to be especially satisfying.

A significant proportion of the calories in nuts also quite literally gets flushed away. The actual number of calories that our systems absorb from nuts may be as much as 20 percent lower than it says on the nutrition label because the calories are encapsulated inside cell walls.¹⁷⁸³ No matter how well we chew, some of the calories remain trapped inside unbroken cells, each of which is surrounded by an indigestible wall of fiber.¹⁷⁸⁴ The calories in whole plant foods are effectively walled off, which may help explain why other higher-calorie-density foods like meat and processed foods are associated with weight gain, whereas nuts are not.¹⁷⁸⁵

As a high-calorie-density food, the admonition to “eat sparingly” still applies, but that’s all one may need. While the optimum benefits of fruits and vegetables may require cups a day, nuts appear so potent that the mortality benefits may be had for mere ounces a week.

FOOD FOR THOUGHT

So how low should we go when it comes to calorie density? The American Institute for Cancer Research has taken the lead on setting calorie-density targets to help lower the rate of obesity-related cancers. The institute recommends that calorie-dense foods, defined as having more than around 70 calories per ounce, only be eaten “sparingly” and set an ambitious public health goal of trying to get the average calorie density of our diets below 35 calories per ounce, or 560 per pound of food.¹⁷⁸⁶

It’s hard to imagine units of weight, though. Volume is easier to visualize. How many calories is that per measuring cup? Thirty-five calories per ounce translates to about 300 calories per cup.¹⁷⁸⁷ Which foods have fewer than 300 per cup, and which foods have more? I made a simple chart for you to stick on your fridge to see at a glance which foods you may want to eat more—or less—of:

Calories per Cup

Eat More	On Target	Eat Less	Eat Sparingly
< 100 calories/cup	< 300 calories/cup	300–600 calories/cup	> 600 calories/cup
most fresh fruit	avocados & bananas	dried fruit	nuts & nut butters
most vegetables	starchy vegetables	french fries & onion rings	oil
	pasta & whole grains	bread	chocolate
	beans, lentils & chickpeas	fried tofu	soy nuts
	yogurt	eggs	cheese
	seafood & wild game	beef, pork & poultry	bacon

Note: Calorie-density calculations typically exclude beverages since all drinks quickly drain out of the stomach at about the same rate.

This volumetric wisdom of choosing foods heavy on bulk and light in calories goes back centuries. The president of the Royal College of Physicians of Edinburgh seemed to be channeling the calorie-density concept in his dietary treatment recommendations for “corpulence” back in the 1700s: “Animal food only once a day and then very moderately. Cheat appetite by eating light things—especially vegetables.”¹⁷⁸⁸

LOW IN MEAT

Should We Stop Meating Like This?

Rather than promoting produce, most of our U.S. taxpayer-dollar subsidies support the production of meat, dairy, oils, and sugar.¹⁷⁸⁹ So while I was excited to discover that there is a National Watermelon Promotion Board, its budget is dwarfed by the combined quarter-billion-dollar might of the federal government-administered American Egg,¹⁷⁹⁰ Cattlemen’s Beef,¹⁷⁹¹ National Dairy,¹⁷⁹² and National Pork boards.¹⁷⁹³ Don’t expect Dollar Menu melons anytime soon.

So given the cheapness of meat, what role might it be playing in the obesity epidemic? The largest study of those eating plant-based diets found that American vegetarians tend to weigh about twenty-five pounds less than those who eat meat.¹⁷⁹⁴ Compared to those chewing meat, those eschewing it also appear to gain less weight as they age.¹⁷⁹⁵ Kids¹⁷⁹⁶ and teens¹⁷⁹⁷ eating more vegetarian meals also tend to be leaner than their nonvegetarian

peers. They aren't smaller in general, though: Vegetarian boys and girls measure up to be about an inch taller than their "omnivorous classmates."¹⁷⁹⁸ They just aren't as wide.

It's certainly not all or nothing, though. Quantity matters. A research team sifted through more than a thousand studies published just since the year 2000 to perform a systematic review on which foods were "determinants of long-term weight change." Not surprisingly, they found that white bread, sweets, and desserts all seem to promote weight gain. Their main finding, however, was that evidence is strongest for high meat intake predicting more weight gain.¹⁷⁹⁹ Those who eat a lot of meat also tend to eat less fruit, whole grains, and nuts,¹⁸⁰⁰ though, all of which may be protective against gaining weight.¹⁸⁰¹ So is the weight gain because they're eating more animal products or because they're eating fewer plants? Or might it be something else entirely? Those who eat more meat also tend to exercise less, for example,¹⁸⁰² or maybe they're just drinking soda with their burgers.

In the same vein, vegans are forty pounds lighter on average than those who eat conventional diets,¹⁸⁰³ but that doesn't mean that cutting out meat, dairy, and eggs will necessarily make you lose forty pounds. Those who eat healthier also tend to live healthier, so it's not necessarily the diet per se. Maybe vegans eat out less and work out more. To see if meat has an independent effect on obesity, we need to control for both dietary and nondietary factors.

When researchers have tried to account for these differences, controlling for other nutritional and lifestyle considerations like fiber intake and exercise, the link between meat consumption and weight gain remained solid.¹⁸⁰⁴ Over a twenty-month period, for example, those eating about three more ounces of meat a day had about three times the risk of gaining five or more pounds.¹⁸⁰⁵ Another study found that those who ate about five ounces of meat a day had eight times the incidence of abdominal obesity over a year compared to those who ate around one ounce of meat daily.¹⁸⁰⁶ (An ounce of meat is about the size of a golf ball.) Meat intake seems to be more closely associated with abdominal weight gain than peripheral gain—that is, bigger bellies rather than bigger thighs.¹⁸⁰⁷ Over a ten-year period, the amount of weight gain associated with eating more than seven servings of meat a week (compared to those averaging less than about one serving of meat every other day) was the same as the amount of weight lost by women who walked or men who jogged or ran four or more hours a week.¹⁸⁰⁸

Even a Paltry Amount of Poultry?

Could it be as simple as people who eat more meat tend to take in more calories?¹⁸⁰⁹ Most of those studies linking meat consumption with weight gain controlled for total caloric intake. This implies that if you have two people eating about the same number of calories, the person eating more meat might gain more weight. To find out which meat may be the most fattening, an epic study was performed. EPIC is actually the name of the study, and it lives up to its moniker, having enrolled hundreds of thousands of men and women, assessing their dietary intakes, and following them out for years.

The EPIC researchers also found total meat consumption linked to increased weight gain, even at similar caloric intakes. They concluded: "Our results are therefore in favor of the public health recommendation to decrease meat consumption for health improvement." The surprise, though, was that poultry appeared to be the most fattening. Consumption of poultry—mostly chicken—was associated with three times the weight gain compared to red meat like beef,^{1810,1811} and this was after taking into account age, gender, physical activity level, smoking status, overall dietary quality, and calorie counts.

How did the meat industry respond to the EPIC findings? By suggesting that perhaps the extra weight gain was muscle mass and not body fat.¹⁸¹² Could the meat have made the subjects beefier rather than fatter? The researchers responded to the industry's challenge by going back and specifically assessing changes in the subjects' waistlines and found the

same thing.¹⁸¹³ Even when eating around the same number of calories, the more meat we eat, the more our bellies may grow. The researchers even calculated how much our waistlines might be predicted to expand, based on our daily meat consumption. It only came out to be one extra inch around the waist over the five-year follow-up for a daily chicken breast's worth,¹⁸¹⁴ but that appears to be *independent* of the calories.

No other such study comes close to EPIC in size, but another one followed thousands of individuals for even longer and confirmed the connection between poultry consumption and increased risk of weight gain over a period of fourteen years. Using statistical methods to adjust for other factors, researchers effectively tried to study men and women who ate about the same number of calories a day, consumed the same amount of vegetables, fruits, and grains, and did about the same amount of exercise—but ate different amounts of meat. On average, at baseline, those who ate less than a small serving of meat a day were not overweight, but the more meat they ate, the heavier they were.¹⁸¹⁵ By one and a half servings a day, they crossed the threshold of a BMI of 25 to become officially classified as overweight.

Over the following fourteen years, chicken consumption was associated most with weight gain in both men and women, and it didn't appear to take much. Compared to those who didn't eat any chicken at all, those eating more than 22.8 grams of chicken a day had a significantly greater increase in their body mass indexes.¹⁸¹⁶ To put that into context, 22.8 grams is less than an ounce, which is about one single chicken nugget a day¹⁸¹⁷ or just one chicken breast once every ten days.¹⁸¹⁸

Chicken Out

The odds of obesity may increase by 18 percent for every 1 percent increase in calories from red meat, poultry, fish, or shellfish.¹⁸¹⁹ As we saw in the previous section, animal protein intake in general has been associated with both increased abdominal obesity and general obesity, even after taking into account other dietary and lifestyle factors.¹⁸²⁰ We know you can't control for everything, though. In the population studies above, poultry appeared to be the worst offender, but interventional trials are required to prove cause and effect.

In a head-to-head test of beef, pork, and chicken, no differences were noted in terms of short-term satiety.¹⁸²¹ What about weight changes over time? No differences there either. People were told to eat mostly beef, pork, or chicken in three-month blocks, and no differences were noted in body composition in any of the three periods.¹⁸²² Might this be like the cholesterol story? There's a common misperception that switching from red meat to white meat lowers cholesterol, but when it was actually put to the test, no significant improvements were noted when people swapped beef, veal, and pork for chicken and fish.¹⁸²³ So are we seeing the same when it comes to weight loss? The only meat shown to be less fattening than chicken in a randomized controlled trial was chicken-free chicken, a plant-based meat made from the mushroom kingdom first popularized in Europe called *Quorn*.

When the meat industry funded an obesity study on chicken, they pitted it against "cookies and sugar-coated chocolates."¹⁸²⁴ This is a classic drug industry tactic: Make your product look better by comparing it to something known to be substandard.¹⁸²⁵ (Apparently, regular chocolate wasn't enough to make chicken look better.) But what happens when chicken is pitted head-to-head against a real control like meatless chicken? Chicken chickens out.

Quorn-brand chickenless chicken was found to be more satiating among both lean¹⁸²⁶ and overweight¹⁸²⁷ individuals, cutting down on subsequent meal intake hours later. Feed people a chicken-and-rice lunch, and four and a half hours later, they eat 18 percent more of a dinner buffet than those who had been given a lunch of chicken-free chicken and rice.

In terms of calories, the chicken-and-rice lunch diners ate about 1,200 calories for dinner, compared to the 1,000 dinner calories eaten by subjects after the Quorn meal. Tofu also beat out chicken in a similar manner.¹⁸²⁸ These findings are consistent with childhood obesity research that found meat consumption seemed to double the odds of schoolchildren becoming overweight, whereas the consumption of plant-based meat products appeared to have no effect. Whole-food sources of plant protein, such as beans, did even better, though, associated with cutting the odds of kids becoming overweight in half.¹⁸²⁹

TMAObesity?

Ancient doctors evidently used to use ants to diagnose people with diabetes.¹⁸³⁰ They (the ants, not the doctors) were attracted to the sugary urine. This is an archaic example of the modern science of metabolomics, which tries to uncover the molecular signatures of disease. For example, with each breath, we exhale hundreds of different compounds.¹⁸³¹ Imagine how, with enough people and enough computing power, we might be able to diagnose a disease like lung cancer with some sort of Breathalyzer test. We just have to figure out the specific patterns of chemicals in the body fluids of those with and without disease. This is how Cleveland Clinic researchers discovered the role of TMAO.

The blood of patients who had experienced a heart attack or stroke was compared to the blood of those who hadn't, and that's how TMAO, short for *trimethylamine oxide*, was identified.¹⁸³² The more TMAO people had in their blood, the more likely they were to go on to suffer a heart attack, stroke, or otherwise die prematurely.¹⁸³³ Where does TMAO come from? Just as short-chain fatty acids are produced by good bacteria in our gut when we eat fiber, TMAO originates from bad bacteria in our gut when we eat lots of choline (concentrated in eggs, but also lecithin supplements) or carnitine (concentrated in meat, but also some energy drinks).

If you eat eggs¹⁸³⁴ or meat,¹⁸³⁵ you get a bump in TMAO levels within hours, unless you recently took antibiotics that wipe out your gut flora. In that case, it can be weeks before your bad bacteria grow back. Alternately, you can prevent the growth of these bad bacteria by not feeding them in the first place. Feed a vegan a steak, and they make virtually no TMAO, presumably because they hadn't been fostering the growth of steak-eating bacteria.¹⁸³⁶

The egg and beef industries combined forces to fund a study showing that eating fish was even worse than their products, but TMAO levels rose within fifteen minutes after eating fish, suggesting the TMAO is preformed in the fish and may be handled differently by the body. Regardless, their own study showed TMAO levels were *lowest* after eating the non-fish, non-egg, non-beef control food: fruit.¹⁸³⁷ Even relatively choline-rich plant foods don't seem to cause a problem. For example, two ounces of pistachios every day actually seemed to cause a reduction in TMAO levels.¹⁸³⁸

TMAO may help explain why those who eat more plant-based diets are more protected from heart disease,¹⁸³⁹ but what about obesity? Well, obese individuals do seem to churn out more TMAO,¹⁸⁴⁰ and blocking TMAO in mice protects them from weight gain, but what we care about is whether avoiding carnitine and choline-rich foods helps with weight loss in people.¹⁸⁴¹ We finally got an answer in 2018 from the POUNDS Lost Trial. (*POUNDS* stands for *Preventing Overweight Using Novel Dietary Strategies*.) Those with greater reductions in carnitine and choline were significantly more likely to experience weight loss and waist slimming, while those with increases in carnitine or choline were about twice as likely to fail to lose weight over a two-year period.¹⁸⁴² But it's not all or nothing.

True, you can feed a vegan an eight-ounce sirloin and not get a TMAO spike,¹⁸⁴³ but even those who eat meat on a regular basis appear to be able to modulate the populations of meat-eating bacteria in their gut. Feed people sausage, egg, and cheese biscuits before

and after being on a five-day high-fat diet (55 percent calories from fat), and they end up producing more TMAO after the five-day binge.¹⁸⁴⁴ This shows we may be able to shift our gut bacteria on a week-to-week basis—for better or for worse.

You (and Your Grandkids?) Are What You Eat

If you expose a pregnant cricket to a predatory wolf spider, her babies hatch exhibiting increased antipredator behavior and, as a consequence, have improved survival from wolf spider attack.¹⁸⁴⁵ The mother cricket appears to be able to forewarn her babies while they are still inside her about the threat so they come out preadapted to their external environments. How is that possible? Isn't their DNA already set in stone?

This same phenomenon happens in plants too.¹⁸⁴⁶ If you take two genetically identical plants and grow one in the sun and the other in the shade, the sun-grown plant will produce seeds that grow better in the sun, while the shaded plant will produce seeds that grow better in the shade—even though the two plants are genetically identical. Same DNA, different behavior. This is the epigenetics I talked about in the Causes section, changes in how the genes we have end up expressing themselves.

Another example can be seen with vole pups birthed in the winter, who are born growing thicker coats.¹⁸⁴⁷ Vole mothers are able to communicate the season to their babies in the womb and tell them to put on a heavier coat even before they're born! And people are no different. You know how some people have different temperature tolerances, resulting in battles over the thermostat in the bedroom or the office? Whether you're born in the tropics or in a cold environment determines how many active sweat glands you have in your skin.¹⁸⁴⁸

What does this have to do with diet? Can what a pregnant woman eats permanently alter the biology of her children in terms of what genes are turned on or off throughout life? Children born during the 1944–45 Dutch famine imposed by the Nazis ended up with higher rates of obesity fifty years later.¹⁸⁴⁹ It seems that the babies' gene expression was reprogrammed before birth to expect to be born into a world of famine and to conserve calories at all cost. But when the war ended, this propensity to store fat became a disadvantage.

What pregnant women eat and don't eat doesn't just help determine the child's birth weight but their future adult weights. For example, maternal animal protein intake during pregnancy (primarily from meat) appears to increase the risk their children will grow up overweight.¹⁸⁵⁰ Every daily portion of meat intake during the third trimester was correlated with about an extra percent of body fat mass in their children by their sixteenth birthday, potentially increasing their risk of becoming obese later in life, and this appeared to be independent of how many calories they ate or how much they exercised.¹⁸⁵¹

Epigenetics, the science of altering the expression of our genes, is good news. That means your DNA is not your destiny. No matter your family history, some genes can be effectively turned on and off by the lifestyle choices you make, affecting you, your children, and maybe even your grandchildren. Being pregnant during the Dutch famine didn't just lead to an increase in diseases among their kids but even, apparently, their grandkids.¹⁸⁵² So what a pregnant woman eats now may affect future generations. The possibility of generation-spanning effects of poor dietary conditions during pregnancy may help shine some light on our explosive epidemics of diabetes, obesity, and cardiovascular disease.

FOOD FOR THOUGHT

Cutting down on meat is just one of the many ingredients of what could be considered an optimal weight-loss diet. If you continue to eat meat, your best choice would likely be wild game¹⁸⁵³ (critically, felled with lead-free ammunition only).¹⁸⁵⁴ Today, even our meat could be considered junk food. For more than a century, one of the major goals of animal agriculture has been to increase the carcass fat content of farm animals. Those with the highest fat-to-lean content are branded "prime" and command the highest prices,¹⁸⁵⁵ but can end up as prime contributors to America's caloric intake.¹⁸⁵⁶ It's not your grandma's meat.

Take chicken, for example. In 1896, the USDA determined chicken was about 23 percent protein and less than 2 percent fat by weight,¹⁸⁵⁷ which is even leaner than some wild game like venison.¹⁸⁵⁸ Today, with ten times the fat, chicken has 1,000 percent more fat than it did just over a century ago.¹⁸⁵⁹ These days, more than 70 percent of the calories in chicken may come from fat. The birds have been genetically manipulated through selective breeding to contain more fat than protein.¹⁸⁶⁰ Chicken Little has become Chicken Big and may be making us bigger too.

LOW IN REFINED GRAINS

Going Against the Grain

Most of what we eat in America is processed junk. *Ultraprocessed* foods are defined as "industrial formulations which, besides salt, sugar, oils and fats, include substances not

used in culinary preparations, in particular additives used to imitate sensorial qualities” of real food.¹⁸⁶¹ Think Frosted Strawberry Pop-Tarts. Ultraprocessed foods comprise an unbelievable 58 percent of the daily caloric intake in the United States.

The number one source of calories in the U.S. diet is refined grains like white flour, followed by added fats like oils. Then come meat and added sugars. Refined carbs and refined fats make up more than half the American diet.¹⁸⁶² Food-wise, grain-based desserts like cakes, cookies, pastries, and pies are our single largest calorie contributor. Second is white bread, followed by soda.¹⁸⁶³ For our children and adolescents, it’s the same top three, but with pizza replacing the bread.¹⁸⁶⁴

When proponents of low-carb diets demonize carbohydrates, public health advocates are quick to point out that it’s the source that matters—carbohydrates can mean everything from lentils to lollipops.¹⁸⁶⁵ Though that’s true, the Standard American Diet sadly tends to lean more toward the lollipop end of the spectrum. We eat about three times as many calories from refined grains and added sugars as we do from all whole plant foods combined.¹⁸⁶⁶ So the problem identified by the low-carb proponents is real. We are awash in refined grain garbage, but the answer isn’t to switch to high-fad, high-fat diets but rather to low-crap ones.

The consumption of refined grain products appears linked to increased weight gain, but is that just because refined grains are components of fatty foods like pizza, sugary foods like SnackWell’s, or the twin menace of fatty sugar bombs like donuts? The Harvard cohort studies involving more than one hundred thousand male and female health professionals found that refined grains like white rice and white bread were associated with weight gain *independent* of all the other dietary and lifestyle factors they measured.¹⁸⁶⁷ This suggests that it’s not just that people who eat lots of Wonder Bread are eating more salami sandwiches or otherwise eating or living unhealthfully. The researchers estimated that every daily serving of refined grains may translate into about a four-tenths of a pound increase in weight over a four-year period. (To put that into perspective, a single large bagel may equal four servings of refined grains.¹⁸⁶⁸)

Are grains in general the problem, or only refined grains? Observational studies in which people and their diets are followed over time have consistently shown whole-grain consumption not only to be neutral but even associated with *better* weight control.¹⁸⁶⁹ Children who consumed more than one and a half servings of whole grains per day were found to have 40 percent lower odds of being obese compared with those who consumed less than one daily serving.¹⁸⁷⁰ In adults, weight gain might be reduced over the long term as much as two pounds for each extra one-ounce increment in daily whole-grain consumption.¹⁸⁷¹ But is seeking out foods like brown rice and whole wheat simply a marker for a healthier lifestyle?

Only 6–8 percent of American adults follow my recommendation to eat at least three servings of whole grains a day,¹⁸⁷² and those who choose oatmeal for breakfast instead of bacon and eggs may also be making other healthy life choices. Indeed, high whole-grain consumers tend to be more physically active, smoke less, and consume more fruits and vegetables.¹⁸⁷³ Statistically, one can try to control these factors like the Harvard studies did, effectively comparing nonsmoking whole-grain eaters to nonsmoking non-whole-grain eaters, all with similar exercise and diet. The result? Whole grains were still found to be associated with better weight control.¹⁸⁷⁴

You can’t control for everything, though. Could it be that people who make the choice to eat whole grains also choose to wear seat belts and bike helmets, install smoke detectors, and forgo sky diving? There are lots of potential mechanisms by which whole grains might facilitate weight loss—higher fiber, lower calorie density, lower glycemic response, a slower eating rate due to more chewing¹⁸⁷⁵—but you don’t know, of course, until you put it to the test.

Separating the Wheat from the Chaff

If you feed people a whole-grain rye porridge for breakfast (like oatmeal, but with rolled rye instead of rolled oats), they report significantly prolonged satiety and lowered hunger and desire to eat for up to eight hours after consumption compared to having eaten the same number of calories of white bread.¹⁸⁷⁶ Because of the high water content of the porridge, a larger portion had to be given to match the calories in the bread. A fairer test would be to compare foods in the same form, like whole-wheat rolls compared to white-flour rolls, which is exactly what a group of British researchers did. A beneficial effect on blood pressures was noted in the whole-wheat group, but no effect was found for appetite or food intake.¹⁸⁷⁷ Even in the porridge study, the whole-grain group said they felt fuller, but that didn't translate into them actually eating any less at lunch later on.¹⁸⁷⁸

Longer-term studies proved similarly disappointing, both for dropping daily caloric intake¹⁸⁷⁹ or body weight in children¹⁸⁸⁰ or adults.¹⁸⁸¹ Though there were other benefits noted when people were randomized to add whole grains to their diets, like improved artery function,¹⁸⁸² decreased inflammation¹⁸⁸³ and blood pressure,¹⁸⁸⁴ why not weight loss?

The WHOLEheart study was one such trial that randomized hundreds of overweight individuals to either continue their usual diets or be provided with a free variety of whole-grain products like granola bars and other snack foods.¹⁸⁸⁵ The subjects in the freebie group were instructed to substitute the foods “like for like” with refined-grain foods in their diets, but you can imagine what actually happened. Dietary reports suggested participants ate the free products as additions, rather than substitutions, to their regular diets.¹⁸⁸⁶ No wonder they didn't lose any weight! Some of the participants apparently also replaced the wrong foods. For example, those who added the most whole grains apparently cut down on their fruit consumption.¹⁸⁸⁷

In the Framingham Heart Study, thousands of individuals underwent CT body scanning to determine precisely how much fat they carried in their abdomens. Those who met my minimum of three daily servings recommendation for whole grains harbored about twenty cubic inches less fat around their abdominal organs and an additional twenty cubic inches less superficial belly flab. That's pretty impressive. The researchers' unique insight, though, was that the whole-grain benefit appeared to vanish among those who were also eating four or more daily servings of refined grains.¹⁸⁸⁸ So it may not be enough to just add whole grains to our diets—we also need to cut the crap.

Compliance is also an issue. Another large study that failed to show a weight-loss advantage to the provision of free whole-grain products sought to understand why by analyzing people's blood. There's a compound in the bran layer of certain whole grains (called alkylresorcinol) that's stripped away when grains are refined. So, by measuring the levels in people's blood, you can get an objective measure of roughly how much whole grain they're eating. After all the time, money, and effort that went into the study, it turns out more than 60 percent of the participants who were ostensibly in the “whole-grain” group had such low blood levels of the compound that it's likely they ate little or none of the whole-grain products that were provided, basically rendering the results meaningless.¹⁸⁸⁹

Other studies didn't provide food at all and instead simply instructed people to choose whole-grain products when they shopped. Now that “Made with WHOLE GRAIN” is plastered on the front of Froot Loops cereal boxes and even cheesecake manufacturers are trying to get in on the trend,¹⁸⁹⁰ it's no wonder such studies may fail to show a benefit. Even in tightly controlled trials, some of the intervention choices were questionable, randomizing people to meat loaf made with whole-wheat bread crumbs versus white bread crumbs,¹⁸⁹¹ or snacks made from whole-wheat flakes, sugar, and M&M's versus refined-grain flakes, sugar, and M&M's.¹⁸⁹² (I couldn't make this stuff up.) What's more, some of the whole-grain

doses used were so small they resulted in less than a half-ounce difference in fiber intake—insufficient, perhaps, to show a difference in body weight regulation.¹⁸⁹³

Grain of Truth

There have been successful whole-grain weight-loss interventions that involved, for example, switching people from white rice to brown rice¹⁸⁹⁴ or incorporating two packets of oatmeal every day versus a placebo-control hot cereal.¹⁸⁹⁵ In both cases, waistlines significantly slimmed, suggesting a change in body fat. A Japanese study that measured body composition changes directly with CT scans found a significant decrease in visceral belly fat in those given whole-wheat versus white bread.¹⁸⁹⁶ Indeed, if you go back and perform a meta-analysis of all the randomized controlled studies, even though an overall weight change didn't materialize, there was a small but significant drop in body fat in the whole-grain groups.¹⁸⁹⁷ Why?

Two main mechanisms have been suggested to explain the apparent benefit. Substituting whole grains for refined grains in a tightly controlled setting leads to (1) an increase in resting metabolic rate and (2) increased calorie loss through the stool.¹⁸⁹⁸ The metabolic boost is attributed to the waste heat produced by the fermentation of fiber in the bowel,¹⁸⁹⁹ and the extra calories flushed are due to the diminished ability of your body to extract energy from a high-fiber diet.¹⁹⁰⁰ The combined effect may add up to a loss of about ninety calories a day, which almost exactly predicts the weight loss found in the Harvard cohorts over a four-year period.¹⁹⁰¹ So whole grains may indeed help with fat loss but only, perhaps, when there's a parallel drop in refined grain junk.

FOOD FOR THOUGHT

To remove refined grains from your diet is to remove America's number one source of calories. Switching to whole grains may help reduce body fat, but there's an even better swap. See the Wall Off Your Calories section for taking your grain game up a notch and graduate from mere whole grains to *intact* whole grains, such as oat groats (also known as *hull-less* or *hulled oats*).

LOW IN SALT

Don't Shake on It

One of the most dramatic changes in our diets has been the skyrocketing intake of salt. For most of human existence, we were only getting the pinch of salt a day naturally found in whole foods.¹⁹⁰² Now, thanks mostly to processed foods, we're exposed to ten times more than our bodies were meant to handle.¹⁹⁰³ What role might this play in our obesity epidemic?

For nearly forty years, studies have linked salt intake to excess body fat.¹⁹⁰⁴ A 2017 meta-analysis of more than a dozen such studies found that higher sodium consumption was associated with nearly a two-inch-larger waist.¹⁹⁰⁵ A subsequent study found an extra pound of body fat for each quarter-teaspoon-higher salt intake a day.¹⁹⁰⁶ Children with the saltiest diets may have double the odds for abdominal obesity,¹⁹⁰⁷ but how do we know it's the salt itself? Think of some childhood favorites: pizza, potato chips, mac 'n cheese. They are packed with sodium, but they're also packed with calories. Perhaps the only reason sodium intake is correlated with obesity is because high salt and calories tend to travel together in the same foods.¹⁹⁰⁸

Why does the food industry add salt to so many products? It's simple: to make processed food more palatable so you'll eat more of it. Which are you more likely to overeat? Unsalted nuts or salted nuts? Unsalted pretzels or salted pretzels? Salty foods can have an addictive

quality. The overlap in pleasure circuitry within the brain between our appetites for salt and the effects of opioids and cocaine has led some to speculate that drug addiction is a hijacking of our inborn salt cravings that kept us alive through the long millennia before the advent of saltshakers.¹⁹⁰⁹ Now, those same salt cravings are killing us (by contributing to cardiovascular disease¹⁹¹⁰ and stomach cancer¹⁹¹¹ risk), but are they also making us fat?

Salt doesn't just make us want to eat more but drink more as well. And what do most Americans over age two drink on a given day? Sugar-sweetened beverages like soda.^{1912,1913} Based on studies measuring fluid intake after manipulating the salt content of people's diets, Americans might end up drinking an estimated forty billion fewer soft drinks per year if we cut our sodium intake in half.¹⁹¹⁴ That's a lot of calories.

Pinch an Inch

Until recently, that was all we thought was going on: Salt increases body fat by causing us to eat and drink more calories. But now, there is growing evidence that there may be a more direct link between sodium intake and obesity.¹⁹¹⁵ Studies controlling for total caloric intake including sweetened beverages *still* found a link between salt intake and body fat or obesity in adults, children, and adolescents,^{1916,1917,1918,1919} but these studies are fraught with difficulties.

Salt can make you retain water, which can affect bioimpedance measurements of body composition.¹⁹²⁰ But studies that have used more rigorous measures like x-ray or MRI scanning have also found a link between salt and body fat.¹⁹²¹ It's also hard to accurately estimate how much salt people are eating without having them carry a jug to collect their urine all day, or how many calories they're consuming without carrying out expensive "doubly labeled" water experiments. But again, even studies that have used these kinds of gold-standard techniques still found a link between salt intake and body fat, independent of how many calories people were eating.¹⁹²² Most of these studies were cross-sectional in nature, only a snapshot in time. When researchers followed hundreds of individuals over time, their salt consumption didn't predict changes in overall body weight in terms of the numbers on a scale, but all the while, body fat appeared to be increasing while their fat-free mass shrank. After controlling for a number of potential confounding factors, those who ate the most salt appeared to shift their body compositions to more fat and less lean tissue.¹⁹²³

Nearly all of these are observational studies and so can't prove cause and effect. Maybe high-salt consumers practice other bad health behaviors like sedentary living. Studies have controlled for physical activity,¹⁹²⁴ but you can't control for everything. The only interventional studies have been performed on rodents. Yes, you can fatten rats just by boosting their salt intakes,¹⁹²⁵ but the opposite effect has been described in mice.¹⁹²⁶ So are we more like rats or mice? Clinical researchers use animals to run tightly controlled experiments, but no matter how good the data, they always end up on the wrong species.

There is one recent human experiment that could provide a mechanism by which salt may contribute to obesity. When people were switched to a low-salt diet, the levels in their blood of the gut hormone ghrelin dropped, and when shifted to a high-salt diet, their ghrelin levels shot up.¹⁹²⁷ Ghrelin, the so-called hunger hormone I discussed in the High in Fiber-Rich Foods section, is the target of attempts by drug companies to create an anti-obesity vaccine,¹⁹²⁸ but we may be able to help block its action naturally by lowering our sodium intake.

Some are so convinced that salt is such a key player in our obesity epidemic they have suggested "partial resection of the nerve branches innervating the lingual mesolimbic receptor system"—in other words, cutting the nerves going to the salt-sensing taste buds of morbidly obese individuals.¹⁹²⁹ The link between salt and weight remains much too speculative for such a drastic approach, but given that sodium consumption is already

considered the leading dietary risk factor for death on the planet,¹⁹³⁰ there's reason enough to cut down, and it may just have the happy side benefit of facilitating fat loss—no scalpel needed.

FOOD FOR THOUGHT

A *New England Journal of Medicine* editorial entitled “Compelling Evidence for Public Health Action to Reduce Salt Intake” argued that since about 75 percent of salt exposure comes from manufactured foods, “the individual approach is probably impractical”¹⁹³¹—as if the consumption of processed foods is somehow preordained. But we not only have control over how much salt we add at home, we also have control over which foods we buy.

In the very least, we can try to steer away from the worst offenders. For adults over fifty, the number one source of sodium intake is bread. For younger adults, the greatest contribution of sodium to the diet is not canned soups, pretzels, or potato chips but a seemingly unprocessed food—chicken.¹⁹³² Salt is actually injected into the chicken meat, in part to solubilize the muscle proteins to a gel for optimum texture.¹⁹³³ The commentary notes that although sodium levels are going down in some sectors of the food industry, the opposite seems to be happening in the meat industry, where “the addition of salt to poultry, meats, and fish appears to be occurring on a massive scale.”¹⁹³⁴ Impractical or not, we can shop for low-sodium options, eat out less, and stop adding salt in the kitchen and dining room.¹⁹³⁵

LOW INSULIN INDEX

The Hormone of Plenty

Insulin can be thought of as the “hormone of calorie prosperity.”¹⁹³⁶ After a meal, our blood is awash with calories. The starches we eat are broken down into simple sugars, the proteins into amino acids, and the fats into fatty acids, all of which are absorbed into our bloodstreams. Insulin then goes to work to distribute and store this bounty. It moves the blood sugars into our muscles to fuel our movement, gets our cells to take up the amino acids to build new proteins, and stockpiles circulating fatty acids into our fat stores. Insulin drives fat storage both by directing fat from our bloodstreams into our fat cells and by telling our fat cells to stop burning calories. Insulin is, after all, the signal of abundance.

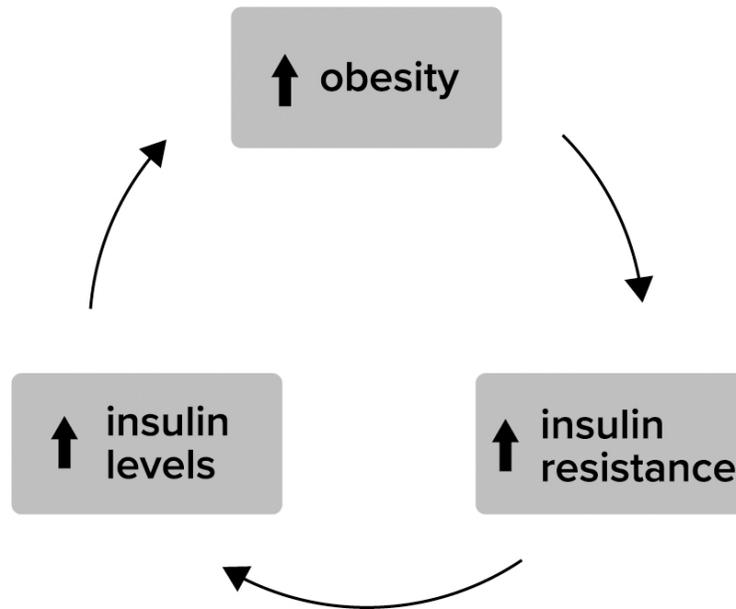
Should we become obese, fat can spill out from our overbloated fat cells back into our bloodstreams and get lodged in our muscles. When this happens, it can interfere with insulin signaling, causing our muscles to become less responsive to insulin, a phenomenon known as *insulin resistance*. Normally, our muscles take up blood sugar in response to insulin, but if they become resistant to the effects of insulin, the sugar remains in the blood and can build up to dangerous levels. To prevent this, our bodies produce even more insulin to force more blood sugar into our muscles. But all that extra insulin in our system can cause additional fat storage and result in a vicious cycle: obesity leading to insulin resistance, which leads to higher insulin levels that then lead to more obesity and even more insulin resistance.

When insulin resistance gets so bad that our insulin production can no longer keep up and overcome it, our blood sugars start creeping up and we become prediabetic and then progress to full-blown diabetes. Instead of treating the cause—insulin resistance—with lifestyle medicine to try to reverse the diabetes, what do most doctors do? Prescribe even *more* insulin, which can perpetuate the cycle. With injections, insulin levels can be forced so high that even resistant muscles will concede, but what effect will all that extra insulin have on our fat stores? Within the first year of starting insulin, type 2 diabetics typically gain between seven and twenty pounds of “insulin-associated weight gain.”¹⁹³⁷

The Insulin-Obesity Cycle

Obesity can kick-start the vicious cycle leading to the insulin resistance, which leads to elevated insulin levels, which leads to more obesity, as illustrated in the figure below.

You can also become insulin resistant without being obese. The fat that ends up clogging our muscles and causing insulin resistance can come from the fat we wear *or* the fat we eat. Normally, we may have as little as 100 $\mu\text{mol/l}$ of free fat floating around in our bloodstreams at any one time, but those who are obese may have up to 800 $\mu\text{mol/l}$. However, skinny people can reach 800 $\mu\text{mol/l}$ just eating a high-fat diet. In other words, a thin person eating a low-carb diet can have the same level of fat in their blood that an obese person does.¹⁹³⁸



Infuse fat into people’s veins through an IV, and, by using a high-tech type of MRI scanner, you can show in real time the buildup of fat in muscle cells within hours, accompanied by an increase in insulin resistance. The same thing happens when you put people on a high-fat diet.¹⁹³⁹ Feed folks even a single high-fat meal, and within six hours, their insulin sensitivity can be cut in half, meaning their insulin resistance shoots up.¹⁹⁴⁰ Do this day after day, and insulin levels can rise to compensate, which can then lead to weight gain as the vicious cycle starts turning.¹⁹⁴¹

Some people are born with higher-than-normal insulin levels and naturally have a higher propensity to gain weight, suggesting that the cycle can also start with an elevated insulin level, leading to elevated obesity and, subsequently, elevated insulin resistance.¹⁹⁴²

The causal role of high insulin levels in obesity was established in a study published in 2018 entitled “Reducing Insulin ... in Adults Reverses Diet-Induced Weight Gain,” but the adults they were talking about were adult mice.¹⁹⁴³ You can prove insulin drives obesity by genetically engineering a low-insulin mouse that is essentially immune to obesity, but how can you prove it in people?¹⁹⁴⁴ The closest we’ve come is the demonstration that drugs that lower insulin levels do cause weight loss in obese adult humans,^{1945,1946} but the drugs also may have direct effects on body fat that could account for the benefit.¹⁹⁴⁷ So while we don’t know for certain, I think there’s enough evidence to try to keep our insulin levels within the normal range.¹⁹⁴⁸

Break the Cycle by Improving Insulin Sensitivity

One way to lower our insulin levels is to make our insulin work better. The reason our bodies pump out so much insulin is to overcome any resistance, so by improving the insulin sensitivity of our muscles, we can make a little insulin go a long way. How? You can do it

with exercise (both endurance and resistance training), weight loss, or reducing your intake of fat—but not necessarily all types of fat.¹⁹⁴⁹ While the monounsaturated fats concentrated in nuts, olives, and avocados appear more likely to be detoxified or safely stored away, the saturated fats concentrated in meat, dairy, and junk can create the toxic breakdown products in our muscle cells thought responsible for the development of insulin resistance.¹⁹⁵⁰

Experimentally shifting people from animal fats to plant fats can improve insulin sensitivity even without changing the overall quantity of fat eaten.¹⁹⁵¹ Thinking this may help explain why those eating more plant-based diets have less insulin resistance, researchers at Imperial College London set out to compare the amount of fat clogging the muscle cells of vegans versus omnivores.¹⁹⁵² So as not to give the vegan group an unfair advantage, the researchers recruited omnivores who were as slim as the vegans. The researchers wanted to know if plant-based eating had a direct benefit beyond simply indirectly pulling fat out of the muscles by helping people lose weight in general. The vegans were found to have significantly less fat trapped in their muscle cells, which can translate into less insulin resistance and lower insulin levels.¹⁹⁵³

So can switching fats help with weight loss? Amazingly, Australian researchers found that even if you feed people about the same number of calories and the same amount of fat, but switch out meat and butterfat for olive oil, nuts, and avocados, you lose nearly six more pounds of fat in a single month.¹⁹⁵⁴ You can certainly overdo plant fats, though. On high-fat diets, the type of fat appears to matter less.¹⁹⁵⁵ Have people drink nearly a half cup of oil, and you can temporarily triple their insulin resistance in a matter of hours.¹⁹⁵⁶

Break the Cycle by Lowering Insulin Spikes

In addition to making our insulin work better by improving our sensitivity to it, we can lower our insulin exposure by choosing foods that cause less of an insulin surge. Although those who are born with¹⁹⁵⁷ or develop higher-than-normal insulin spikes after meals are at elevated risk of weight gain¹⁹⁵⁸ and obesity,¹⁹⁵⁹ anyone can get an exaggerated insulin response to Wonder Bread.

High glycemic loads are the primary stimulus for insulin release as our bodies desperately try to sock away blood sugar from the rapidly digested sugars and starches, as I described in the Low Glycemic Load section. Randomized controlled trials clearly show that swapping out refined grains in favor of whole grains reduces insulin spikes¹⁹⁶⁰ (likely due to the fiber content).¹⁹⁶¹ Remember, though, insulin doesn't just deal with carbohydrates after a meal but protein and fat as well.

To their credit, low-carb and paleo diet advocates identify insulin as playing a role in the obesity epidemic, but they often don't appear to recognize the broader scope of insulin triggers. Since carbs increase insulin, the argument goes, we should eat lots of meat, which is just fat and protein with zero carbs. That wouldn't cause an increase in insulin, right? Wrong. We've known for more than a half century that if you feed people a steak, their insulin levels go up.¹⁹⁶² Pretty much pure protein (like whey powder) and pure fat can have a similar effect.¹⁹⁶³ Have people eat some lentils with butter, and you get a 60 percent higher insulin reaction to pure sugar compared to lentils alone.¹⁹⁶⁴ That's why we need more than a glycemic index. We need an insulin index. We need to feed people dozens of different foods and just measure what kind of insulin reactions they get. And that's exactly what researchers did.

What do you think causes the biggest insulin reaction: a large apple, an orange, a cup of oatmeal, a cup and a half of white-flour pasta, four Chips Ahoy! chocolate chip cookies, a bunless burger, or a fish fillet?

Is that your final answer?

Well, surprisingly, beef and fish cause more insulin to be released.^{1965,1966} In terms of meat, the original study looked only at beef and fish, but subsequent studies found the insulin response to chicken and pork was just as high.¹⁹⁶⁷ It turns out meat protein causes almost exactly as much insulin release as pure sugar.¹⁹⁶⁸ So, based on their own logic, low carbbers and paleo folks should be reaching for big bowls of pasta rather than meat.

Those eating plant-based diets average significantly lower insulin levels and have less insulin resistance, even compared to nonvegetarians at the same body weight.^{1969,1970} In fact, those who eat meat have up to 50 percent higher insulin levels in their bloodstreams.^{1971,1972} Might that just be because they're more sedentary or something? Researchers from the University of Memphis decided to put it to the test by placing men and women on a plant-based diet and got significant drops in insulin within just three weeks.¹⁹⁷³ But add some egg whites to the plant-based diet, and you can cause a "dramatic"¹⁹⁷⁴ rise in insulin output—as much as 60 percent within just four days.¹⁹⁷⁵

Fish and poultry may be even worse than the egg whites.¹⁹⁷⁶ Add about half a can of tuna to some spaghetti, and induce about a 70 percent higher insulin spike in diabetics.¹⁹⁷⁷ Skinless chicken breast and white rice cause an insulin reaction closer to straight sugar than rice alone.¹⁹⁷⁸ Compared to chicken, the meat-free tastes-like-chicken Quorn causes up to 41 percent *less* of an insulin reaction within fifteen minutes.¹⁹⁷⁹

Low-Carb and Paleo Diets Put to the Test

In a study out of MIT, researchers increased the carbohydrate intake of subjects by up to hundreds of grams a day, yet their insulin levels went down.¹⁹⁸⁰ How is that possible? The researchers weren't feeding people jelly beans and sugar cookies; they fed them whole plant foods—lots of whole grains, beans, fruits, and vegetables.

What if you instead put someone on a very-low-carb diet like an Atkins diet? Low-carb advocates such as Dr. Eric Westman, author of the *New Atkins Diet* books and the person who took over after the old Dr. Atkins died, assumed doing so would lower insulin levels.¹⁹⁸¹ But what they found was that there is no significant drop in insulin levels on very-low-carb diets. Instead, there is a significant rise in bad LDL cholesterol levels¹⁹⁸² and a significant crippling of artery function,¹⁹⁸³ which helps explain why those eating more low-carb diets tend to live significantly shorter lives.¹⁹⁸⁴

Atkins is an easy target, though. No matter how many newer-than-new Atkins diets come out, it's still old news. What about the paleo diet? The paleo movement gets a lot of things right. It tells people to ditch dairy and donuts, eat lots of fruits, nuts, and vegetables, and cut out a lot of processed junk. But a study published in the *International Journal of Exercise Science* has raised concerns.

Researchers took young healthy people and put them on a paleo diet along with a CrossFit-based, high-intensity circuit training exercise program. If you lose enough weight by any means, whether by exercise, stomach stapling, chemotherapy, or a hearty cocaine habit, you can temporarily drop your cholesterol levels no matter what you eat. After ten weeks of hard-core workouts and weight loss on the paleo diet, however, the study participants' LDL cholesterol *still* went up—and it was even worse for those who started out the healthiest. Those who started the study with optimal levels (under 70) had a 20 percent elevation in this leading risk factor for heart disease, our number one killer.¹⁹⁸⁵ The researchers concluded that "the Paleo diet's deleterious impact on blood lipids [fats] was not only significant, but substantial enough to counteract the ... improvements commonly seen with improved fitness and body composition."

Exercise is supposed to make things better.

On the other hand, put people on a plant-based diet and a modest, mostly walking-based exercise program, and within three weeks, their bad cholesterol can drop 20 percent and their insulin levels can plummet 30 percent, despite a 75–80 percent carbohydrate diet.¹⁹⁸⁶ In contrast, the paleo diet appeared to have "negated the positive effects of exercise."¹⁹⁸⁷

Animal Protein vs. Plant Protein

What about plant proteins? Although isolated soy protein causes an insulin surge similar to meat, dairy, and eggs, comparing foods to foods,¹⁹⁸⁸ adding fish or egg whites to rice amplifies the insulin reaction, but adding tofu does not.¹⁹⁸⁹ Similarly, a whole soy food significantly lowers insulin levels, but soy protein supplements do not.¹⁹⁹⁰

Add tuna to mashed potatoes, and the insulin reaction is about 50 percent higher than eating the mashed potatoes alone.¹⁹⁹¹ Adding broccoli instead, however, results in the insulin response being cut about 40 percent within the first thirty minutes.¹⁹⁹² This didn't

appear to be a fiber effect, since giving the equivalent amount of isolated broccoli fiber provided no significant benefit. The differential effect of plant versus animal protein has been attributed to their contrasting amino acid profiles.¹⁹⁹³

Plant proteins tend to be lower in the branched-chain amino acids (BCAAs) and the sulfur-containing amino acid methionine, which both have been associated with insulin resistance.¹⁹⁹⁴ To date, most of the research on restricting methionine intake has been about preventing cancer growth and slowing aging,¹⁹⁹⁵ but more recently, it has been presented as a “useful nutritional strategy” to combat insulin resistance.¹⁹⁹⁶ Sticking to plant-based sources of protein would cut methionine intake about in half, resulting in significantly lower blood levels.¹⁹⁹⁷ As such, following purely plant-based diets has been put forth as a feasible “life extension strategy,”¹⁹⁹⁸ but there are myriad reasons why plant-based diets have been shown to improve insulin resistance.¹⁹⁹⁹ You can’t prove methionine is playing a specific role until you isolate it out. To date, the trials demonstrating better insulin sensitivity on diets that just specifically restrict methionine have all been done on rodents,²⁰⁰⁰ but that’s not the case for branched-chain amino acids.

What Are Amino Acids?

Amino acids are the building blocks of proteins. There are about twenty different kinds,²⁰⁰¹ similar to the number of letters in the alphabet. Just as different sentences can be made from different combinations of letters, different proteins are made from stringing together different sequences of the various amino acids. Three of the amino acids—leucine, isoleucine, and valine—have fatty side-chains that branch off from their central structure and are thereby referred to as *branched-chain amino acids*.

Branch Out Your Proteins

When researchers analyzed differences in the blood among people with different insulin levels,²⁰⁰² in addition to finding the saturated fat connection, they uncovered that the levels of branched-chain amino acids in the blood were correlated with insulin resistance.²⁰⁰³ A number of potential mechanisms were identified, from toxic metabolites²⁰⁰⁴ to the stimulation of a fat-generating enzyme complex.²⁰⁰⁵ Since that initial publication, an “overwhelming” number of studies²⁰⁰⁶ have consistently shown that blood and urine levels of branched-chain amino acids are tied to insulin resistance. This doesn’t necessarily mean that decreasing intake of BCAAs will help, though, since there are other factors that influence BCAA levels in the blood.²⁰⁰⁷

Short-term dietary tweaks like swapping out meat lasagna for vegan lasagna can lower levels a bit,²⁰⁰⁸ but even those sticking entirely to plant proteins only have about 5 percent lower BCAA levels in their bloodstreams.²⁰⁰⁹ Is that enough to make a difference? Well, meat consumption is associated with increased insulin levels,²⁰¹⁰ weight gain,²⁰¹¹ and higher diabetes risk,²⁰¹² and substituting in even just 5 percent of plant protein for animal protein may decrease diabetes risk by 23 percent.²⁰¹³ These data circumstantially support the contention that insulin resistance could help explain the meat-obesity connection,²⁰¹⁴ but you don’t know if amino acids are playing a starring role until you run the experiment and put it to the test.

Indeed, just like you can make someone insulin resistant by infusing fat into their bloodstreams, you can do the same thing by infusing amino acids.²⁰¹⁵ Down a protein drink of just straight whey and water, and it can cause insulin resistance within hours.²⁰¹⁶ Give some vegans BCAAs, and you can make them as insulin resistant as omnivores.²⁰¹⁷ Or you can do it the other way: Take some omnivores and put them through even just a “48-hour vegan diet challenge,” and you can produce significant improvements in metabolic health. After two days on a healthy plant-based diet, not only did cholesterol and triglycerides drop but so did insulin and insulin resistance, presumed to be due in part to the “strong

modulatory effect” on circulating BCAA levels. Because the benefits appeared so rapidly, the researchers suggested metabolic benefits could be gotten from an “intermittent vegan diet” or even the “flexitarian approach” of alternating between animal and plant protein choices.²⁰¹⁸

In that case, does protein manipulation then translate to weight loss? To see if lowering amino acids would improve insulin resistance—and, ultimately, accelerate weight loss—researchers put a group of overweight men on a “protein-restricted diet,” which is to say a *normal* protein diet. The recommended dietary allowance for protein is about 50 grams a day (46 for women, 56 for men).²⁰¹⁹ The researchers took men who were averaging twice that—112 grams, which is about the average of what many American men get²⁰²⁰—and randomized them down to 64 grams of protein a day. They were still getting more protein than they needed.

The levels of branched-chain amino acids circulating in the lower-protein group dropped as suspected, but did they lose weight? Both diets were designed to have the same number of calories, so six weeks later, both groups should weigh the same, right? The body weight and fat mass of the regular protein group didn’t change, but the lower protein group lost about six pounds.²⁰²¹ BCAAs may explain why those randomized to a plant-based diet eliminate significantly more of the deeper, more dangerous fat, even when taking in the *same* number of calories.²⁰²²

FOOD FOR THOUGHT

Given the metabolic harms of excess BCAA exposure, leaders in the field have suggested the invention of drugs to block BCAA absorption, which “may represent a translatable and sustainable approach to promote metabolic health and treat diabetes and obesity without reducing caloric intake.”²⁰²³ Or we can just not eat so many branched-chain amino acids in the first place. BCAAs are found mostly in meat, including chicken and fish, dairy products, and eggs.²⁰²⁴ This is one postulated explanation of why animal protein has been associated with higher diabetes risk, whereas plant protein appears protective.²⁰²⁵

Figuring out the “appropriate upper limits” of animal protein intake “may offer a great chance for the prevention of T2D [type 2 diabetes] and obesity,”²⁰²⁶ but it need not be all or nothing. Cutting down on dairy consumption may not be enough,²⁰²⁷ but even “intermittently substituting vegan meals in otherwise animal-based diets” may be beneficial in this regard.²⁰²⁸

From an insulin standpoint, the worst of both worlds would presumably be the combination of animal protein and a high glycemic load—think burger on a bun, meat and potatoes, or a deli meat sandwich. The joint induction of insulin resistance and spiking blood sugars is a bad combo.²⁰²⁹

The advice to avoid eating animal protein and refined carbs together was one of the tenets of the “food combining” dogma popularized in books like *Fit for Life*. Though the rationale given at the time was “frankly laughable”²⁰³⁰ from a scientific standpoint, they may have stumbled onto something. When people were randomized to a “low-insulin-response” diet that included advice to separate out the consumption of foods rich in carbohydrate or protein at different meals, their insulin levels dropped and they lost an extra six pounds over twelve weeks compared to people on a diet designed with the same number of calories but no special insulin-reducing aspects.²⁰³¹

Thankfully, the combo effect doesn’t appear to extend to legumes. Despite being rich in protein and starch, the insulin index of legumes, such as beans, split peas, chickpeas, and lentils, appears to parallel their very low glycemic index.²⁰³² So to reduce insulin levels to potentially facilitate weight loss: Rule #1: Avoid high-glycemic foods; Rule #2: Make plant protein your preference; and Rule #3: When you do eat animal protein, try to pay particular attention to Rule #1.

MICROBIOME-FRIENDLY

Tenant Building

Surrounded on all sides by fattening temptations, our obesogenic—obesity-generating—environment is hard to escape,²⁰³³ though some people do manage to navigate their svelte selves through. If the epidemic were purely due to external factors, wouldn’t everyone be obese? Some individuals seem to be more susceptible than others, which suggests a genetic component. Partial heritability is supported by studies of twins and adopted kids,

but the genes we've identified only account for a small amount of the variation in body size between individuals.²⁰³⁴ Might a role be played by the variation in our "other genome"? That is, the DNA contained in all the different microbes that inhabit our bodies? We have one hundred times more bacterial genes inside us than human genes.²⁰³⁵

We have trillions of bacteria living inside each of us. One professor emeritus went as far as to say, "*Nous sommes toutes les bacteries*," which translates to "We are all bacteria,"²⁰³⁶ a provocative way of acknowledging there are more bacterial cells and genes in our own bodies than there are human cells and genes. And most of those bacteria live in our gut.

The colon used to be viewed as merely a retention tank for waste and that water absorption was its big biological function.²⁰³⁷ Our ignorance arose from "difficult access to the large intestine"²⁰³⁸ and the fact that we weren't able to culture most of the gut flora outside of the body. About three-quarters of gut microbes fail to grow under standard laboratory conditions,²⁰³⁹ and so remained the "dark matter" of fecal matter.

How do you study something you can't study?

Today, we have advanced DNA fingerprinting techniques to unravel the mystery. The first time scientists attempted to sequence all the genes of a bacterium, it took thirteen years.²⁰⁴⁰ These days, the same feat might take only a few hours.²⁰⁴¹ With all this new knowledge, what we learned is that each one of us can be thought of as a superorganism, a kind of human-microbe hybrid.²⁰⁴²

The human colon has been considered the most biodense ecosystem in the world, meaning there's more life concentrated in our colons than anywhere else on Earth.²⁰⁴³ Many probably think that stool is composed primarily of undigested food, but most of it—about 75 percent—is pure bacteria.²⁰⁴⁴ Trillions and trillions of them—about half a trillion per teaspoon, in fact.²⁰⁴⁵ We are bacteria factories. As Neil deGrasse Tyson put it, "More bacteria live and work in one linear centimeter of your lower colon than all the humans who have ever lived."²⁰⁴⁶

What's in it for us? What do we get for housing these trillions of tenants? Rent is paid in the form of boosting our immune systems, balancing our hormones, improving digestion, and making vitamins for us. We feed them, and they feed us right back. Our gut bacteria have been referred to as a "forgotten organ."²⁰⁴⁷ They weigh as much as one of our kidneys and are as metabolically active as our livers.²⁰⁴⁸ They may have control over as many as one in ten metabolites measured in the bloodstream.²⁰⁴⁹ We have about twenty-three thousand genes,²⁰⁵⁰ but, collectively, our gut bacteria have about three *million* genes. Our gut flora don't just constitute any organ but perhaps the "main organ" involved in the cause of obesity.²⁰⁵¹

A Bitter Pill

How do we know gut bacteria have anything to do with gaining weight? More than seventy years ago, we learned that low doses of antibiotics fattened farm animals,²⁰⁵² but, when penicillin is fed to "bubble boy" chicks hatched without any gut bacteria into a sterile environment, the antibiotics have no effect on their weights.²⁰⁵³ That was how it was first discovered microbes could affect body weight.

According to the FDA, animal agriculture now feeds about thirty million pounds of antibiotics to livestock every year,²⁰⁵⁴ four times the amount sold to treat human infections.²⁰⁵⁵ This has raised concerns about the fostering of antibiotic resistance,²⁰⁵⁶ but if these drugs can cause weight gain in farm animals, might exposure to antibiotic residues left in meat contribute to the human obesity epidemic? Public health scientists have raised this as a theoretical possibility,²⁰⁵⁷ especially given the rise in fish farming.²⁰⁵⁸ It can take as much as a half pound of antibiotics to produce just one pound of salmon,²⁰⁵⁹ for example, which helps explain why the researchers found most of the samples from common seafood

in the United States tested positive for trace amounts of antibiotics.²⁰⁶⁰ The dose consumed would be minuscule compared to that which doctors too often overprescribe, though.

The average American child may receive three courses of antibiotics by age two, about ten courses by the age of ten, and around seventeen antibiotics courses by age twenty. This is more than twice that of countries like Sweden, suggesting much of the prescribed antibiotic use in the United States is unnecessary.²⁰⁶¹ The American Academy of Pediatrics estimates that as many as ten million antibiotic prescriptions are given out unnecessarily every year.²⁰⁶² Undoubtedly, antibiotics can be lifesaving wonder drugs, but they should be used judiciously—not only to prevent the development of resistant strains but because even a common seven-day regimen can alter your gut flora for years.²⁰⁶³ What role might this be playing in the obesity epidemic?

A compilation of more than a dozen studies involving about a half million children found that exposure to antibiotics during infancy was associated with an increased risk of becoming overweight during childhood.²⁰⁶⁴ And the greater the exposure, the greater the risk.²⁰⁶⁵ Each additional course of antibiotics in early life was found to be associated with a 7 percent increased risk of our kids becoming overweight.²⁰⁶⁶ How do we know it's cause and effect, though? Maybe parents who overfeed their kids are more likely to pester doctors for prescriptions?²⁰⁶⁷

Studies have shown that, compared to control subjects, those treated with antibiotics gain more weight—and in some cases, much more weight, like an average of nine pounds over a control group.²⁰⁶⁸ The controls didn't need antibiotics, though, because they weren't sick. Perhaps simply having an infection may lead to weight gain,²⁰⁶⁹ or even having an infection cleared up. For example, a group of patients with a stomach infection called *Helicobacter pylori* were randomized to either antibiotics or placebo. The antibiotic group gained more weight, but maybe it was due to their appetites being restored because their infections were cleared.²⁰⁷⁰ How can we know for certain?

To truly put it to the test, you'd have to randomize healthy people to either antibiotics or sugar pills. Just such a study was published on U.S. Navy recruits in 1955.²⁰⁷¹ Those on the antibiotics gained about a pound a month more than the placebo group, suggesting that our gut flora do indeed play a role in controlling our weight.

Eating for Trillions

When antibiotics are necessary, doctors can try to limit their collateral damage by using a more laser-like approach in their prescribing, rather than carpet-bombing germs with broad-spectrum antibiotics. There's even been a proposal to “bank every healthy child's fecal specimen” so we can chase each antibiotic course with a dose of their pretreatment microbes.²⁰⁷² Another controversial suggestion involves how to best start our children's gut flora out on the right foot.

Most of the microbes populating our colons first originate from our mothers' vaginal flora, which we acquire during birth. What about those born via cesarean section? Instead of getting their mothers' vaginal flora, infants born by cesarean delivery start out with microbiomes more closely representing that of the operating room.²⁰⁷³ This may help explain why children born by C-section have a 33 percent greater risk of childhood obesity.²⁰⁷⁴ With so much at stake, “vaginal seeding” has been proposed, in which maternal vaginal fluids are transferred into the mouths of cesarean babies. The American College of Obstetricians and Gynecologists opposes the practice for fear of transmitting any STDs,²⁰⁷⁵ but a study in which women were first screened for such infections found that vaginal seeding was successful in establishing a more natural gut flora in their infants.²⁰⁷⁶

Breast milk naturally contains special compounds that can nourish the infant's microbiome, which may help explain why breastfed infants are less likely to become obese as children.²⁰⁷⁷ This benefit appears to be limited to those who didn't receive antibiotics

during the breastfeeding period, however, underscoring the importance of our gut flora for weight control.²⁰⁷⁸ Breast is best, but after weaning, what should we eat, and what should we avoid to promote a healthy, slimming microbiome?

They Are What We Eat

Every food choice we make may affect the growth of trillions of bacteria.

I've already explored some of the effects of what we feed our flora, from the benefits of the short-chain fatty acids produced when we feed them fiber to the risks from the TMAO when we feed them meat or eggs. What we eat affects not only what our gut microbes make but also which microbes exist. Remember the steak-munching vegan [here](#)? Just as they didn't harbor the bad bugs that make TMAO, those who've been living off cheeseburgers and milkshakes their whole lives may take months to realize the full potential of increased fiber consumption as they slowly build up the communities of fiber-eating organisms.²⁰⁷⁹

No known single microbial signature exists for obesity,²⁰⁸⁰ but when the microbiomes of obese and nonobese individuals are compared, there are some specific bugs associated with more, or less, weight gain over time. One influential study found eight species of bacteria that appeared protective against weight gain, and they all ate fiber.²⁰⁸¹

There's a hormone called *FIAF*, which stands for *fasting-induced adipose factor*. When you fast, your body stops storing fat and instead starts burning it off. FIAF is one of the hormones that signal our bodies to make this switch. This may be one way our gut flora manage our weight. Some bacteria repress this hormone, thereby increasing the tendency to store fat, whereas the short-chain fatty acids made by our fiber-eating bacteria can boost FIAF production.²⁰⁸²

Eating fiber-rich foods has the double benefit of directly resulting in the formation of short-chain fatty acids and selectively cultivating the bugs that make it. Ounce for ounce, the colon contents of those eating more plant-based diets have nearly three times the capacity to form short-chain fatty acids.²⁰⁸³ In this way, eating healthfully not only provides more raw materials for short-chain fatty acid production but improved microbial machinery to churn out more of it. In contrast, putting people on a low-carb diet can slash short-chain fatty acid production by up to 75 percent.²⁰⁸⁴

Another way your gut flora can differentially affect your weight is through enhanced or reduced energy harvest. Some types of bacteria are better than others at extracting calories from our gut contents. Feed a group of people the exact same 2,400 calories, and based on the calorie content of their stools, some retain 2,350 of those calories, while others may only hold on to about 2,200.²⁰⁸⁵ Calories that end up in the toilet are calories that can't end up on our hips.

Certain obesity-related bacteria in your colon can take your waste, break it down even further, and release calories that are then absorbed back into your bloodstream. Just when your body is trying to get rid of all your waste, the calories can come bouncing right back. Take, for example, a grouping of bacteria called *Firmicutes*. A 20 percent relative increase in *Firmicutes* was associated with an increase of about 150 calories in daily calorie absorption, whereas a 20 percent increase in a different grouping of bacteria was associated with a *decrease* of about 150 daily calories.²⁰⁸⁶ This may help explain some of the edge those eating more plant-based diets have for weight control, as DNA fingerprinting of vegetarian feces has found significantly more of the lean-type bacteria.²⁰⁸⁷

Change Your Diet, Change Your Microbiome

More than two thousand species of bacteria have been characterized in the human gut, yet each of us tends to have a unique collection.²⁰⁸⁸ Remarkably, however, all of humanity appears to cluster toward one of two broad categories called *enterotypes*.²⁰⁸⁹ Enterotypes

are not like blood types, which put us distinctly into specific immutable categories.²⁰⁹⁰ Instead, our gut flora exist in more of a continuous gradient with tendencies to drift one way or another. And when it comes to our gut flora, there are apparently two types of people in the world: those who grow mostly *Bacteroides* species and those who grow mostly *Prevotella*.

It's pretty amazing that despite so many different types of gut bacteria, people tend to settle into just one of two groups. Researchers figure our guts are like ecosystems.²⁰⁹¹ There are a lot of different species of animals on the planet, for example, but they aren't randomly distributed. You don't find dolphins in the desert. In the desert, you find desert species, and in the jungle, you find jungle species, because each ecosystem has different selective pressures like rainfall or temperature. The enterotype data suggest there are two types of colon ecosystems, so you can split humanity into people whose guts grow a lot of *Bacteroides*-type bacteria and those whose guts are better homes for *Prevotella* species.

Your enterotype doesn't seem to depend on where you live, whether you are male or female, or how old you are. What matters is what you eat. Researchers looked at more than one hundred different food factors, and it turns out *Bacteroides* and *Prevotella* are kind of opposites. *Bacteroides'* prevalence is correlated to the consumption of components found in animal foods, such as animal fat, cholesterol, and animal protein, whereas *Prevotella* are linked to constituents found almost exclusively in plant foods.²⁰⁹² *Prevotella* are fiber-feeders and pump out more short-chain fatty acids.²⁰⁹³

Native Africans who eat largely plant-based diets tend to have a *Prevotella* enterotype, while African Americans eating a typical Western diet tend to be in the *Bacteroides* camp. This may help explain why African Americans have fifty times more colon cancer, since short-chain fatty acids don't just protect against obesity but have anticancer properties as well.²⁰⁹⁴ The question then becomes: *How long does it take to shift your gut flora from one enterotype to the other?*

Researchers started giving Africans an American-style diet and African Americans a much more plant-based, African-style diet. Perhaps skeptical that Americans would actually eat real food, the researchers made exchanges like swapping out hot dogs in favor of veggie dogs rather than feeding them more typical African fare (such as phutu, a grain-based porridge).²⁰⁹⁵ Still, within only two weeks, remarkable mirror-image changes were found in the gut flora in the respective groups, with the colonic health of the Africans taking a dive and that of the Americans significantly improving.²⁰⁹⁶

What's the absolute fastest you can change your microbiome? Researchers came up with diets from both extremes to find out: a plant-based diet rich in grains, beans, fruits, and vegetables, and an "animal-based" diet composed of meats, eggs, and cheeses. Within twenty-four hours of switching between the two diets, there was a substantial shift. So, to answer the question: basically as soon as food hits our colons. What happened, for example, to the lifelong vegetarian who got placed on the animal-based diet? Predictably, he started out *Prevotella*, but within days, his *Prevotella*-to-*Bacteroides* ratio completely flipped. His entire gut flora got turned on its head.²⁰⁹⁷

The fact that our gut can so rapidly switch between herbivorous and carnivorous functional profiles presumably has evolutionary benefits. If you take down a mammoth and eat meat for a couple of days before reverting to plants, you want your gut to be able to adjust. This flexibility is manifest in the diversity of human diets to this day, but what's the healthier state to be in most of the time? On the plant-based diet, the subjects' guts yielded more protective short-chain fatty acids, fewer carcinogens, and less of the rotten-egg gas hydrogen sulfide. Hydrogen sulfide is made by pathogens such as *Bilophila wadsworthia*, which increased on the animal-based diet. That stinks because ... well ... it stinks and because hydrogen sulfide can damage DNA.²⁰⁹⁸ (The only pathogens found more of on the plant-based diet were plant viruses such as those that attack spinach.²⁰⁹⁹)

The benefits of plant-based eating need not be all or nothing, though. Those highly adherent to a Mediterranean diet filled with fruits, vegetables, and beans, while averaging no meat (including fish), eggs,²¹⁰⁰ or dairy on a day-to-day basis, had comparable short-chain fatty acid levels to vegans, even though the Mediterranean diet adherents weren't completely plant-based all the time.

Garden Variety

Having a greater diversity of gut flora, a greater “bacterial richness,” is also associated with less body fat²¹⁰¹ and less weight gain over time.²¹⁰² The richest microbiomes ever recorded were those of the Yanomami tribe in the Amazon jungle who had no previous contact with the modern world.²¹⁰³ Traditional societies tend to have more diverse gut flora in general, and the key is thought to be their extraordinary fiber intakes, which can reach 120 grams a day,²¹⁰⁴ nearly eight times the American average.²¹⁰⁵

Our modern, low-fiber diet is considered a “key reason of microbiome depletion.”²¹⁰⁶ Pregnant women who eat more fiber have heightened microbial richness, which may have long-term effects on the future health of the next generation.²¹⁰⁷ We're slowly losing more and more of our microbes with every generation, placing some of our good bacteria at risk for extinction.²¹⁰⁸ It may be a case of *use it or lose it*. “You just might consider choosing a salad at lunch today or an extra serving of beans at dinner,” one microbiologist commented. “Future generations may thank you, too.”²¹⁰⁹

Can't you just take a fiber supplement? Unfortunately, they don't seem to work in terms of improving richness of the microbiome,²¹¹⁰ whereas whole foods can. Feed folks whole-grain barley, brown rice, or both for a month, and microbiome diversity improves.²¹¹¹ Interestingly, the combination of equal portions of barley and brown rice resulted in metabolic benefits superior to the benefits from either grain alone, suggesting a synergistic effect. This may help explain the discrepancy between the apparent benefits of whole grains found in population-based studies, versus the disappointing results found in many interventional studies—namely, the failure to produce weight loss.²¹¹² Perhaps simply switching to whole-wheat rolls from white bread may be insufficient to diversify the gut.²¹¹³

Food Additives That May Make Your Gut Leak

Our skin keeps the outside world outside, and so does the lining of our gut. Should our intestinal barrier break down, bacteria can slip into our bloodstreams and trigger inflammation. This may not only spark inflammatory bowel diseases²¹¹⁴ but also, potentially, obesity.²¹¹⁵ How can we keep our gut from getting leaky?

Fiber appears to play a vital role in maintaining our gut barrier,²¹¹⁶ but how? We have specialized cells lining our gut that secrete a mucus layer that forms our first line of barrier defense. When we starve our microbial selves by eating a fiber-depleted diet, our famished flora may turn to munching our mucus as an alternative fuel source and thereby undermine our defenses.²¹¹⁷ Researchers were able to re-create layers of human intestinal cells in a lab and showed that *E. coli* bacteria could be prevented from breaching the barrier by dripping fiber onto the cells at dietary doses. (They used plantains and broccoli.)

The researchers also made a second discovery. Bacterial invasion was facilitated by the food additive polysorbate 80,²¹¹⁸ an emulsifier commonly found in such processed foods as ice cream, whipped toppings, and cottage cheese.²¹¹⁹ Food additives like polysorbate 80 and carboxymethylcellulose (a thickener sometimes found in foods such as ice cream, salad dressing, and sauces) have in fact been shown to cause weight gain in mice, but they've never been tested directly in people.²¹²⁰ Until they've been proven to be safe, you may want to scrutinize ingredient labels, as well as make sure to rinse your dishes. Traces of dishwashing detergent could have similar adverse effects. Apparently, some people wash dishes and then just leave them to dry without rinsing them, which some gastroenterology researchers have suggested is probably not a good idea.²¹²¹

Eat Lots of Big MACs

If our microbiome is to be considered a separate organ in our body, it's an organ that runs on MAC, or microbiota-accessible carbohydrates. *MAC* is another name for *prebiotics*, primarily the fiber and resistant starch that fuel our gut flora, and is one reason why you

can get an increase of nearly two grams of stool for every one gram of fiber: You're boosting bacterial growth.²¹²² When we eat a whole plant food like fruit, we're telling our gut flora to be fruitful and multiply.

If you don't eat healthfully enough, you can actually starve your microbial self.²¹²³ It's like when astronauts return from spaceflights missing most of their good bacteria because they had limited access to real food. Too many of us may be leading astronaut-like lifestyles here on Earth by not getting enough fresh fruits and vegetables. Astronauts have been documented losing nearly 100 percent of their *Lactobacillus plantarum*,²¹²⁴ a particularly strong fiber-feeder, but most Americans don't have any to begin with. Common in probiotic preparations, these bacteria were found to be missing from the guts of 76 percent of those eating a Standard American Diet. Close to two-thirds of those eating plant-based diets, however, house this friendly flora.²¹²⁵

What we eat today can affect our microbiomes tomorrow. Stool and saliva samples were collected from study subjects for an entire year while hundreds of diet and lifestyle factors were tracked daily. Flossing was found to benefit the microbiome in their mouths, and fiber was found to benefit the microbiome in the gut within a single day.²¹²⁶ But do those benefits translate into weight loss?

Most prebiotic intervention studies to date show improvements in satiety²¹²⁷ and a reduction in body fat,²¹²⁸ including among overweight children²¹²⁹ and adolescents.²¹³⁰ Some used prebiotic powders versus matched placebos, and others tried exchanging different foods. For example, swap out meat for the same number of calories of whole grains, and people lose more weight. The noted increase in microbial diversity may be one of the factors contributing to the extra weight loss.²¹³¹

The Three Ps

The Three Ps for gut health restoration are *prebiotics*, *polyphenols*, and *probiotics*.²¹³² Polyphenols are a class of phytonutrients (health-promoting plant compounds) that have long been investigated as potential candidates to explain some of the benefits of better diets against disease.²¹³³ Polyphenols are produced by plants to protect themselves,²¹³⁴ and we may be able to expropriate and commandeer them for the same purpose.²¹³⁵

Plants live the ultimate sedentary lifestyle. Because they can't move, they've had to evolve a whole other way to respond to threats, and they do so biochemically. They manufacture—from scratch—a dizzying array of compounds to deal with whatever's coming their way.²¹³⁶ For example, if we get too hot, we can move into the shade. But if plants get too hot, they're stuck—they *are* the shade!

Plants have had nearly a billion years to create a whole chemistry set of protective substances, some of which can play a similar role in us. When plants get infected, they produce aspirin, which can come in handy when we get infected ourselves. Plants heal wounds, and so do we, using similar signaling systems.²¹³⁷ Plants have DNA they need to protect from free radical damage, so they cook up complex antioxidants that we can use for ourselves instead of reinventing the wheel. In a sense, the crispers in our fridges are like nature's medicine cabinet.

Naysayers of the power of polyphenols often point to studies showing their low bioavailability. For example, up to 85 percent of the polyphenol pigments that make blueberries blue don't even get absorbed and end up getting dumped into our colons.²¹³⁸

But that may be exactly where some of the magic happens.

Mix those blueberry polyphenols²¹³⁹ with a culture of fecal bacteria, and out pops the growth of beneficial bugs like *Bifidobacteria* and *Lactobacillus*.²¹⁴⁰ Just as plants establish symbiotic relationships with bacteria living inside them (like the nitrogen-fixing bacteria in the roots of legumes that provide built-in fertilizer), they may be able to get along with our gut flora too.

Protein, carbs, and fat are *macronutrients* because we eat them by the gram each day, whereas vitamins and minerals are *micronutrients*, as we may only get thousandths or even millionths of a gram a day. (A gram is about the weight of a raisin.) Even those eating pitifully few plants may take in as much as a full gram of polyphenols a day, though.²¹⁴¹ What effect might they have on our gut bacteria and body weight?

Boosting *Bifidobacteria*

Given the complexity of the human microbiome and our poor state of knowledge, researchers often restrict their focus to the effects of foods on a few familiar species that serve as a proxy for the overall balance of benefit. The bifidogenic effects of foods, for example, may be a good starting point.²¹⁴² *Bifidogenic* refers to foods that foster the growth of *Bifidobacteria*, generally recognized as beneficial bugs. Several studies have reported a relative depletion of *Bifidobacteria* correlating with the development of obesity²¹⁴³ in both children and adults,²¹⁴⁴ and as such, they are commonly found in commercial probiotics.

Certain *prebiotics* like inulin, concentrated in such vegetables as garlic and onions, can have a “huge” bifidogenic effect.²¹⁴⁵ Ironically, inulin is a type of FODMAP, or fermentable oligo-, di-, and monosaccharides and polyols, which are actively avoided by some people with irritable bowel syndrome. Those placed on FODMAP-restricted diets do seem to end up with depleted levels of *Bifidobacteria*, so, in theory, such diets could actually be counterproductive for long-term gut health.²¹⁴⁶

Polyphenols can boost *Bifidobacteria* growth in a test tube within a matter of hours, but can those results be replicated in the real world with polyphenol-rich foods?²¹⁴⁷ Randomize people to about a cup of wild blueberries,²¹⁴⁸ and you can get a significant bump in *Bifidobacteria* in their stools,²¹⁴⁹ but how do you know it was due to the polyphenols and not just the fiber? Well, apples boost *Bifidobacteria*, too,²¹⁵⁰ but the isolated apple fiber pectin alone does not.²¹⁵¹ Bananas have a similar fiber content to berries, but fewer polyphenols. Does eating bananas significantly boost *Bifidobacteria*? No,²¹⁵² which again suggests polyphenols may be playing a special role.

Polyphenol-rich beverages probably provide the best proof. Tea leaves and coffee beans have lots of polyphenols that end up in the brew, leaving behind the fiber. Both green tea²¹⁵³ and coffee²¹⁵⁴ are bifidogenic. For example, three cups of coffee a day can significantly raise *Bifidobacteria* levels in the gut within three weeks.²¹⁵⁵ Adding milk, though, may block some of the benefits. Proteins from dairy, as well as eggs, bind to the polyphenols in coffee.²¹⁵⁶ Soy protein does, too, but unlike milk proteins, your gut flora apparently can strip away the polyphenols from the plant protein in the gut to release them.²¹⁵⁷

So does eating polyphenol-rich foods lead to weight loss? The Harvard studies, following more than one hundred thousand professional men and women, and their diets, for decades, found that those who choose high-polyphenol fruits and vegetables, such as apples, pears, berries, and peppers, gained significantly less weight. This association appeared to be independent of other diet and lifestyle factors, such as total daily fiber intake.²¹⁵⁸ Polyphenols could be another reason to help explain why people randomized to eat three apples or pears a day lose more weight.²¹⁵⁹

Do Probiotic Supplements Work?

If *Bifidobacteria* are so good, why not just take them in a probiotic pill? Probiotic supplements have been shown to be effective in randomized placebo-controlled trials for conditions such as antibiotic-associated diarrhea,²¹⁶⁰ but what about weight loss? Can't hurt, right? Well, a study published out of the Netherlands has raised concerns about probiotic safety.²¹⁶¹

Acute pancreatitis is on the rise and can become life-threatening in some cases. This sudden inflammation of the pancreas allows bacteria to break through our gut walls and infect our internal organs.²¹⁶² Antibiotics don't seem to prevent this complication, but how about probiotics? They seem to work on rats. If you cause inflammation by mechanically damaging the pancreas, not only may probiotics show "strong evidence for efficacy," but there were "no indications [of] harmful effects."²¹⁶³ But that was with rats—what about us? Clinical researchers decided to put it to the test.

Half of a group of pancreatitis patients were given probiotic pills, while the other half got sugar pills. Within ten days, the mortality rates in the probiotics group shot *up* compared to placebo. More than twice as many people died on the probiotics. Thus, the researchers concluded, probiotics "can no longer be considered to be harmless." The researchers were criticized for not cautioning patients about the risk before they signed up for the study.²¹⁶⁴ (The study subjects were told probiotics had what the researchers described as "a long history of [safe] use" with no known side effects.²¹⁶⁵) In response to the criticisms, the researchers replied that there were no known side effects—*until* their study.²¹⁶⁶

Risks for healthy individuals are likely to be rare,²¹⁶⁷ but probiotics still may not work as intended. Animal agribusiness doesn't only fatten farm animals with antibiotics but probiotics as well.²¹⁶⁸ A compilation of studies found that human probiotics like *Lactobacillus acidophilus*, for example, commonly found in fermented dairy products, may cause significant weight gain²¹⁶⁹ in piglets²¹⁷⁰ and persons.²¹⁷¹

What about probiotics in general? Probiotic supplements are a multibillion-dollar industry, which raises concerns about conflicts of interest and "publication bias" in the scientific literature.²¹⁷² We know that Big Pharma is infamous for this; industry-funded studies that yield negative results are quietly shelved and buried, so all your doctors get to read are the glowing reports. In making evidence-based decisions for our patients, the peer-reviewed medical literature is the gold standard, but all too often, those with the gold make the standards.²¹⁷³

An investigation into bias in the probiotics literature uncovered that conflicts of interest were commonly not reported, even when the authors were sponsored directly by a yogurt company, for example, and as many as twenty unflattering studies appear to have been hidden from public view.²¹⁷⁴

Still, put all the studies on treating obesity with probiotics together, and overall, a small loss in body weight was found—though there was no significant loss of body *fat*, which is what we really care about when it comes to weight loss.²¹⁷⁵ That small loss in body weight was on average, though, and there are endless variations of probiotic bacterial combinations and dosing, so it's difficult to make sweeping generalizations. However, even some of the most successful trials appear to show only modest benefit, such as a two-pound weight loss over a three-month period.²¹⁷⁶

Probiotics Bearing Fruit

Is it better to get probiotics the way nature intended? If you've ever made sauerkraut at home, you know you don't have to add starter bacteria to get the cabbage to ferment. Why? Because the cabbage leaves acquire lactic acid-producing bacteria while growing out in the fields. This suggests raw fruits and vegetables may not only be a source of prebiotics—that is, fiber—but also a source of probiotics.²¹⁷⁷ Some may even help us reap the rewards. There are bacteria on cruciferous vegetables, for example, that express that magical enzyme myrosinase I talked about in *How Not to Die*. So by eating broccoli-family vegetables, for instance, you may be lining your gut with the very microbes necessary to maximize their benefits.²¹⁷⁸

While working on characterizing these bacterial communities on plants, researchers found that populations on each produce type were significantly distinct from one another.

The tree fruits harbored different bacteria from vegetables on the ground, for example, and grapes and mushrooms seemed to be off in their own little worlds. So if indeed these bugs turn out to be good for us, that discovery would underscore the importance of eating not just a greater quantity but also a greater variety of fruits and vegetables every day. The researchers also found that there were significant differences in the microbiomes of conventional versus organic produce, though we don't yet know enough about these bugs to understand any potential health implications.²¹⁷⁹

Note that it's still important to wash and scrub your fruits and veggies under running water to cut down on food-poisoning bacteria. Don't worry, you're not going to eliminate all the potentially good microbes, since many actually live inside the plant tissues and couldn't be washed off even if you tried.²¹⁸⁰ Because microbes and fresh produce are inseparable, cancer centers used to put patients undergoing chemotherapy on *neutropenic* diets devoid of uncooked fruits and vegetables for fear of foodborne infections in their immunocompromised states. When actually put to the test, though, none of the randomized controlled trials showed a benefit to restricting fresh produce,²¹⁸¹ and one study even found evidence of a *higher* rate of infections.²¹⁸² The researchers speculated that the produce was protective because the friendly flora from fruits and vegetables may have successfully crowded out any bad bugs in the gut.

The Tao of Poo

Given our limited understanding of which bugs are best, combined with the lack of regulatory oversight and quality control in the supplement industry,²¹⁸³ wouldn't it make more sense to reestablish good gut flora with actual gut flora? If our microbiome is an organ, what about an organ transplant?

During World War II, soldiers in Africa were recommended by Bedouins to treat dysentery with "consumption of fresh, warm camel feces," but wouldn't healthy human dung work better?²¹⁸⁴ Remarkably, this concept dates back to the fourth century, when patients with severe diarrhea in China were treated with various preparations of fecal matter, euphemistically presented as "yellow soup" or "golden syrup."²¹⁸⁵ Incidentally, this came from the same medical text that described wormwood as an effective herb against malaria,²¹⁸⁶ a discovery that led to a Nobel Prize in Medicine 1,700 years later in 2015.²¹⁸⁷

What do we know about fecal transplants? Such research could not only offer the potential to treat disease, it could cement the cause-and-effect relationship between our microbiomes and our health.²¹⁸⁸ The first fecal transplant trials were for a potentially life-threatening overgrowth of a hospital-acquired pathogen called *Clostridium difficile*. Prior to the advent of centralized stool banks, patients would have to seek "donations" from friends or relatives.²¹⁸⁹ (It's like what one fly said to the other: "Is this stool taken?")

Once the "logistical challenges of delivering fresh treatment preparations"²¹⁹⁰ were overcome, the specimens were homogenized using a "dedicated" blender and then infused from the bottom up with an enema or top down through a nasogastric tube (a hose through the nose).²¹⁹¹ No turkey basters necessary. More recently, capsules have been developed, but a single dose requires swallowing up to forty large capsules. Definitely not the time to suffer from reflux!

For *Clostridium difficile* infection, fecal transplantation can be a lifesaver. After thousands of successful transplants, it has been proven to be the single most effective therapy for recurrent infection,²¹⁹² with symptom resolution seen in 85 percent of cases.²¹⁹³ (Want to learn more about how you can "Save Lives. Earn Money. Donate Your Stool" to a nonprofit stool bank? Visit www.givepoop.org.)

Doctors who want to try fecal transplants for other conditions must first acquire a special FDA permit.²¹⁹⁴ This is due largely to theoretical concerns about disease transfer. (No such cases have yet been reported.²¹⁹⁵) A case report published in 2015 called "Weight Gain

After Fecal Microbiota Transplantation” definitely raised the stakes, though, for both the potential risks and benefits of the procedure.

A thirty-two-year-old woman “had always been of normal weight” until she received a fecal transplant from a healthy but overweight donor (her daughter).²¹⁹⁶ This was in the United States, so by “normal,” they mean the patient was actually slightly overweight herself with a BMI of 26. After the transplant, however, she gained more than forty pounds, ballooning to obesity at a BMI of 34.5. “She said she felt like there was a switch inside her body,” her gastroenterologist reported.²¹⁹⁷ “No matter how much she ate or exercised, she couldn’t take the weight off ... she’s very frustrated.” The fecal transplant researchers concluded: “We recommend selecting non-overweight donors.”²¹⁹⁸

The same thing happens in mice. Giving mice fecal pellets from an obese mouse resulted in a near doubling in fat mass compared to lean mouse pellets, despite eating the same number of calories.²¹⁹⁹ This proves gut flora can play a pivotal role in obesity ... in mice. What about in people?

Taking a Crack at Weight Loss

Researchers decided to study pairs of human twins “discordant” for obesity, meaning one twin was fat and the other was skinny. What would happen if you switched their microbiomes? The siblings may have been squeamish, so the researchers reverted again to mice. Mice fed stool from the obese twin rapidly swelled in size, but not those fed from the lean twin, despite comparable caloric intakes. Cohousing the mice together prevented the weight gain, however. The lean-type bacteria jumped over to rescue the mouse fed stool from the obese twin, but only in the context of a healthier diet—that is, the microbial cure only worked when the mice were fed diets low in saturated fat and high in fiber, which makes sense since the lean-type bacteria appeared to be fiber-munching, short-chain fatty-acid producers. “Together,” the researchers concluded, “these results ... illustrate how a diet high in saturated fats and low in fruits and vegetables can select against human gut bacteria ... associated with leanness.”²²⁰⁰

The results of the twin study suggest that the role of our gut flora in obesity is simply to help take fuller advantage of a more healthful diet. So if the twins had actually swapped their stools, the obese twins might have only lost weight if they had combined the microbial makeover with healthier eating to aid the colonization of the better bugs.²²⁰¹ With the new bacteria on board, though, the healthier diet could have resulted in more weight loss, even while eating the same number of calories. But you don’t really know until you put it to the test.

If you were surprised by the case report of the mother-daughter fecal transplant, there are even stranger accounts coming out of that world. One gastroenterologist, for example, described a man with alopecia (baldness) who started growing hair after getting a stool transplant.²²⁰² You can’t know if these anecdotes are just one-offs without subjecting them to rigorous randomized controlled trials. Currently, just such a study is under way at Harvard: Stools from lean individuals are being transplanted into obese individuals to see if they suddenly start to lose more weight.²²⁰³ Stay tuned.

There was one study in which gut flora were transferred from lean to obese folks to see if their metabolic states would improve.²²⁰⁴ The researchers wanted it to be a placebo-controlled study. For drug trials, that’s easy: Just give a sugar pill. When you’re sticking a tube down someone’s throat and transplanting feces, though, what do you use as a “poo-bebo”? Both the lean donors and the obese subjects brought in fresh stools, and the obese subjects were randomized to get transplanted with either the donor stool or their own collected feces. That was the placebo—you get your own back! Isn’t that brilliant?

The insulin sensitivity of the skinny donors was up around 50 $\mu\text{mol/kg/min}$. That’s a good thing, because high insulin sensitivity means their insulin resistance, the cause of type 2

diabetes and a potential risk factor for worsening obesity, is low. The obese subjects started out down around 20 $\mu\text{mol/kg/min}$. After an infusion of their own feces, they stayed at around 20 as you'd expect. However, the insulin sensitivity of the group of obese subjects who got the skinny transplant shot up to near where the slimmer folks were.²²⁰⁵ Eureka! Finally, proof in the power of poop.

Some lean-donor stools delivered more benefit than others. It turns out this “super-donor effect” is most likely conveyed, once again, by the numbers of short-chain fatty acid-producing fiber-feeders.²²⁰⁶ Within a few months, however, the bacterial composition returned back to baseline, so the effects on the obese subjects were only temporary.²²⁰⁷ You can get similar benefits by just feeding what few good gut bacteria you may already have. In my NutritionFacts.org video on the subject, we have an animation to illustrate this concept using a bunny analogy:

Imagine you have a shed full of rabbits. If you just fed them pork rinds, they would all die. Of course, you can always repopulate the hutch by infusing new bunnies, but if you keep feeding them pork rinds, they'll eventually die off too. That's like taking probiotics or getting a fecal transplant without changing your diet. On the other hand, even if you start off with just a few bunnies, if you feed them what they're meant to eat, they'll grow and multiply on their own.

Stool transplants and probiotics may only be temporary fixes if we keep putting the wrong fuel into our gut. If we don't change our diets, it may be a waste of money to go shopping for vegan poop on the black market (brown market?). On the other hand, by eating foods rich in *pre*biotics, in other words, increasing “whole plant food consumption,” we may select for *and* foster the growth of our own good bacteria.²²⁰⁸

Is Obesity Contagious?

The fat twin / thin twin study proved obesity could be transmissible from human to mouse, but what about human to human? We've known for years that people who live together share a greater similarity in gut bacteria than those who live apart.²²⁰⁹ Is this just because people living together are eating similar diets, or might they be inadvertently swapping bacteria back and forth? A clue to this mystery came when it was realized that family members don't just share gut microbes with each other but also with the family dog,²²¹⁰ who, one would hope, is eating a different diet.

It turns out homes can harbor a distinct microbial fingerprint. Just by swabbing the doorknobs and light switches, you can tell which family lives in which house. When a family moves, the microbial community in their new house becomes rapidly colonized toward that of their old home. Experimental evidence suggests that individuals raised in a household of thin people may be protected against obesity—no fecal transplant necessary.^{2211,2212} (Instead, people may be sharing gut bacteria from kitchen stools!)

A famous study published in *The New England Journal of Medicine* found that a person's chances of becoming obese increased by more than 50 percent if they had a friend who became obese, suggesting one's social network can also have a big effect.²²¹³ This was chalked up to peers affecting each other's norms and behaviors, such as when a group of friends go out to eat the same fattening food together. Given the evidence implicating the role of gut bacteria in obesity, however, this “raises up the possibility that cravings and associated obesity might not just be *socially* contagious,” a group of scientists speculated, “but rather truly infectious, like a cold.”²²¹⁴ A more positive spin was captured by a pair of Harvard obesity researchers in their editorial in a journal called *Cell Host & Microbe* they entitled “Eat Well, or Get Roommates Who Do.”²²¹⁵

FOOD FOR THOUGHT

What we eat can change the composition of our gut flora—for good or for ill—within twenty-four hours. The most important thing we can do to foster the growth of good gut bacteria is keep them well fed with their favorite foods—the fiber and resistant starch concentrated in whole grains and legumes. [Here](#), I talk about my daily morning BROL bowl, a prebiotic blend you can add to soup, eat as a sweet or savory porridge, or use in all manner of culinary creations. The road to health is paved with good intestines!

RICH IN FRUITS AND VEGETABLES

Do the Studies Bear Fruit?

There is convincing evidence that increasing consumption of fruits and vegetables reduces the risk of three of our leading causes of death—heart disease, stroke, and high blood pressure—and probable evidence it helps protect us from cancer, our other top killer.²²¹⁶ What about obesity? Wouldn't it be a refreshing change from all the restrictive "eat less" messaging to hear a positive "eat more" message? Sometimes proscriptions can backfire and make people want what's been labeled taboo even more²²¹⁷—just ask Eve. Can we flip this "forbidden fruit" effect on its head and start encouraging more fruit?

Studies that followed a combined total of a half million people and their diets over the years have found that those who tend to eat the most fruits or vegetables seem to have 17 percent lower odds of weight gain or abdominal obesity.²²¹⁸ Another study found that over a ten-year period, those who ate more than about three servings of vegetables a day lost as much weight as those who walked four or more hours a week.²²¹⁹ However, people who consume more fruits and vegetables also tend to be more educated and practice other healthy lifestyle behaviors.²²²⁰ The ten-year study did adjust for education, smoking habit, and a few dietary factors, such as meat intake, though.²²²¹ Three Harvard cohort studies went even further. Following more than one hundred thousand men and women for up to twenty-four years, researchers adjusted for a dozen other dietary aspects and took into account lifestyle factors from sleep habits to hours spent watching television. They, too, found consumption of both fruits and vegetables was associated with weight loss over time.²²²²

Although randomized controlled trials are necessary to prove cause and effect, observational studies like these offer the ability to examine dietary influences over the longer term—years or even decades. There have also been some exciting short-term interventional studies, like the study I mentioned earlier in which people lost weight after adding three apples or pears to their daily diets.²²²³ Certain other fruits were not as successful, though. Adding three grapefruit halves, around three kiwifruits, or half a mango a day didn't result in significant weight loss (although it didn't result in weight gain either). Other benefits were noted—for example, grapefruits lowered blood pressure,²²²⁴ kiwifruits improved DNA repair,²²²⁵ and daily mango consumption improved blood sugars²²²⁶—but rather than being studies demonstrating "eat more, weigh less," they ended up being "eat more, weigh the same."

Though a compilation of interventional fruit-and-veggie studies found that most did result in weight loss, they often included other dietary changes, such as swapping out desserts for added fruits.²²²⁷ More recent systematic reviews of the evidence have been more muted in their enthusiasm, finding the overall average of weight reduction to be small²²²⁸ or concluding that simply telling people to eat more fruits and vegetables is in fact fruitless without also having them cut down on things like junk.²²²⁹

On the Juice

Issues have been raised about both the quality and quantity of vegetables prescribed and/or provided in studies. On average, the difference between the "high" and low fruit-and-vegetable groups in studies ended up only being about one and a half servings a day.²²³⁰ Beyond the problem of inadequate "dosing," sometimes the interventions involved processed fruit and vegetable products containing added fat and sugar.²²³¹ For example, one study in which the added-fruit-and-veggie group actually gained weight counted french fries and fruit juice toward their daily intake goals.²²³² Even nonfried potatoes, like mashed, and other starchy vegetables may not have the same weight-reducing potential as nonstarchy veggies,²²³³ and fruit juice can carry the same sugar load as soda²²³⁴ and the

same amount of fiber: zero. Even “high pulp,” “extra pulp,” and “most pulp” orange juices are not significant sources of fiber. It’s all pulp fiction.

Just as population studies have found that greater whole fruit consumption is associated with lower risk of type 2 diabetes yet more fruit *juice* consumption is linked to higher risk,²²³⁵ consuming whole fruits can facilitate weight loss, while drinking fruit juice may promote weight gain.²²³⁶ Even children given 100 percent fruit juice as toddlers tend to be at higher risk of becoming overweight.²²³⁷ This could be in part because juice may be a “gateway drink” to soda consumption.²²³⁸ Either way, the American Academy of Pediatrics, the American Heart Association, and the Institute of Medicine have all recommended that fruit juice be restricted, encouraging whole fruit consumption instead.²²³⁹

How can 100 percent fruit juice be fattening but, at the same time, whole fruit slimming? It’s apparently not just the fiber. Liquid calories in general may be less satiating. If you feed people four hundred calories of fruit juice, they go on to eat 75 percent more of a test meal of mac ’n cheese than if you had instead fed them four hundred calories of whole fruit, even if the equivalent amount of fiber had been stirred into the juice.²²⁴⁰

Could it be because you can down juice in no time, but it takes a while to actually chew through the fruit? That extra time might give your appetite control mechanisms more of a chance to kick in. Researchers put that exact question to the test by measuring satiety after subjects slowly sipped a pound of apple juice in the same time it would take to eat a pound of apples (which is 17.2 minutes, it turns out). Even with the rate of consumption equalized, the apples, not just their juice, were more satiating.²²⁴¹

Some fruit juices, however, don’t seem to cause the same weight gain. Why? To understand that, you need to understand why the body handles the sugar in fruit differently from that of corn syrup and table sugar.

Breaking Down the Walls

How can adding fruits and vegetables to our diets result in weight loss? The obvious answer is that they would displace other foods. Since produce tends to furnish so few calories, swapping in fruits and vegetables for the same weight or volume of most anything else would lower caloric intake. However, some studies have shown weight loss with more fruits and veggies *even with no change in overall calories*.²²⁴² How do we explain that?

In foods, there are intracellular calories and extracellular calories—in other words, calories that are confined inside cells and calories that are free to be absorbed directly. Processed plant foods like fruit juice, refined grains, and sugar are letting it all hang out, and their calories are free for the taking. In contrast, all the calories in *whole* plant foods are not only trapped inside cells—they’re also trapped inside cell walls. Animal cells are encased only in easily digestible membranes, which allow the enzymes in our gut to effortlessly liberate the calories within a steak, for example. Plant cells, on the other hand, have walls that are made out of indigestible fiber.

Our bodies do their best to chew through those walls—literally—to get to all the goodness inside, but in the end, it’s not about what we eat but what we absorb. The way you measure how many calories a food has is to burn it and see how much energy it releases. When it comes to whole plant foods, the combustible calories significantly exceed the metabolizable calories—that is, the calories that actually make it into your bloodstream.²²⁴³ So, by eating extra fruits and vegetables, on paper, it looks like you’re taking in more calories, but when researchers have actually put it to the test and taken careful measurements, they’ve found that you can actually end up with fewer calories in your system.²²⁴⁴

Vegetables may offer the additional advantage of changing the expression of the genes that control our metabolisms. Greens can affect your genes. If you take biopsies of fat from people before and after a few weeks of feeding them extra vegetables, the expression of

hundreds of genes is ramped up or down. By correlating those changes to the same ones you get losing weight through caloric restriction, you can uncover the weight-loss pathways and processes that appear affected by the bump in veggie intake.²²⁴⁵ Give people on a weight-loss diet one to two cups of vegetable juice (low-sodium V8), for example, and they lose more weight than those given none.²²⁴⁶ Vegetables tend to contain less sugar than fruit, though.

What About All the Sugar in Fruit?

Fruit's influence on obesity has been called a "paradoxical effect" thanks to its sugar content.²²⁴⁷ Fruit contains sugars such as fructose, which is also found in table sugar and corn syrup. If sugar is bad for us, how is fruit so good for us?

If you directly compare the effects of a diet restricting fructose from both added sugars and fruit to one that only restricts fructose from added sugars, the diet that kept the fruit did *better*.²²⁴⁸ People lost more weight with the extra fruit present in the diet than when all fructose was restricted across the board.

Is it just the dose? To get the average intake of added sugars in the American diet²²⁴⁹ in fruit form, you'd have to eat about six and a half cups of apple slices a day²²⁵⁰ or nearly eight cups of watermelon.²²⁵¹ Even if you did, though, it wouldn't have the same effect as getting that same amount of sugar from processed sources. As the *Harvard Health Letter* put it, the problems associated with fructose and sugar in general "come when they are *added* to foods." Fruit, on the other hand, is not just harmless but described as "beneficial in almost any amount."²²⁵² *Almost any amount? Can we eat ten servings of fruit a day? How about twenty? That's actually been put to the test.*

Seventeen people were made to eat twenty servings of fruit a day for up to six months. Despite their extraordinarily high fructose intakes—presumably the equivalent of drinking about eight cans of soda a day—the investigators found the subjects actually lost weight and their blood pressures improved,²²⁵³ insulin levels dropped, and cholesterol and triglycerides got better.²²⁵⁴ This is the opposite of what one might expect eating the same amount of fructose in added sugars. Why do our bodies handle the sugars in fruit differently from the sugars added to foods and beverages?

If you drink a glass of water with three tablespoons of table sugar mixed in, which is like a can of soda, you get a big spike in blood sugar within the first hour. Your body freaks out and releases so much insulin you actually overshoot the mark such that, by the second hour, you end up relatively hypoglycemic, dropping your blood sugar below where it was even before you had consumed anything. In response, your body dumps fat into your bloodstream, which can have a variety of adverse effects, such as increasing insulin resistance.²²⁵⁵ That's one of the reasons we shouldn't be drinking soda, aka liquid candy. But what if you added nature's candy—berries?

What if you eat blended berries in *addition* to the sugar? What would happen if you were to repeat the same experiment but add nearly an *additional* tablespoon of sugar—this time in fruit form, the way nature intended, rather than table sugar? Still, downing four tablespoons of sugar instead of three should cause an even bigger blood sugar spike, right? Not only did that not happen, there was no hypoglycemic dip afterward. Blood sugar simply went up and down without that overshoot and without the surge of fat into the blood.²²⁵⁶

Initially, the researchers attributed the difference in response to the thickening effects of the berries, as the soluble fiber in the berries would presumably have a gelling effect. Compared with just guzzling straight sugar water, the berry addition might slow both the rate of stomach emptying and the release of sugars in our intestines. To test to see if it was the fiber, researchers repeated the experiment with berry *juice*, which had nearly all the sugar but none of the fiber. A clear difference was observed early on in the blood sugar response. At the fifteen-minute mark, the blood sugar spike was significantly reduced by

the blended berries, but not by the berry juice, although the rest of the beneficial responses were almost the same between the whole fruit and juice, suggesting there's more at play than just the fiber.²²⁵⁷

Just Beet It

Fiber content isn't the only difference between table sugar and the source of most table sugar these days, sugar beets.²²⁵⁸ There are also the thousands of phytonutrients that are stripped away in the sugar-refining process. It turns out some of the polyphenols in fruit can block the transport of sugars through the intestinal lining, slowing absorption.²²⁵⁹ In fact, adding fruit can actually blunt the insulin spike from high-glycemic foods. For example, white bread creates a big insulin spike an hour after eating it. Eat that same white bread with some berries, though, and even though you just effectively added more sugar, you're able to blunt the spike, because the sugar was in fruit form.²²⁶⁰ So if you're going to make pancakes or muffins, make them blueberry.

We can finally explain why some juices are better than others. Cloudy apple juice has more polyphenols, which may help explain why whole apples lower cholesterol compared to clear apple juice but not compared to cloudy apple juice.²²⁶¹ Have people drink cups of cloudy apple juice every day, and they lose body fat compared to a polyphenol-free control beverage with the same number of calories.²²⁶² Similar results were found for Concord (purple) grape juice. Have people drink two cups of a grape-flavored drink like Kool-Aid every day for a few months, and they gain a few pounds, but not when the same number of calories were added in the form of grape juice. Sorry, Welch's (the study's funder), but whole grapes would have probably done even better.²²⁶³

Free the Fruit

In a study entitled "Not Enough Fruit and Vegetables or Too Many Cookies, Candies, Salty Snacks, and Soft Drinks?" public health researchers suggested fruit and vegetable promotion campaigns were distractions from the larger problem of excess junk.²²⁶⁴ Many urban populations may suffer less from "food deserts," where corner stores lack fresh produce, than from "food swamps."²²⁶⁵ "It may be politically more expedient to promote an increase in consumption of healthy items rather than a decrease in consumption of unhealthy items," they concluded, "but it may be far less effective."²²⁶⁶

To find out which approach worked better, a group of overweight women were randomized to one of two dietary approaches: Avoid high-fat foods or eat more fruits and vegetables. The advice was bolstered with group and individual sessions with a dietitian to try to keep the respective groups on track. Though the group just given the positive messaging to eat more fruits and vegetables lost weight over a period of six months, the restrictive-messaging group lost significantly more.²²⁶⁷ Win-win, but obviously not either-or.

We don't have to choose between adding fruits and veggies or subtracting fattening foods. All the strategies in this book aim to complement each other.

Given the myriad benefits, how can we get more people to eat more fruits and vegetables? Well, we could make them free. Offering free fruits and veggies in a cafeteria setting nearly quintupled the likelihood of people reaching their daily recommended intakes.²²⁶⁸ Does this translate into weight loss? A study in Norway tested out a free fruit program among schoolchildren. Compared to control schools, a year of free fruit for ten- to twelve-year-olds resulted in a 40 percent lower prevalence of being overweight seven years later.²²⁶⁹

Concerns have been raised, however, that by subsidizing healthy food, people might just have more money to spend on junk.²²⁷⁰ To test this, a small group of low-income, overweight individuals were provided supermarket gift cards worth forty dollars each month. Half were randomized to cards that could buy any food at the grocery store, and

the other half to cards good only for fruits and vegetables. After three months, the buy-anything group gained weight, whereas the subsidized-fruit-and-veggie group lost weight, ending up nearly ten pounds lighter than the control group.²²⁷¹ Unfortunately, this study appears to be the exception.

A recent study in Toronto found that providing free produce boosted fruit and vegetable intake about 50 percent more than just advising people to eat more of them. Even then, however, the free-fruit-and-veg group only ended up consuming about a total of three servings a day and, not surprisingly, lost no more weight after six months than the control group.²²⁷² The recommended *minimum* number of daily servings of fruits and vegetables a day is seven to thirteen, but most Americans don't even get five.²²⁷³ After the Centers for Disease Control and Prevention realized that even a recommendation of five daily servings seemed "unachievable," it changed the National Cancer Institute's "5 A Day Program" to "Fruits & Veggies—More Matters." (It also considered the slogan "Appetite for Life" to emphasize how our food choices are truly life or death, but such messaging was thought perhaps too "rational," needing a "stronger emotional appeal."²²⁷⁴)

Ideally, on a population scale, fruits and vegetables should be better promoted. The National Fruit & Vegetable Alliance gave failing grades to the federal government for inadequate produce marketing and nutrition education,²²⁷⁵ and the private sector may be even worse. The U.S. Federal Trade Commission subpoenaed dozens of food, beverage, and restaurant companies to release information about their marketing expenditures that focus on children and adolescents.²²⁷⁶ The findings? Fruit and vegetable promotion constitutes less than half a penny of each dollar spent.²²⁷⁷

Garlic Press

In the Harvard cohorts, the categories of berries and apples/pears appeared to stand out on the fruit side in terms of foods associated with the most weight loss, and cauliflower and tofu/soy did so on the vegetable side.²²⁷⁸ As I've noted, apples and pears were put to the test in a randomized controlled trial and shown to produce weight loss even compared to same-calorie controls.²²⁷⁹ Have there been any similar such studies on other fruits and vegetables?

Garlic can reduce the body fat of rats²²⁸⁰ and mice²²⁸¹ even at the same caloric intakes (so it wasn't because they didn't like the taste), but rodent studies found the same for tomatoes,²²⁸² and that didn't seem to necessarily translate to people.²²⁸³ There was a study in which a few cloves of crushed raw garlic a day appeared to have a waist-slimming effect, but without a control group, you don't know if the subjects may have just lost the weight because they were under observation.²²⁸⁴ Garlic is so potent, though. What if you stuffed it into a pill and designed not just a randomized controlled study but one that's double-blind with a placebo by giving people coated tablets containing garlic powder versus sugar pills?

One such study tried giving people with metabolic syndrome placebo or actual garlic tablets adding up to a half teaspoon of garlic powder a day. And it worked, resulting in a drop in both weight and waistlines within six weeks.²²⁸⁵ A half teaspoon of garlic powder costs less than four cents. What about trying garlic supplements, like the fancy aged garlic extract ones you may have seen advertised. No weight-loss benefits were found.^{2286,2287}

How about just a quarter teaspoon of garlic powder a day? About one hundred overweight men and women were randomized to two 400 mg garlic powder tablets a day or placebo, and those unknowingly taking the two cents' worth of daily garlic powder lost nearly six pounds of straight body fat over the next fifteen weeks.²²⁸⁸ The only caveat (besides possible decreased kissability) is that garlic can have blood-thinning effects, so it should be stopped a week before elective surgery.²²⁸⁹ It may also overly detoxify and interfere with the efficacy of an HIV drug known as *saquinavir* (sold as Invirase or Fortovase).²²⁹⁰

FOOD FOR THOUGHT

Does it matter when you eat your fruits and vegetables? In my Negative Calorie Preloading section that's coming up in part IV, I explore the benefits of making them the first choice for your first course. There's even a public health campaign in Japan called "Eat Vegetables First at Meals."²²⁹¹ Just changing the order of foods you eat can have meaningful metabolic impact. Compared to the exact same meal eaten in a different order, eating vegetables first can decrease blood sugar and insulin excursions in diabetics²²⁹² and prediabetics,²²⁹³ resulting in significantly better blood sugar control over the long term.²²⁹⁴ However, this may be due in part to the fact that those randomized to receive advice to eat vegetables first ended up eating more vegetables overall.²²⁹⁵ This may also help explain why children who eat vegetables first during a meal may have less than 50 percent of the odds of being overweight compared to those who ate meat/fish first.²²⁹⁶ So the best time to eat them may in fact be anytime you can.

Just as keeping candy out of plain view can help keep junk out of sight, out of stomach,²²⁹⁷ increasing the visibility and accessibility of healthy snacks may help. Those randomized to keep a bowl of fruit on the kitchen counter instead of inside the fridge ended up closer to meeting their daily needs.²²⁹⁸ What about vegetables? Serving greater quantities of veggies was found to significantly increase vegetable intake by preschool children,²²⁹⁹ as well as adults.²³⁰⁰ One of the "Top Ten Tips for Weight Loss" used in the studies I discuss [here](#) is "Do not heap food on your plate (except vegetables)."²³⁰¹

For the most delicious produce, explore local farmers' markets, community-supported agriculture, and pick-your-own orchards, or garden yourself. Fruits and vegetables today are bred to survive long-distance shipping, not necessarily to taste their best.²³⁰² Even heritage breeds can lose flavor after traveling eight thousand miles from New Zealand. Did you know the "fresh" apple you buy at the grocery store may be ten months old?²³⁰³ It's wonderful that we can get produce year-round, thanks to new storage technologies, but if you've never eaten an apple picked straight off a tree, you are missing out.

My favorite fruit in the whole world can't even be sold commercially because it's too fragile. Have you ever had a pawpaw, North America's largest native fruit? Think luscious tropical banana-mango custard. For a few weeks in September across the Midwest and mid-Atlantic, you can forage for them in the wild or find them at farmers' markets (unless I get there first). See you at the next pawpaw festival!

RICH IN LEGUMES

The Hispanic Paradox

According to a national dietary survey, those who eat beans tend to be healthier and have less obesity risk, lower body weight, and smaller waist sizes.²³⁰⁴ This finding has been used to explain what's known as the *Hispanic paradox*: Despite higher poverty rates and disparities in health care and education,²³⁰⁵ Hispanic Americans tend to live longer than everyone else.²³⁰⁶ Hispanics have a 24 percent lower risk of premature death, thanks to lower risks of nine of the fifteen leading causes of death, including notably less cancer and heart disease.²³⁰⁷

What's powerful enough to overcome lower socioeconomic status, education level, health literacy, insurance coverage, and disproportionate employment in high-risk occupations?²³⁰⁸

Public health researchers suggest it may be "time to spill the beans"²³⁰⁹—or, more broadly, the legumes. Legumes, including beans, split peas, chickpeas, and lentils, can be considered "potent tools in the prevention and treatment of chronic disease."²³¹⁰

Just because people who eat beans tend to be slimmer and healthier ²³¹¹ doesn't necessarily mean legumes deserve the credit. Each bean burrito may mean one less beef burrito. Researchers were able to show a variety of metabolic benefits randomizing people to swap out two servings of meat for legumes three days a week,²³¹² but is the benefit from what is being eaten or what is being replaced? In the Harvard studies, the food category most associated with weight loss over time was soy food products, with nearly ten times the weight reduction associated with vegetable consumption.²³¹³ But how many people are eating bacon double-cheese tofu burgers? Indeed, bean consumption is associated with less saturated fat and cholesterol intake,²³¹⁴ so it may just be a marker for a healthier diet in general. Nevertheless, the Harvard studies controlled for a whole array of dietary and lifestyle factors yet still found a significant link between beans and better health.

Dozens of randomized controlled trials have found that soy can lower cholesterol²³¹⁵ and blood pressure,²³¹⁶ but what about non-soy legumes? Compilations of more than sixty randomized controlled trials have found that other beans also lower cholesterol,²³¹⁷ as well as benefit blood sugars and lower insulin levels,²³¹⁸ but consumer surveys suggest most Americans are unaware of these benefits.²³¹⁹ One could say they don't know beans about beans!

The Lentil Effect

What about interventional studies on beans and weight control? In the famous “satiety index” study that compared the hunger-slaking power of dozens of different foods, both fiber and protein content were associated with appetite-suppressing effects.²³²⁰ This would seem to make legumes ideal candidates,²³²¹ and indeed, we've known for more than thirty years that meals featuring beans can disproportionately delay the return of hunger.²³²² Does this then translate into reduced caloric intake throughout the day?

What do you think happened when people were given a cup of chickpeas or the same number of calories of white bread and butter? Those who had eaten the chickpeas ate nearly two hundred fewer calories of a meal served a few hours later.²³²³ Navy beans may work even better than chickpeas, and lentils best of all.²³²⁴ How do legumes fare compared to something a little more substantial than Wonder Bread, though?

Researchers compared patties made with fava beans and split peas to protein-matched patties made out of meat. The title of the study gives it away: “Meals Based on Vegetable Protein Sources (Beans and Peas) Are More Satiating Than Meals Based on Animal Protein Sources (Veal and Pork).” Even lower-protein patties in which most of the mashed beans and peas were replaced with potato held their own against the meat.²³²⁵ The researchers suggested this may help explain why intake of animal protein has been associated with subsequent weight gain, but consumption of plant protein hasn't.²³²⁶ Beans are free of the baggage inherent to animal protein sources, such as saturated fat and cholesterol, and instead offer a bonus in the form of fiber, which likely explains their satiety benefits.²³²⁷

It's no wonder legumes are more satiating than white bread. Both fiber and water have no calories, so to get the same number of calories in bean form, you have to feed people more food. You can imagine how eating a cup of chickpeas would be more filling than eating two pieces of white bread, which you could probably squeeze into a little ball in your fist. Only a minority of studies showed bean consumption actually cut down on subsequent caloric intake at later meals, though, but that may be because the researchers simply might not have waited long enough.²³²⁸ The satiating power of legumes is thought to arise from the effects of the slowly digesting resistant starch and fiber lower down in the intestines, which may not be reflected in studies lasting fewer than three hours.

In 1982, an extraordinary discovery was published. It had already been demonstrated that beans cause an “exceptionally” low blood sugar response, half that of other common foods.²³²⁹ What was discovered was that eating legumes could benefit your metabolism hours later ²³³⁰ or even the next day. Eat lentils for dinner, and eleven hours later, your body reacts differently to breakfast.²³³¹ Even when made to drink straight sugar water the next morning, your body is better able to handle it. At the time, the researchers dubbed it the “lentil effect,” but subsequent studies found chickpeas appear to work just as well. It has since been christened the “second meal effect.”²³³²

How is that even possible? Remember how we feed our gut bacteria and they feed us right back? Good gut flora can take fiber and produce valuable short-chain fatty acids that get absorbed into our bloodstreams and circulate throughout our systems. So if we eat a bean burrito for dinner, by the next morning, our gut bacteria are eating that same burrito, and the by-products they create may affect how our breakfasts are digested and how full we feel.

This second-meal effect can include changes in appetite. Eat half a can of brown beans at dinner, and you feel less hungry after breakfast the next day than had you instead eaten the same number of calories in non-bean form the night before.²³³³

Researchers solved the mystery of the second-meal effect by giving people rectal infusions of the number of short-chain fatty acids our good bacteria might make from a good beany burrito. The stomach responded within minutes.²³³⁴ So I guess if you forgot to eat any kind of beans for dinner and needed to blunt the effect of your breakfast donut, it's *theoretically* not too late, but, in general, I encourage people to take their food by mouth.

Adding Beans vs. Portion Control

Does all this talk of legumes translate into weight loss? Let's feed people some beans and find out. If you feed overweight and obese individuals three-quarters of a cup of canned navy beans a day for a month, they end up dropping about an inch off their waists.²³³⁵ The study had no control group, though, so we don't know if the subjects would have slimmed down without the daily dose of beans.

As we've discussed, designing dietary trials can be challenging when trying to come up with a proper control. If you simply ask people to add chickpeas to their diets and then analyze their subsequent dietary changes, the single biggest change they make is to reduce their consumption of non-chickpea legumes.²³³⁶ If the subjects are just swapping out one bean for another or eating fewer vegetables to compensate, one would not expect the full benefit to materialize. This may help explain why the interventional trials on legumes for weight control have been disappointing overall, showing on average only a small effect in people randomized to add an average of one serving of legumes to their daily diets.²³³⁷

The better-designed trials yielded better results, though.²³³⁸ For example, in one study, more than one hundred participants were randomized to either increase legume intake by at least one cup per day or to instead add whole-grain foods to their diets, so both groups would be bumping up their fiber intakes with healthy foods. After three months, the whole-grain group lost a little weight, but the legume group lost significantly more, resulting in about an inch off their waists.²³³⁹

My favorite bean study was published in 2012 out of the University of Toronto. (I assume everyone has a favorite bean study?) The researchers recognized that calorie cutting is the cornerstone of most weight-loss strategies, but the majority of people who lose weight by eating smaller portions gain it back. Starving ourselves almost never works long term. Therefore, the researchers concluded, "it is important to identify foods that can be easily incorporated into the diet and spontaneously lead to the attainment and maintenance of a healthy body weight."²³⁴⁰ *Spontaneously* is the key word there—in other words, lose weight without really trying. They figured legumes might be a good candidate, so, for the first time ever, beans were pitted head-to-head against caloric restriction.

The legume group was asked to eat about three-quarters of a cup of lentils, chickpeas, split peas, or navy beans a day, and the calorie-restriction group was tasked with cutting five hundred calories out of their daily diets. So, in effect, the bean group was asked to eat more food and the calorie-cutting group was asked to eat less. After two months, both groups slimmed about an inch off their waists.²³⁴¹

Increasing diet quality appeared to work as well as decreasing diet quantity.

Starch Blockers

Eating legumes achieved weight loss even in studies meant to be weight-neutral like cholesterol- or blood sugar-lowering trials.²³⁴² Part of the reason may be because nearly 20 percent of bean starch slips through our small intestines undigested, so beans can end up contributing fewer calories than are listed on the can's label.²³⁴³ Some of the starch in legumes is tightly packed into double-spiraled crystals, which our digestive enzymes have

trouble infiltrating, and there are also compounds in legumes that directly target our starch-munching enzymes.²³⁴⁴ This is where the concept of starch blocking comes from.

Crude bean extracts, commercialized as “starch blocker” supplements, have a sordid history. By the early 1980s, the American public was swallowing a million starch-blocker tablets a day for weight loss.²³⁴⁵ Despite a lack of human testing, hundreds of such products had flooded the market.²³⁴⁶ Finally, data from clinical trials started to trickle in, and the findings were universally negative, with emblematic titles such as “‘Starch Blockers’ Are Ineffective in Man”²³⁴⁷ or simply “Starch Blockers Do Not Block Starch Digestion.”²³⁴⁸ And that was the problem. Apparently, the bean compounds were not stable in pill form.²³⁴⁹ Starch-blocker pills were all yanked from the market in 1982 by the Food and Drug Administration.²³⁵⁰

Subsequently, manufacturers were able to create a more active product,²³⁵¹ so, at the very least, it could be put to the test. A compilation of studies on the newer generation of starch blockers found they could reduce body fat compared to placebo.²³⁵² Unsurprisingly, the majority of studies were funded by the manufacturers themselves. Funding bias aside, the bigger concern is the lack of industry regulation that too often calls into question the purity, safety, and label accuracy of dietary supplements.²³⁵³ So while I can’t recommend starch blockers in pill form, I can recommend them in food form. The starch-blocking capacity of whole beans survives cooking and may therefore play a role in the prevention and treatment of obesity.²³⁵⁴

What About Lectins?

In 2017, a book called *The Plant Paradox* was published, purporting to expose “the hidden dangers in ‘healthy’ foods that cause disease and weight gain.” The so-called dangerous, disease-causing, and weight-gaining foods included beans, whole grains, and tomatoes. What? In a rehashing of the since discredited²³⁵⁵ “blood type diet” from decades ago, the author accuses lectins of contributing to chronic disease. *The Plant Paradox* was written by an M.D., but if you’ve seen any of my medical education videos, you’ll know that’s effectively an *anti*-credential when it comes to writing diet books. Graduating from medical school basically advertises to the world that you’ve received likely little or no formal training in nutrition. Dr. Atkins was, after all, a cardiologist.

The thesis of the book doesn’t even seem to pass the sniff test. If lectins are bad for you, then beans would be the worst. In that case, shouldn’t bean counters find legume lovers have shortened lives? The exact opposite seems to be true: Legumes have been found to be perhaps “the most important dietary predictor of survival in older people” around the world.²³⁵⁶ As Dan Buettner points out in his Blue Zones longevity work, lectin-packed foods like legumes are the “cornerstones” of the diets of all the healthiest, longest-lived populations on the planet.²³⁵⁷

When I heard about *The Plant Paradox*, my first thought was, *Let me guess. He sells a line of lectin-blocking supplements. And what do you know? “SHIELDING YOUR BODY FROM LECTINS”* for only \$79.95 a month, his website assures. That’s like \$1,000 a year. But wait. There’s more. The dozens of supplements he hawks on his website could add up to nearly \$20,000 a year if taken as recommended. He must be making a fortune stoking, then preying on people’s fears. Oh, did I not mention his skin care line? He’ll generously sell you a jar of his “Firm + Sculpt” cream for the low, low price of only \$120—discounted if you subscribe to his “VIP Club.”

In the 1800s, a compound was discovered in castor beans, which we would come to know as the first of a class of lectin proteins—natural compounds found throughout the food supply, but concentrated in beans, whole grains, and certain fruits and vegetables.²³⁵⁸ Every decade or two, it seems, a question is raised as to whether dietary lectins may be causing disease. It’s easy to raise hysteria about lectins. After all, that first one, found back in 1889, went by the name *ricin*, which is known to be a “potent homicidal poison” used by the Kremlin to assassinate anti-Communist dissidents—or (*Breaking Bad* spoiler alert!) by rogue chemistry teachers.²³⁵⁹ Ricin is a lectin. Thankfully, however, many lectins are nontoxic, such as those found in tomatoes and other common foods,²³⁶⁰ and even the ones that can cause problems, like those found in raw kidney beans, are utterly destroyed by proper cooking.²³⁶¹

What would happen if kidney beans were eaten raw? Because of the lectins, you would be doubled over with nausea, vomiting, and diarrhea within hours.²³⁶² But how would you even eat raw kidney beans? The only way they’re sold uncooked is as dried beans, which are as hard as rocks. In the first outbreak reported in the medical literature, “an impromptu supper was made” with a bag of beans dumped in a skillet and soaked in water overnight, but never cooked.²³⁶³ You can’t even just throw them in a slow cooker. Dried kidney beans have to be boiled. According to some researchers, they should be soaked in water for at least five hours and then boiled for at least ten minutes.²³⁶⁴ I’m no Iron Chef, but ten minutes? Kidney beans wouldn’t be done in only ten minutes. Cooking presoaked beans for a couple of minutes can destroy the lectins, but it takes about an hour of boiling before the beans are soft enough to eat, when they’re easily flattened with a fork.²³⁶⁵ So the lectins would be long gone before they’re palatable.

The same goes for pressure cooking. Without presoaking, it takes forty-five minutes in a pressure cooker to get rid of all the lectins in kidney beans, but an hour to make the beans edible,²³⁶⁶ so, again, they’d be lectin-free before

you ate them. Even twelve hours at 65°C (150°F), which is about the temperature of hot tea, won't do it, though, but you could tell they weren't cooked enough because they'd be firm and rubbery. Folks have, however, tried putting undercooked kidney beans in something like a "raw" vegetable salad, and people have gotten sick. There have been dozens of such incidents reported, but each could have been "easily prevented" had the beans been cooked properly²³⁶⁷ or if canned beans had been used instead. Canned beans are cooked beans. The canning process is a cooking process. None of the confirmed incidents was ever due to canned beans.

The purported "plant paradox" is that, on the one hand, whole, healthy plant foods are the foundations of a good diet, but on the other hand, we supposedly need to avoid lectin-containing foods since they can supposedly lead to inflammation. But feed people four servings a week of beans, split peas, chickpeas, and lentils, and you can get a whopping 40 percent drop in C-reactive protein,²³⁶⁸ a leading indicator of systemic inflammation. More beans equals *less* inflammation. Greater consumption of each of the major categories of whole plant foods—fruits, vegetables, whole grains, beans, and nuts—is associated with living significantly longer,²³⁶⁹ so there's really no paradox after all.

FOOD FOR THOUGHT

On any given day, only about 8 percent of Americans eat beans.²³⁷⁰ This may be due in part to an unfamiliarity with how to prepare and incorporate them into our diets. Some people seem intimidated by legumes, imagining overnight soakings and long cooking times, but they can be as easy to prep as a few twists of a can opener.²³⁷¹ Rather cook them from scratch? Harvard's Institute of Lifestyle Medicine recommends starting with lentils: Combine three cups of water for every one cup of lentils. Bring to a boil and then simmer for twenty minutes until soft. Drain and enjoy. I encourage you to make extra and freeze them in portions.

Split red or orange lentils are even easier. They're ready in five minutes, quicker than boiling pasta.²³⁷² Once they've softened, rinse them to cool, then mix with herbs and lemon juice for a basic legume salad. Another favorite of mine is to cook lentils a little longer so they thicken into almost a purée before adding spices like curry, turmeric, cumin, and garam masala for a thick, savory, and healthy Indian-inspired sauce.

Once you're ready to branch out, I'd recommend an electric pressure cooker. Add dried beans and water, press one or two buttons, and beans are cooked to perfection without any presoaking necessary. The cooker even shuts itself off automatically. It couldn't be easier or more foolproof. I used to buy canned (BPA-free, of course) beans by the case, so my electric pressure cooker easily paid for itself, given how incredibly inexpensive dried beans are. It's not that I'm unwilling to splurge the few extra cents for canned—I just prefer the texture of home-cooked beans. I now find canned beans can be a little mushy, which is fine for making hummus, bean dips, or some soup I'll end up blending, but if I'm eating the actual beans, I've become spoiled for a slightly firmer bite.

There's a reason legumes have earned the hallowed distinction of being officially recognized in the federal dietary guidelines as belonging to both the vegetable group and the protein group. They're loaded with protein, iron, and zinc, as you might expect from other protein sources like meat, but legumes also offer nutrients concentrated in the vegetable kingdom, such as fiber, folate, and potassium. You therefore get the best of both worlds with beans, all the while enjoying foods that are naturally low in saturated fat and sodium, and completely free of cholesterol.

Fearful of flatulence? Stop by your local library and check out the Clearing the Air About Beans and Gas section in the beans chapter in *How Not to Die*. The bottom line (no pun intended) is that most people either don't experience any gastrointestinal side effects after adding beans to their diets or the symptoms dissipate within the first few weeks.²³⁷³

SATIATING

Built for Gluttony

The importance of satiety is underscored by a rare genetic condition known as *Prader-Willi syndrome*. Those born with this disease have impaired signaling between their digestive systems and their brains, so they don't know when they're full. With no sensation of satiety, they can accidentally eat so much they fatally rupture their stomachs. Without satiety, food could be a death sentence.²³⁷⁴

Protein is often described as the most satiating macronutrient.²³⁷⁵ People tend to report feeling fuller after eating a protein-rich meal compared to a carbohydrate- or fat-rich one. But does that feeling last? From a weight-loss standpoint, satiety ratings only matter if they end up cutting down on subsequent caloric intake,²³⁷⁶ and even a review funded in part by the meat, dairy, and egg industries acknowledges this does not seem to be the case for protein.²³⁷⁷ Hours after consumption, that protein eaten earlier doesn't tend to end up cutting calories.

Fiber, on the other hand, contributes to suppressing hunger up to ten hours after it's eaten²³⁷⁸ and can reduce subsequent meal intake.²³⁷⁹ Why? Its site of action is twenty feet down in the lower intestine. Remember the ileal brake from the High in Fiber-Rich Foods section? Secretly infuse nutrients into the end of the small intestine, and people spontaneously eat as many as hundreds of fewer calories at the next meal²³⁸⁰ because of a signal to our brains that we are full from head to tail.

We were built for gluttony. It's a hedge against times of scarcity. Stumbling across a rare bounty, those who could stuff themselves the most to build up the greatest reserves would be most likely to pass along their genes. You might say it was the survival of the fullest. So we are hardwired to eat not just until our stomachs are full but also until our entire digestive tracts are occupied. Only when our brains sense food all the way at the end of our lower intestines may our appetites dial down fully.

Fiber-depleted foods rapidly get absorbed early on, though, so not much ever makes it down to the lower gut. Given how little fiber the average American eats, it's no wonder we're so hungry and always overeating: Our brains keep waiting for the food that never arrives. Indeed, this is why, even after a stomach-stapling surgery that leaves just a tiny, two tablespoons-sized stomach pouch, people can still eat enough to regain most of the weight they initially lost. Without sufficient fiber transporting nutrients all the way down our digestive tracts, we may never feel fully satiated.²³⁸¹

Two Hundred Pounds Without Hunger

Anyone can lose weight eating less food. Anyone can be starved thin. Starvation diets are rarely sustainable, though, since hunger pangs drive us to eat. We feel unsatisfied on low-calorie diets. Unsatiated. We do have some level of voluntary control, but our deep-seated instinctual drives may win out in the end.

For example, you can consciously hold your breath. Try it right now. How long can you go before your body's self-preservation mechanisms take over and overwhelm your deliberate intent not to breathe? Your body has your best interests at heart and is too smart to allow you to suffocate yourself—or starve yourself, for that matter. But if our bodies were really that smart, how could they let us become obese? Why don't our bodies realize when we're too fat and allow us the leeway to slim down? Could it be that our bodies *are* actually aware—and actively trying to help—but we're somehow undermining those efforts? How could we test this theory to see if that's true?

So many variables go into choosing what and how much we eat. There are psychological, social, cultural, aesthetic, and other factors. To strip away all of that and stick just to the physiological, Columbia University researchers designed a series of famous experiments using a "food dispensing device."²³⁸² The term *food* is used very loosely here. Their feeding machine was a tube hooked up to a pump that delivered a mouthful of bland liquid formula every time a button was pushed. Research subjects were instructed to eat as much or as little as they wanted at any time. In this way, eating was reduced to just the rudimentary hunger drive. Without the usual trappings of sociability, meal ceremony, and the pleasures of the palate, how much would people be driven to eat?

Put a normal-weight person in this scenario, and something remarkable happens. Day after day, week after week, with nothing more than their hunger to guide them, they ate exactly as much as they needed, perfectly maintaining their weights. They required about three thousand calories a day, and that's just how much they gave themselves. Their bodies just intuitively seemed to know how many times to press that button to get food.²³⁸³

What happened when obese people were put in a similar scenario? Driven by hunger alone with the enjoyment of eating stripped away, they wildly undershot and gave themselves as little as 145 calories a day. Fewer than 200 total calories for the entire day! The obese subjects could eat as much as they wanted, but they just weren't hungry. It's as

if their bodies knew how grossly overweight they were and so dialed down their natural hunger drives to almost nothing. One research subject started out at four hundred pounds and steadily lost weight. After 252 days, even after switching to drinking the “food” out of a cup at home, he lost two hundred pounds.²³⁸⁴

Initially, this groundbreaking discovery was interpreted by some to mean that obesity is not caused by some sort of metabolic disturbance that drives people to overeat. Instead, overeating appeared to be a function of the meaning people attached to food beyond its use as fuel, whether as a source of pleasure or perhaps relief from boredom or stress.²³⁸⁵ Obesity, then, seemed more psychological than physical. However, subsequent experiments with the feeding machine suggest quite the opposite.²³⁸⁶

If you take a lean study subject and covertly double the calorie concentration of the formula, they unconsciously cut their consumption in half to continue to perfectly maintain their weights. Their bodies somehow detected the change in calorie load and sent signals to their brains to press the button half as often to compensate. Do the same thing with obese persons, and nothing changes. They continue to undereat just as much as before. Their bodies appeared incapable of detecting or reacting to the change in calorie load, suggesting a physiological inability to regulate intake.²³⁸⁷

Could the brains of obese people somehow be insensitive to internal satiety signals? We don't know if it's cause or effect—that is, maybe that's why they're obese in the first place, or maybe the body knows how obese it is and is shutting down the hunger drive regardless of the calorie concentration. Indeed, the obese subjects continued to steadily lose weight eating out of the machine regardless of the calorie concentration. It would be interesting to see if they regained the ability to respond to changing caloric intake once they reached their ideal weights. Either way, what can we take from these studies to facilitate weight loss out in the real world?

Hyperpalatable Hijacking

At first glance, it might seem like a no-brainer that removing the pleasurable aspects of eating would cause people to eat less, but remember, that's not what happened. The lean study subjects continued to eat the same amount, taking in thousands of calories of the bland liquid formula. Only those who were obese dropped from eating thousands of calories a day down to just hundreds, and this happened inadvertently without them even feeling the difference. Only after eating was disconnected from the reward was the body able to start rapidly reining in the weight.

We have two separate appetite control systems: the homeostatic system and the hedonic system. The homeostatic pathway maintains our calorie balance by making us hungry when energy reserves are low and abolishing our appetites when energy reserves are high. In contrast, our hedonic, or reward-based, regulation can overwhelm our homeostatic pathways in the face of highly palatable foods.²³⁸⁸ This makes total sense from an evolutionary standpoint.²³⁸⁹ In the rare cases in our ancestral history when we'd stumble across some calorie-dense food, like a cache of unguarded honey, it would make sense for our hedonic drives to take over the driver's seat to speed us toward devouring the scarce commodity. Even if we didn't need the extra calories at the time, our bodies wouldn't want us to pass up the rare opportunity.

Nowadays, such opportunities are not so rare anymore. With sugary, fatty foods everywhere we look, our hedonic drives may end up in perpetual control, overwhelming the intuitive wisdom of our bodies.

The Spice of Life

How did we evolve to solve the daunting task of selecting a diet that supplies all the essential nutrients? Dietary diversity. By eating a variety of foods, we increase our chances

of hitting all the bases. If we ate solely for pleasure, we might just stick with our favorite foods to the exclusion of all others. Thankfully, we have an innate tendency to switch things up.

For example, we end up eating more calories when provided with three different yogurt flavors than just one, even if that one and only one is our chosen favorite.²³⁹⁰ So variation can trump sensation. This appears to be something we're born with. Studies on newly weaned infants dating back nearly a century show that babies naturally choose a variety of foods even over their one preferred food.²³⁹¹ This tendency seems to be driven by a phenomenon called *sensory-specific satiety*.²³⁹²

Within minutes, the pleasantness of the taste, smell, texture, and appearance of an eaten food drops off compared to the uneaten foods.²³⁹³ It's like how the first bite of chocolate tastes better than the tenth bite. Our bodies tire of the same sensations and seek out novelty by rekindling our appetites every time we're presented with new foods. This helps explain the "dessert effect," where we can be stuffed to the gills but get a second wind when dessert arrives.²³⁹⁴

What was adaptive for our ancient ancestors to maintain nutritional adequacy, however, may be maladaptive in the age of overabundance and obesity.

Feed people a four-course meal, and they eat 60 percent more calories than when presented with the same dish served at each of the four courses.²³⁹⁵ It's not just due to boredom. Our bodies have different physiological reactions. Give people a squirt of lemon juice, and their salivary glands respond with a squirt of saliva. But give someone a squirt of lemon juice ten times in a row, and they salivate less and less each time. What happens if you switch to lime juice? Their salivation jumps right back up.²³⁹⁶ We're hardwired to respond differently to new foods.

On the same plate,²³⁹⁷ at the same meal,²³⁹⁸ or even on subsequent days,²³⁹⁹ the greater the variety, the more we tend to eat. Give overweight kids the same mac 'n cheese dinner five days in a row, and they end up eating hundreds of fewer calories by the fifth day compared to kids who got a variety of different meals each day.²⁴⁰⁰ Even just switching the *shape* of food can lead to overeating. Give kids the same mac 'n cheese but change the elbow macaroni to spiral noodles, and they end up eating significantly more of the new pasta shape.²⁴⁰¹ Even *perceived* variety may get people to eat more. Give people a bowl filled with ten different colors of M&M's, and even though all the colors taste the same, people reportedly eat 43 percent more than if there were only seven colors of the candies offered.²⁴⁰² The greater the difference, the greater the effect. Alternating between sweet and savory foods can have a particularly appetite-stimulating effect. In this way, adding a diet soda to a fast-food meal can lead to overconsumption.

The staggering array of modern food choices may be one of the factors conspiring to undermine our appetite control.²⁴⁰³ There are now tens of thousands of different foods being sold.²⁴⁰⁴ In fact, the wide variety available at our groceries is one of the most successful ways to make rats fat. When researchers first tried to make rats fat in a lab, it didn't work. The richer the rat chow, the less the rats ate to maintain their weights. Attempt after attempt failed. "We therefore used a more extreme diet," the researchers recalled. "We fed rats an assortment of palatable foods purchased at a nearby supermarket (e.g., cookies, cheese, marshmallows, chocolate.)" And what do you know? On what became known as the *supermarket diet* (and later the *cafeteria diet*), the animals rapidly gained weight.²⁴⁰⁵

It's kind of like the opposite of the original food-dispensing device. Instead of the all-you-can-eat bland liquid, researchers offered free all-you-can-eat access to elaborate vending machines stocked with forty trays with a dizzying array of beverages and foods like pastries and french fries. Participants seemed to find it impossible to maintain energy balance, consuming an average of 127 percent of their calorie requirements.²⁴⁰⁶

Our understanding of sensory-specific satiety can be used to get people to gain weight, but how can we use it to our advantage? For example, would limiting the variety of unhealthy snacks help people lose weight? Two randomized controlled trials attempted, yet failed, to show significantly more weight loss in the reduced variety groups, but they also failed to get people to make much of a dent in their diets at all. Just cutting down on a few snack types seems insufficient to make much of a difference.^{2407,2408} A more drastic change may be needed.

Meatball Monotony and Veggie Variety

Sensory-specific satiety may be one of the reasons meal replacements and fad “mono diets” like the cabbage soup diet and the oatmeal diet can result in better adherence and lower ratings of hunger compared to less restrictive diets.²⁴⁰⁹

An all-potato diet would probably take the (Yukon) gold for blandest and most monotonous and satiating. In fact, in “A Satiety Index of Common Foods,” the landmark study I mentioned in the Rich in Legumes section in which dozens of foods were put to the test, the most satiating food researchers found was the boiled potato.²⁴¹⁰ Two hundred and forty calories of boiled potatoes were found to be more satisfying in terms of quelling hunger than the same number of calories of any other food they tested. No other food even came close.

No doubt the low calorie density played a role. To feed people 240 calories of potatoes, they had to feed them nearly a pound of spuds, compared to just a few cookies, but that’s kind of the point. They did have to feed people even more apples, grapes, and oranges, though, yet each of those fruits was still about 40 percent less satiating than the potatoes.²⁴¹¹

The mono diet is the poster child for unsustainability—and thank heavens for that. Over time, eating just one thing day after day can lead to serious nutrient deficiencies—like blindness from vitamin A deficiency in the case of white potatoes.²⁴¹² The satiating power of potatoes can still be brought to bear, though. Boiled potatoes beat out pasta and rice in terms of a satiating side dish, cutting as much as about two hundred calories of intake off a meal.²⁴¹³ Fried potatoes or even baked fries, however, do not appear to have the same satiating effect.²⁴¹⁴

To exploit sensory-specific satiety for weight loss while maintaining nutrient abundance, you could limit the variety of unhealthy foods you eat, while expanding the variety of healthy foods.²⁴¹⁵ In that way, you can simultaneously take advantage of the appetite-suppressing effects of monotony, while diversifying your fruit-and-vegetable portfolio. Studies have shown that a greater variety of calorie-dense foods like sweets and snacks is associated with excess body fat, but a greater variety of vegetables appears protective.²⁴¹⁶ When presented with more diverse options of fruits,²⁴¹⁷ vegetables,²⁴¹⁸ and vegetable seasonings,²⁴¹⁹ people may consume a larger quantity, crowding out less healthy options.

For the first twenty years of the *Dietary Guidelines for Americans*, it recommended generally eating “a variety of foods.” In the new millennium, the guidelines have gotten more precise, specifying a diversity of healthier foods only. As dietitians at Harvard and NYU concluded in a paper on dietary variety as an overlooked weight-loss strategy, “Choose and prepare a greater variety of plant-based foods,” recognizing that a greater variety of less healthy options could be counterproductive.²⁴²⁰

FOOD FOR THOUGHT

How can we respond to industry attempts to lure us into temptation by turning our natural biological drives against us? Should we never eat really delicious food? No, but it may help to recognize the effects hyperpalatable foods can have on hijacking our appetites and undermining our bodies’ better judgment. We can also use some of those

in a sugary sauce atop white rice—may not include any of the optimum weight-loss ingredients, whereas a dish from the vegetable section—like broccoli with garlic sauce—might incorporate at least half of them. At a quick-service Mexican joint, a bean burrito bowl salad could let you tick off most of them, especially if you hold the white rice, but nothing beats the control you have at home to prepare a healthy dish without added salt, sugar, and fat.

To reverse engineer the optimal weight-loss diet, we can figure out what constitutes the ideal meal by ranking individual foods—and the more boxes they check, the better. Most fruits and vegetables would top the list at sixteen out of seventeen. By my count, legumes, whole grains, and nuts and seeds together would hit fifteen, fourteen, and thirteen, respectively, but refined grains and animal products would slip down into single digits. Ultraprocessed fatty and sugary snacks might only score one or two, and a product that's both, like Slim Jim's maple-flavored bacon jerky, might completely flop.

Note that some of these criteria are much more important than others. For example, while the value of eating anti-inflammatory foods remains theoretical, there are multiple randomized controlled trials validating the benefits of reducing calorie density. Read through the sections and decide which are most convincing to you and may be easiest to fit into your daily routine.

To varying degrees, any one of these criteria alone may facilitate weight loss. Even just cutting out added sugars without making any other changes at all, for example, could cause you to lose weight.

Now imagine if you tried putting them all together.

III. The Optimal Weight-Loss Diet

INTRODUCTION

Beyond the Seventeen Ingredients

Diets don't work almost by definition. Going on a diet implies that, at some point, you will go off the diet. Short-term fixes are no match for long-term problems.²⁴²¹ Lifelong weight control requires lifelong lifestyle changes. That's why there are four other factors that need to be considered alongside my seventeen efficacy criteria, bringing us to twenty-one total ingredients for an optimal weight-loss diet. See the chart on the next page.

First, a diet has to be sustainable. Consider water-only fasting, for example. No diet works better. It's 100 percent effective, but also 100 percent fatal if you manage to stick with it. This is why an optimal weight-loss diet needs additional building blocks to ensure long-term viability.

As well as being efficacious and sustainable, it needs to be safe. Books touting liquid protein diets in the 1970s sold millions of copies, but the diets started killing people.²⁴²² Safety is about losing weight without losing your health.

Any long-term eating pattern must also be nutritionally complete, containing all essential vitamins and minerals. A vegan diet, for example, can fail at this criterion, as it lacks vitamin B12, which is not made by plants but by microbes that blanket the earth. In today's sanitized modern world, we now chlorinate the water supply to kill off any bacteria, so we don't get a lot of B12 in our water anymore—but we don't get a lot of cholera either, which is a good thing! Without that vitamin, though, vegans eventually risk blindness,²⁴²³ psychosis,²⁴²⁴ paralysis,²⁴²⁵ and death,²⁴²⁶ which is why B12 supplements or B12-fortified foods are critically important for anyone adopting a plant-based diet.²⁴²⁷

diet business thrives off two things—preposterous promises and repeat customers—and one leads naturally to the other.²⁴³⁴

Heartbreakers

The authors of the meta-analysis that found the same weight loss for both low-carb and low-fat diets concluded, “This supports the practice of recommending any diet that a patient will adhere to in order to lose weight.”²⁴³⁵ That seems like terrible advice. Would they recommend the Last Chance Diet, which evidently consisted of a “liquid formula made from leftover byproducts from a slaughterhouse,”²⁴³⁶ that was linked to at least sixty deaths?²⁴³⁷ An ensuing failed lawsuit, *Smith v. Linn*, from one widower set the precedent for First Amendment protection for deadly diet books.²⁴³⁸

The health impacts of a typical low-carb ketogenic diet like Atkins are vastly different from a low-fat, plant-based diet like Dean Ornish’s. Not only would they have diametrically opposed effects on cardiovascular risk factors in theory (based on fiber, saturated fat, and cholesterol contents),²⁴³⁹ but when low-carb diets were actually put to the test, they were indeed found to impair artery function.²⁴⁴⁰ Over time, blood flow to the heart muscle itself has been shown to improve on an Ornish-style diet while it diminished on a low-carb diet.²⁴⁴¹

It is possible to construct a healthy low-carb diet²⁴⁴² or an unhealthy low-fat diet (a diet of cotton candy would be zero fat), but heart disease tends to progress on typical weight-loss diets²⁴⁴³ and actively worsen on low-carb diets,²⁴⁴⁴ but may be reversed by a healthy plant-based diet.²⁴⁴⁵ Given that heart disease is the number one killer of men and women, “recommending any diet that a patient will adhere to in order to lose weight” seems irresponsible.

Making Daily Allowances

When people diet, they often increase their risk of not meeting all their essential nutrient requirements. Ketogenic diets tend to be so nutritionally vacuous that one assessment estimated that in order to get a sufficient daily intake of all essential vitamins and minerals, you’d have to eat 37,500 calories a day.²⁴⁴⁶ Choosing a healthier diet may be easier than adding about fifty sticks of butter to your morning coffee.

A comparison of dietary quality of popular weight-loss plans scored Ornish’s low-fat, plant-based diet the highest and Atkins’s low-carb, more ketogenic diet the lowest.²⁴⁴⁷ In general, using a variety of nutritional quality indexes, researchers found that the more plant-based people eat, the healthier their diet scores.²⁴⁴⁸ Ironically, even though plant-based eaters are restricting entire categories of foods, they end up getting more nutrition. A paper entitled “A Vegetarian Dietary Pattern as a Nutrient-Dense Approach to Weight Management” found that those eating more plant-based were getting higher intakes of nearly every nutrient: more fiber, more vitamin A, more vitamin C, more vitamin E, more of the B vitamins thiamine, riboflavin, and folate, and more of the minerals calcium, magnesium, and iron.²⁴⁴⁹ This came as no surprise. The *Journal of the American Dietetic Association* editor in chief responded, “What could be more nutrient dense than a vegetarian diet?”²⁴⁵⁰

These days, it seems that most published cases of classic nutrient-deficiency syndromes showing up in U.S. emergency rooms are people eating crazy diets. An American servicemember hospitalized for a muscle tear due to scurvy reported eating only two things: chicken without the skin and candy bars.²⁴⁵¹ Ironically, one of the healthiest eating patterns, an exclusively plant-based diet, is perhaps the most life-threateningly incomplete, lacking B12, a vitamin made by bacteria, as I mentioned earlier. In our modern sanitary world, vitamin B12 is found reliably only in animal products, supplements, and B12-fortified foods. Vegetarians and vegans are recommended to take supplements containing at least

50 mcg of cyanocobalamin (the most stable form²⁴⁵²) a day or at least 2,000 mcg once a week²⁴⁵³ (or brush twice daily with a B12-fortified toothpaste²⁴⁵⁴).

We're getting closer to the optimal weight-loss diet, but we aren't quite there—yet.

Having It Both Ways

Just because a weight-loss technique is effective doesn't mean it's healthy. Smoking is the classic example. I will not be including a chapter on choosing the best cigarettes, nor will I explore how best to infect yourself with tuberculosis or develop an addiction to methamphetamine. The goal of weight loss is not to lighten the load for your pallbearers.

Thankfully, you don't need to mortgage your long-term health for short-term weight loss. We can have the best of both worlds. Think about the foods that ranked highest in the ideal weight-loss criteria—whole plant foods such as fruits and vegetables. As I explored in *How Not to Die*, these are the very same foods that in some cases may help prevent each of our top fifteen killers: (1) heart disease, (2) lung diseases, (3) iatrogenic (“death by doctor”) causes, (4) brain diseases, (5) digestive cancers, (6) infections, (7) diabetes, (8) high blood pressure, (9) liver diseases, (10) blood cancers, (11) kidney disease, (12) breast cancer, (13) suicidal depression, (14) prostate cancer, and (15) Parkinson's disease.

The best-of-both-worlds eating pattern may therefore be a whole food, plant-based diet.

PLANT YOURSELF

A plant-based diet is defined as an eating pattern that minimizes the intake of meat, eggs, dairy, and processed junk and maximizes consumption of whole plant foods, such as fruits, vegetables, legumes (beans, split peas, chickpeas, and lentils), whole grains, nuts and seeds, mushrooms, and herbs and spices.²⁴⁵⁵ Plant-based is often confused with vegetarian or vegan, but it can have very different health implications. Vegetarian (meat-free but may include eggs and dairy) and vegan (free of any animal-derived ingredients) diets may exclude animal products for religious or ideological reasons without necessarily focusing on healthy choices.

An exhaustive collation of pooled meta-analyses and systematic reviews on the chronic health effects of different food groups has been published, and 96 percent of the reviews on whole plant foods associated them with effects that were protective or neutral. At the same time, 77 percent of the reviews on animal-based foods and 90 percent of those on refined grain and sugary drinks linked them to having deleterious or neutral effects. So, when it comes to diet-related diseases, such as cancer, diabetes, or heart, bone, or liver conditions, nine out of ten study compilations show that whole plant foods are, in the very least, not bad, whereas eight or nine out of ten of the reviews on animal products or processed foods show them to be not good.²⁴⁵⁶

Easy as Pie

Just because a diet is healthy and effective doesn't mean it's sustainable. Obviously, diets can only work if people can stick with them. When Dean Ornish, the first to prove heart disease could be reversed with a plant-based lifestyle program, criticized the authors of a famous Mediterranean diet study for exaggerating the benefits—noting there was no reduction in heart attack rates or overall mortality²⁴⁵⁷—the authors replied, acknowledging Ornish-type diets might be superior but the “major problems ... are its poor palatability and the marginal long-term compliance.”²⁴⁵⁸ Excuse me? In reality, Ornish and others got extraordinary adherence with healthy plant-based diets, with no differences noted in any measured acceptability scores. For example, study participants reported the same level of enjoyment compared to their regular diets.²⁴⁵⁹ They even got success in barbecue country, rural North Carolina.²⁴⁶⁰ Stricter diets may meet greater acceptance because they may

work better. Ornish and colleagues showed that greater adherence meant greater disease reversal.²⁴⁶¹

Even those who are young and healthy with no health issues appear to have little problem sticking to a plant-based diet. There was a crossover study in which women were instructed to eat plant-based foods for a few months to see how it would affect their menstrual cycles. But then they were to switch back to their baseline diets to note the contrast, a so-called A-B-A study design where you reverse the experimental variable. The problem is that some participants felt so good eating healthfully—they were losing weight without any calorie counting or portion control, they had more energy, their periods got better, and they experienced better digestion and better sleep—that some refused to go back to their regular diets, which kind of messes up the study.²⁴⁶² Because they didn't comply with the protocol and go back to their baseline diets, their data had to be thrown out. So, ironically, the plant-based diet worked a little too well.

Leaner and Greener

With enough portion control, anyone can lose weight. Lock someone in a room, and you can force them to lose as much body fat as you want. Chaining someone to a treadmill could have a similar effect. But what is the most effective weight-loss regimen that doesn't involve caloric restriction or exercise (or a felony)? If you look throughout the published, peer-reviewed medical literature at all the randomized controlled trials, what is the single most successful strategy? If you've been paying close attention, you should be able to hazard a guess.

Let's run through the ingredients for an optimal weight-loss diet. Which eating pattern contains the most anti-inflammatory foods? Which is cleanest, the lowest in potentially obesogenic pollutants? Which diet is highest in fiber- and water-rich foods, yet lowest in addictive and processed foods, glycemic and insulin loads, calorie density, fat, meat, refined grains, salt, and sugar? Which is friendliest to our microbiomes, satiating, and rich in fruits, vegetables, and legumes, while, at the same time, is safe, sustainable, nutritious, and healthy?

It should come as no surprise that the most successful intervention to date is a whole food, plant-based diet.²⁴⁶³ And as we'll see, unlike entirely too many weight-loss methods where you're forced to essentially mortgage your health to achieve short-term gains, plant-based diets offer the best of both worlds: effectiveness and healthfulness.

Any diet that results in reduced caloric intake can cause weight loss. Dropping pounds isn't so much the issue; the problem is keeping them off. A key difference between plant-based nutrition and more traditional approaches to weight loss is that people are encouraged to eat *ad libitum*, which is, as I've noted, Latin for *at one's pleasure*. In other words, people on a healthy enough plant-based diet can eat as much as they want. No calorie counting, no portion control—just eating. The strategy is improving the quality of the food rather than restricting the quantity of the food.

We've known for more than thirty years that those eating predominantly plant-based diets weigh, on average, about twenty to thirty pounds less than the general population.^{2464,2465} The largest such study, which involved more than ninety thousand people, found that the more plants people ate, the lower their weights seemed to drop.²⁴⁶⁶

To review again, a body mass index of 30 or higher is considered obese, 25–29 is overweight, and under 25 is “normal.” Well, not so normal anymore. Given that the average American today is overweight, a BMI under 25 is more of an *ideal* weight. In the ninety-thousand-person study, the average BMI of nonvegetarians was 28.8, bordering on obesity.²⁴⁶⁷ Semi-vegetarians or flexitarians, those who ate meat a few times a month but not every week, were at a BMI of 27.3. Those who ate no meat except fish came in at 26.3, and vegetarians were at 25.7. *Vegetarian diet* may seem a contradiction in terms, since

how many vegetarians are on diets? But in the United States, even the average vegetarian is overweight. Only those eating purely plant-based diets were, on average, at an ideal weight with an average BMI of 23.6.²⁴⁶⁸ However, as I've said again and again, it's certainly not all or nothing.

Those who eat meat regularly may still benefit from eating more plants. One study found that whole plant foods constituted about 10 percent of the diets of obese individuals, 20 percent of the diets of those overweight but not (yet) obese, and closer to 30 percent for ideal-weight individuals.²⁴⁶⁹ When whole plant foods made up about 40 percent of the diet, weight gain tended to decline with age rather than creep up.²⁴⁷⁰ Although 40 percent might not sound like a lot, because unprocessed plant foods tend to be so low in calorie density, getting 40 percent of your calories from whole plant foods may mean they take up 75 percent of your plate.

Tracking people over time, those who already eat plant-based diets or even just move toward eating more plants tend to gain less weight.²⁴⁷¹ Every additional year of eating purely plant-based is associated with a 7 percent drop in obesity risk among adults.²⁴⁷² In school-aged children, meat, eggs, and dairy consumption has been associated with higher odds of obesity, whereas plant-based equivalents like veggie burgers were not, and whole plant foods like grains, beans, and nuts appeared to be protective.²⁴⁷³

These kinds of data led the former chair of the nutrition department at Loma Linda University²⁴⁷⁴ (as well as Dr. Benjamin Spock,²⁴⁷⁵ perhaps the most esteemed pediatrician of all time) to suggest raising our kids plant-based to help combat the childhood obesity epidemic. Getting diabetes as a child can cut nearly twenty years off their life.²⁴⁷⁶ What parent wouldn't go to the ends of the earth to add decades to their children's lives? We need to realize that we are making life-and-death decisions at the grocery store when we buy food for our families.

Heftier Diets, Lighter Bodies

Obesity rates among vegans may run as low as 2–3 percent,²⁴⁷⁷ which makes it difficult to tease out the health effects of plant-based eating. Are the lower disease rates associated with plant-based eating due directly to the diet itself or indirectly to the ease of weight loss and maintenance? To find control groups of individuals eating typical diets who were as slim as a group of whole-food vegans, studies have had to recruit long-distance endurance athletes running an average of forty-eight miles per week for twenty-one years. Apparently, people who run the equivalent of almost two marathons a week for two decades can be as slim as a vegan no matter what they eat! What's more, the purely plant-based eaters in the studies were sedentary, exercising for less than an hour a week.²⁴⁷⁸ So run two thousand miles a year, and your weight may rival that of some vegan couch potatoes? What's their secret?

The simplest explanation is that those eating more plant-based may just be eating fewer calories—as many as 464 fewer calories a day, in fact.²⁴⁷⁹ That would certainly do it. That's nearly the 500-a-day caloric restriction recommended in the federal dietary guidelines for weight loss.²⁴⁸⁰ But this calorie reduction was achieved without significantly changing the amount of food eaten. Some studies show that those eating purely plant-based diets are actually eating nearly a half pound more food a day compared to nonvegetarians.²⁴⁸¹ That's the beauty of foods with low calorie density: more food, less weight.

Metabolic Boost

Yes, those eating plant-based may be eating fewer calories, but they may also *need* fewer calories. Heavier people have higher calorie requirements because of the energy it takes just to move around all that extra mass, so it could go both ways. Higher caloric intake can lead to obesity, and obesity can also lead to higher caloric intake. But in fact, some studies

have found that those eating more plant-based had the same^{2482,2483} or even higher caloric intakes,^{2484,2485} which makes it even more curious that plant-based eaters are slimmer.

A study in Israel, for example, found that vegetarians weighed about twenty pounds less than nonvegetarians, yet they appeared to be eating about four hundred more calories every day.²⁴⁸⁶ As we saw in the High in Fiber-Rich Foods section, it's not what you eat but what you absorb, and the Israeli vegetarians were eating extraordinarily healthy diets, averaging nearly seventy grams of fiber a day. This could help explain why those eating more whole plant foods seem to lose more weight even at the same estimated caloric intake.²⁴⁸⁷ Interestingly, a similar paradox arose in rural China at even half the fiber intake.²⁴⁸⁸

Before the Westernization of their diets, the rural Chinese got about 90 percent of their protein from plants. Even the least active "office workers" ate 30 percent more calories than Americans, yet were 25 percent leaner.²⁴⁸⁹ Of course, they may have been biking to the office or something, but the calories still didn't seem to add up. It turns out that those eating more plant-based may effectively be burning more calories in their sleep.

In 1994, researchers discovered that those eating more plant-based for at least two years had an 11 percent higher resting metabolic rate.²⁴⁹⁰ Their metabolisms just seemed to be revved up naturally, which could help account for the greater weight loss. However, three subsequent studies failed to replicate this finding, but the reported fiber intakes of those studies averaged only eleven grams a day,^{2491,2492,2493} which is less than what is consumed on the Standard American Diet. The only way for vegetarians to get that little fiber is to center their diets around highly processed junk. (The rural Chinese, in comparison, were getting thirty-three grams a day.) The latest study, which involved a more respectable fiber intake, found a 22 percent higher resting metabolic rate, which translates into burning off hundreds of extra calories a day without doing a thing. The researchers concluded that this "underlines the need to encourage people to follow a plant-based diet."²⁴⁹⁴

Eat Seven Pounds, Lose Seven Pounds

All the studies that have consistently shown that those who eat more vegetarian meals tend to be slimmer could have been confounded by other diet or lifestyle factors. Even the studies that take such factors as physical activity, smoking, and socioeconomic class into account may not control for other dietary aspects. For example, vegetarians and vegans tend to drink less soda, eat fewer sweets, and use less added fats.²⁴⁹⁵ Maybe any eat-less-junk-food diet would have similar benefits. You don't know until you put it to the test.

A meta-analysis of a dozen randomized controlled trials involving more than a thousand research subjects found that those placed in the more plant-based groups lost significantly more weight.²⁴⁹⁶ This included studies that compared plant-based nutrition to other diets also emphasizing healthier eating. A larger systematic review of clinical trials lasting at least a month or more found that those who stuck to the more plant-based diets lost about ten pounds, and this was without any instruction for exercise or caloric restriction. Even more remarkably, weight loss wasn't even the specific goal for most of the studies. They were just set up to test the effects of plant-based diets on conditions like arthritis, diabetes, or painful periods, and the weight loss appeared to be just an inadvertent, happy side effect.²⁴⁹⁷

Just like in the observational studies showing the more plant-based people ate, the leaner they appeared to be, the same trend was uncovered when people were randomized to different degrees of plant-based eating.²⁴⁹⁸ Those randomized to eat purely plant-based lost more weight than those just avoiding meat, as well as those eating pesco-vegetarian, semi-vegetarian, or full omnivore. By the end of the six-month study, those randomized to eat a completely plant-based diet lost twice as much weight compared to those who ate

any fish or other meat, with 7.5 percent of their body weights lost, compared to about 3 percent.²⁴⁹⁹ That may only translate into a few pounds of steady weight loss a month, but, again, this was achieved without added exercise, calorie counting, or portion control. Subjects on the plant-based diet were instructed to eat however much they wanted, whenever they wanted. That's the kind of diet one can stick to long term.

Those who follow a whole food, plant-based diet for years can lose dozens of pounds.²⁵⁰⁰ In Dr. Dean Ornish's landmark heart disease reversal study, those randomized to the plant-based lifestyle group dropped an average of twenty-four pounds even though most weren't obese or explicitly attempting to lose weight, and they did so while eating as much as they wanted.²⁵⁰¹ They did, however, have the added motivation of a heart disease diagnosis to stick with the program.

Residential plant-based programs, where you may stay in a spa-like setting for a week, can be very successful for the time you're there. For example, participants in Dr. John McDougall's live-in program lose an average of three pounds a week eating unlimited, all-you-can-eat buffets.²⁵⁰² One whole-food immersion demonstrated more than seven pounds lost in one week eating nearly seven pounds of food a day.²⁵⁰³ Live-in programs can be great for optimizing clinical benefits because they can exert greater control over people's diets, but not only are such programs expensive, participants are dumped right back into their toxic food environments at home—the very ones that caused the problems in the first place.

Hans Diehl, the first director of research at the Pritikin Center, recognized the limitations of the live-in approach. Inspired by the amazing results he was seeing (including those of a certain beloved Grandma Greger), he developed a volunteer-run education program that could be offered in the community. He called it *CHIP*, the Coronary Health Improvement Project.

The Weight-Loss Program That Got Better with Time

Residential lifestyle programs can cost thousands of dollars in addition to missed work time, whereas *CHIP* was designed to be cheap. And what good is it to spoon-feed people an ideal diet only to unleash them back home to their cupboards of cookies? *CHIP* offers evening classes to teach people how to eat and stay healthy within their home environments. The focus of the program is what *CHIP* calls the Optimal Diet, one centered around whole plant foods. The program isn't dogmatic. Instead, it simply encourages people to move along the spectrum toward incorporating more "foods as grown" into their diets.²⁵⁰⁴

CHIP doesn't provide meals—just advice and encouragement, empowering people with knowledge.²⁵⁰⁵ Within a month on the program, blood sugars, cholesterol, and blood pressures dropped enough for many participants to drop their antidiabetic, cholesterol-lowering, and blood pressure-lowering medications. Better numbers on fewer drugs, along with an average six-pound weight loss.²⁵⁰⁶ But what about long term? The only true test of any lifestyle intervention is whether or not it actually changes your lifestyle. So researchers followed up with *CHIP* participants after eighteen months to see if any of the healthy habits stuck.

By the end of the four-week educational program, people were averaging about three hundred fewer calories per day, even though they were explicitly told to eat as much as they wanted.²⁵⁰⁷ There was no calorie or carb counting and no portion control. Instead of eating less food, they just ate healthier food. Great news, but that three hundred fewer daily calories was the case immediately after four weeks of classes. Where were the participants eighteen months later?

Those familiar with weight-loss studies know how this works. You can excite anyone in the short term to lose weight using nearly any kind of diet, but what happens six months

later or a year later? Most tend to gain it all back, or even more. CHIP participants, who had been eating about three hundred fewer calories a day during the program, were eating *four hundred* fewer calories eighteen months later.²⁵⁰⁸ Hold on. What kind of diet can work even *better* the longer you're on it? The participants were eating even fewer calories more than a year *after* finishing the educational program. That's one of the strengths of a diet centered around whole plant foods. Many weight-loss programs restrict caloric intake by limiting portion sizes or using meal replacements, which can result in hunger and dissatisfaction, thereby contributing to poor compliance and weight regain.²⁵⁰⁹ The satiety-promoting, all-you-care-to-eat, plant-based, whole-food dietary approach may therefore be a potent tool for sustainable weight loss.

The CHIP program has since become perhaps the most well-published community-based lifestyle intervention in the medical literature,²⁵¹⁰ with studies involving more than five thousand participants.²⁵¹¹ People didn't just lose weight and improve their physical health; they achieved significant improvements in feelings of stress and sleeping disorders. After four weeks on the program, there was a greater than 50 percent drop in reported insomnia, restless sleeping, easy emotional upset, and feelings of fearfulness or depression.²⁵¹² With randomized controlled trials showing both physical²⁵¹³ and mental health²⁵¹⁴ benefits, CHIP's name was changed from the Coronary Health Improvement Project to the Complete Health Improvement Program.

Dr. Diehl put it best when he said:

*As a society, I think we are largely at the mercy of powerful and manipulative marketing forces that basically tell us ... what to eat.... Everywhere we look, we're being seduced to the "good life" as marketers define it, but ... this so-called "good life" has produced in this country an avalanche of morbidity and mortality [disease and death].... What I would like to see in America is not this "good life" but the "best life." The best life is a simpler lifestyle—one characterized by eating more whole foods, foods-as-grown.*²⁵¹⁵

All in It to Win It

Dieting comes with an expiration date—the time at which we go off the diet (and all too often back to the habits that got us into trouble in the first place). Permanent weight loss requires permanent dietary changes. Healthier habits just need to become a way of life. That means the new eating pattern has to be one you can stick with and also, ideally, be health-promoting overall. If it's going to be lifelong, you want it to lead to a long life. Is it too much to ask for one diet to be effective, sustainable, and life-extending?

Might there be an inherent conflict between efficacy and sustainability? Wouldn't smaller changes be easier to maintain? Even in the barbecue capital of Memphis, Tennessee, researchers got about an 80 percent six-month compliance rate with a purely plant-based diet, with no adherence benefit found for adding a small daily portion of meat and dairy.²⁵¹⁶ As we've discussed, completely avoiding some problem foods may paradoxically sometimes be even easier than attempting to moderate their intakes.²⁵¹⁷ This is readily apparent in the substance-use literature, where entirely avoiding alcohol is more effective and, ironically, easier for a problem drinker than just cutting down.²⁵¹⁸

Studies recommending greater dietary changes can produce greater changes in behavior.²⁵¹⁹ For example, in that study randomizing people to four different degrees of plant-based eating—(1) entirely plants, (2) just meat-free, (3) meat-free except for fish, or (4) flexitarian with some meat—all four diets ended up with similar acceptability and adherence, even among those who were initially unhappy with their assignments.²⁵²⁰ In fact, even among those who ended up being noncompliant, those assigned to the completely meat-free groups ended up making more changes (and losing significantly

more weight) than the omnivore controls.²⁵²¹ So rather than “All things in moderation,” a better aphorism may be “Big changes beget big results.”²⁵²² That old adage “Shoot for the moon—if you fail, you will land among the stars” was obviously written by someone without even the vaguest understanding of astronomy, but the reverse does make decent dietary sense. *So shoot for the stars!*

Success breeds success. After a few weeks of eating more healthfully, you may *feel* so much healthier that your resolve is reinforced. When surveyed, those who choose to eat plant-based for health reasons say it’s mostly for general wellness or disease prevention, or to improve their energy levels or immune function. They report it gave them a sense of control over their health, helped them feel better emotionally, and improved their overall health. Most who made the transition for a specific health problem (most commonly for high cholesterol, weight loss, high blood pressure, or diabetes) say it helped them a great deal.²⁵²³ But let’s not just take their word for it. Let’s put it to the test.

The Best Diet for Weight Loss

In 2017, a group of researchers in New Zealand published the BROAD study, a twelve-week randomized controlled trial bringing a whole food, plant-based diet to the poorest region of the country with the highest obesity rates. Overweight individuals were randomized to receive either standard medical care or semiweekly classes offering advice and encouragement to eat a low-fat diet centered around fruits, vegetables, whole grains, and legumes. The researchers had the subjects focus solely on diet rather than increasing exercise in order to isolate out the effects of striving to eat more healthfully. No meals were provided, and the intervention group was merely informed about the benefits of plant-based eating and encouraged to incorporate it into their own lives, families, homes, and community.²⁵²⁴

Even without any restrictions on portions and being able to freely eat all the healthy foods they wanted, the plant-based intervention group lost an average of nineteen pounds by the end of the three-month study. (The weight of the control group didn’t change significantly either way.) Nineteen pounds is a respectable weight loss, but what happened next? At the end of the twelve weeks, class was dismissed and no more instruction was given.

The researchers were curious to find out how much weight the subjects had gained back after being released from the study, so everyone was invited to return at the six-month mark to get reweighed. The plant-based intervention group had left the three-month study nineteen pounds lighter. Six months later, though, they were only down about ... twenty-seven pounds! The plant-based group had been feeling so good both physically and mentally, and had been able to come off so many of their medications, that they were sticking with the diet on their own and the weight had continued to come off.²⁵²⁵

What about a year later? Even in studies that last a whole year, where participants are coached to stay on a particular diet the entire time, by the end of the year, any initial weight lost in the first few months tends to creep back. The BROAD study’s intervention had only lasted three months, yet after it was over, the participants who had been randomized to the plant-based group not only lost dozens of pounds, they kept them off.²⁵²⁶

They achieved greater weight loss at six and twelve months out than any other comparable trial in which caloric intake wasn’t limited or regular exercise mandated—and that was months after the study had already ended. A whole food, plant-based diet achieved the greatest weight loss ever recorded at six and twelve months compared to any other such intervention published in the medical literature.²⁵²⁷ The record-breaking study can be read in full for free at www.nature.com/articles/nutd20173.

The Best of Both Worlds

Obviously, with very-low-calorie starvation diets, you can drop people down to any weight, but quick fixes tend to quickly unravel,²⁵²⁸ whereas the whole point of whole food, plant-based nutrition is to maximize long-term health and longevity. I mean, even if, for example, low-carb, ketogenic diets were found to be as effective (and they don't appear to be),²⁵²⁹ the point of weight loss is not to fit into a skinnier casket.

Beyond just the increased rates of constipation, headache, bad breath, muscle cramps, general weakness, and rash reported on low-carbohydrate diets,²⁵³⁰ people whose diets simply tend to sway that way appear to live significantly shorter lives.²⁵³¹ On the other hand, eating plant-based²⁵³² or even just trending in the direction of eating more healthy plant foods is associated with increased likelihood of living longer.²⁵³³ Those who start out more plant-based but then add meat to their diets at least once a week not only appear to double or triple their odds of diabetes, stroke, heart diseases, and weight gain but suffer an associated 3.6-year drop in life expectancy.²⁵³⁴

Thank goodness it's hard to stick to something like a ketogenic diet, since the long-term, adverse health effects could be devastating. Whereas low-carb diets have been shown to impair artery function²⁵³⁵ and worsen heart disease,²⁵³⁶ whole food, plant-based diets have been shown to actually *reverse* heart disease.²⁵³⁷

So what appears to be the most effective weight-loss diet just so happens to be the only diet ever proven to reverse heart disease in the majority of patients. If that's all a plant-based diet could do—reverse the number one killer of men and women—shouldn't that be the default diet until proven otherwise? And the fact that it can also be effective in treating, arresting, and even reversing other leading killers like high blood pressure and type 2 diabetes would seem to make the case for plant-based eating simply overwhelming. Only one diet has ever been shown to do all that: a diet centered around whole plant foods.

We don't have to forsake our health to lose weight. The single healthiest diet may also be the most effective diet for weight loss.

Health by Design

Isn't it all a bit too convenient? The same foods that check off the most ideal weight-loss ingredients are the same foods that rack up the most points on health and longevity? And whole plant foods aren't just heart-healthy, but brain-, kidney-, and liver-healthy too. What are the odds?

This becomes clearer when we think about some of the underlying physiology. Yes, whole food, plant-based nutrition is the only diet proven to reverse heart disease in the majority of patients, opening up arteries without drugs or surgery. However, the heart muscle isn't the only organ that requires blood flow to bring in oxygen and nutrients and to clear out waste products. Perhaps it's no coincidence then that the diet found best to improve blood flow can support the health of all our organ systems. There are other causal factors such as inflammation that could explain why such an anti-inflammatory diet could affect multiple disease conditions at once, including obesity.

It may also be instructive to take an even further step back and look at our ancestral history. Millions of years before we learned how to sharpen spears, mill grains, or boil sugarcane, our entire physiology is presumed to have evolved in the context of eating what the rest of our great ape cousins eat—leaves, stems, and shoots (in other words, vegetables), fruits, seeds, and nuts.²⁵³⁸ The Paleolithic period, when we started using tools, only goes back about two million years. We and other great apes have been evolving since the Miocene era, more like *twenty* million years ago.²⁵³⁹ So for the first 90 percent of our hominoid existence, our bodies evolved on mostly plants.²⁵⁴⁰

We've known for more than a century that you can clog the arteries of herbivores like rabbits by feeding them meat, eggs, and dairy,²⁵⁴¹ but it's virtually impossible to induce atherosclerosis in a carnivore with cholesterol because that's part of their natural diets.²⁵⁴²

Similarly, rats eating rat food don't get fat, but give them Oreos and it's a different story. Perhaps it's no wonder that our bodies may thrive best on the diet we were designed to eat. So maybe we should go back to our roots. (Pun intended!)

IV. Weight-Loss Boosters

INTRODUCTION

Offering maximum nutrition with minimum calories, a diet centered around whole, healthy plant foods is the best form of girth control. Whole food, plant-based nutrition best checks off the criteria for the optimal slimming diet. It's the tried-and-true recipe with the most ideal weight-loss diet ingredients—so why isn't this the end of the book?

Just eating healthfully enough should do it. Obese individuals randomized to eat plant-based at home lose nearly a cubic inch of deep visceral belly fat a week.²⁵⁴³ Start packing your diet with real food that grows out of the ground, and the pounds should come off naturally, taking you down toward your ideal weight. The average person eating completely plant-based has a BMI down around the perfect range,²⁵⁴⁴ but there is a bell curve. Even if the average is on target, some people naturally fall to either side, so I wanted to offer an array of tools that can drive or boost further weight loss for any stubborn pounds that remain.

That was the reason all the chapters in *How Not to Die* on the leading killer diseases were longer than just the three words: *Eat more plants*. Yes, those who go all in end up with perfect blood pressures and perfect cholesterol levels *on average*, for example, but if you're doing everything right and your numbers are still off, I wanted to go through all the dietary tweaks you could use to optimize your condition. That way, you could create a portfolio of specific foods to help with each specific condition. I want to do the same thing with this book.

My hope with part IV is to give you an arsenal of weapons in your fight against fat.

The average, purely plant-based person has an ideal BMI, which greatly incentivizes sticking with that way of eating, but if that's not where you end up or if you just want to get there quicker, are there specific plants that have an edge? And not some tabloid-y, fat-busting "breakthrough" extrapolated from test-tube data or mouse models but from actual randomized, controlled clinical trials showing objective outcomes?

Yes, there are specific foods shown in interventional studies to cause you to burn more fat, suppress your appetite, rev up your metabolism, block the absorption of calories, and effectively take away even more calories than they provide. What's more, the *context* in which we eat matters too. The same number of calories eaten at a different time of the day, in a different meal distribution, or after different amounts of sleep can translate into different amounts of body fat. Distinct forms of the exact same foods can be distinctly fattening. Combining certain foods together can have a different effect from eating them apart.

What we eat matters most, but how we eat and when can also make a difference.

In part II, we learned that a calorie is not necessarily a calorie. One hundred calories of chickpeas has a different impact than one hundred calories of chicken or Chiclets, based on their different effects on factors like absorption, appetite, or our microbiomes. Here in part IV, we go a step further and see that even the exact same foods eaten differently can have different effects.

Importantly, these tricks and tweaks serve to supplement a healthy, lifelong eating pattern, not replace it. Eliminating obesity requires treating the cause, the underlying diet, but this section is for those who want all the extra help they can get.

ACCOUNTABILITY

Scared Skinny

What is the most effective obesity treatment ever published in the medical literature that doesn't involve surgical fixes like jaw-wiring? The Trevoise Behavior Modification Program.²⁵⁴⁵ Named after a town in Pennsylvania, the program has been running all-volunteer, self-help support groups since 1970, offering lifetime treatment at no cost. The most demonstrably successful weight-loss program in history is free? Why haven't more people heard about it? Probably because it *is* free and doesn't have a massive promotional budget like billion-dollar corporation Weight Watchers, which spends hundreds of millions on advertising every year.²⁵⁴⁶

After two years on Weight Watchers, the average weight loss is about six pounds.²⁵⁴⁷ After two years in the Trevoise program, the average weight loss is thirty-nine pounds.²⁵⁴⁸ No Weight Watchers trial has ever lasted longer than two years,²⁵⁴⁹ but after five years in the Trevoise program, participants were still down thirty-five pounds.²⁵⁵⁰ Although that was only applicable to the 22 percent of patients who stayed in the program for five years,²⁵⁵¹ as many as 70 percent drop out of commercial weight-loss programs like Weight Watchers within just *three months*.²⁵⁵² What appears to be the secret to the Trevoise Behavior Modification Program's success? Extreme accountability.

The Trevoise program has been likened to "weight-loss boot camp,"²⁵⁵³ but its rigor is in the rules, not the methods. The program utilizes the standard array of traditional techniques—calorie cutting, exercise, weekly weigh-ins, and group support—but what sets it apart is the strictness of its enforcement. If members fail to attend meetings or meet their weight-loss goals, they are kicked out immediately and can never return. The program accepts almost anyone with one critical exception: No past participants are allowed. There are no second chances, no bargaining, no do-overs, no excuses. When people sign up, they understand it is for a once-in-a-lifetime opportunity.²⁵⁵⁴

Weighing In

Trevoise's tough-love approach may not be for everyone, but some of its key principles such as social support may be universal. A randomized trial found that group therapy tends to produce greater results than going it alone, even among those who initially expressed a preference for individual treatment.²⁵⁵⁵ Similarly, health coaches can also help people stay engaged and accountable.²⁵⁵⁶ Self-monitoring, another important takeaway, is considered the cornerstone of behavioral change for weight loss.²⁵⁵⁷ Without awareness of your progress, how can you ever reach your goals?

There are now high-tech wearable activity trackers to monitor our exercise to facilitate weight loss,²⁵⁵⁸ but the best device for monitoring caloric intake remains the humble bathroom scale. Until recently, though, frequent self-weighing for weight control was actively discouraged. Clinicians were afraid dieters might be discouraged by the slow rate of weight loss²⁵⁵⁹ or, even worse, suffer negative psychological effects.²⁵⁶⁰ However, evidence has since accumulated that suggests frequent weighing is a safe and effective tool for weight control.²⁵⁶¹

Self-weighing was identified as a core weight-control strategy, along with exercise and a low-calorie, lower-fat diet, in the National Weight Control Registry, the largest study of individuals successful at long-term maintenance of weight loss.²⁵⁶² Of the thousands of

registrants who, on average, lost about seventy pounds and kept it off for years, 79 percent weighed themselves on at least a weekly basis.²⁵⁶³ Over time, a decrease in self-weighing frequency was associated with greater weight gain, but which came first? Did the lack of monitoring allow the weight to creep up, or did the creeping weight produce an ignorance-is-bliss, head-in-the-sand ostrich effect preventing you from weighing yourself?

Findings from more than a dozen such prospective studies have consistently shown regular self-weighing to be associated with successful weight loss and maintenance,²⁵⁶⁴ but they are all stricken with the same nagging question. Does self-weighing lead to more weight loss, or might weight loss lead to more victory-lap weighing? Could there be a third factor related to both? Those with the self-discipline to weigh themselves every day may also have the self-discipline to stick more closely to a diet.²⁵⁶⁵ What's the only way to prove cause and effect? That's right: Put it to the test.

Randomized controlled trials have shown that those assigned to daily weighing, accompanied by weekly email messaging tailored to their progress, lost more weight,²⁵⁶⁶ were better able to resist weight gain,²⁵⁶⁷ and maintained more weight loss.²⁵⁶⁸ The control groups, however, received no continued monitoring, so it's hard to separate the effect of the weighing from the effect of the regular email contact. Just providing obese individuals with a scale and telling them to weigh themselves every day without giving them any useful instruction or feedback doesn't appear to help significantly.²⁵⁶⁹

Self-monitoring has been shown to be an effective behavioral technique for helping people eat more healthfully, exercise more,²⁵⁷⁰ and drink less alcohol,²⁵⁷¹ but unlike in those cases, self-weighing is monitoring an *outcome* rather than specific behaviors.²⁵⁷² If people don't know what to do about the fact that they're gaining weight, getting on a scale may not help at all. Self-weighing is merely a feedback tool to allow for personal accountability and to offer reinforcement, both positive and negative, for whatever strategies are being employed.²⁵⁷³

The evidence supporting frequent self-weighing as a part of weight-management interventions is now considered so strong²⁵⁷⁴ that it's been incorporated into the official weight-management guidelines put out by the Obesity Society, as well as the American Heart Association and the American College of Cardiology.²⁵⁷⁵ The National Institutes of Health calls regular self-weighing "crucial" for long-term weight control.²⁵⁷⁶

So how often should we weigh ourselves? There is insufficient evidence to support a specific frequency of weighing, whether weekly or daily.²⁵⁷⁷ One study found that twice daily—upon waking and again right before bed—appeared superior to once a day (about six pounds versus two pounds of weight loss over twelve weeks).²⁵⁷⁸

Early on, concerns were raised that self-weighing might be a double-edged sword, potentially putting one at risk for depression about body image issues.²⁵⁷⁹ Thankfully, there does not appear to be an association between self-weighing and mood, self-image, or disordered eating.²⁵⁸⁰ Although there may be a negative impact for normal-weight adolescents,²⁵⁸¹ self-weighing among overweight and obese adults appears to actually improve psychological health and well-being.²⁵⁸² Among those adults needing to lose weight, self-weighing seems to be associated with less depression, less disordered eating, and less body dissatisfaction, but this may be confounded by the fact that regular self-weighing improves weight loss.²⁵⁸³

FOOD FOR THOUGHT

Weigh yourself regularly to monitor your progress. If you are able to splurge, consider treating yourself on your weight-loss and maintenance journey with a Wi-Fi and/or Bluetooth-enabled wireless scale that can automatically transmit your data and graph your trajectory. You can even have the information sent to a friend or support group for added accountability.

AMPING AMPK

The Fat Controller

The universal energy currency in all of biology is a molecule called *adenosine triphosphate*, commonly known as *ATP*. The *tri* in triphosphate means *three*, as in tricycle or, in this case, ATP's three phosphates, where energy is stored. Plants make ATP with energy from the sun, and animals make it by burning fat, carbohydrates, and protein. The energy is spent by releasing the phosphates, which transforms ATP to AMP—adenosine *monophosphate*, with *mono* meaning *one*—which then can be juiced up with two more phosphates back to ATP, and the cycle continues. In this way, every cell in our bodies and in every living thing is like a little rechargeable battery; AMP molecules are charged up with phosphates to ATP using sunlight or food and then drained back down to AMP to do the cell's work. This brings us to AMPK, or *AMP-activated protein kinase*.

A kinase is a type of enzyme. What might be the function of an enzyme activated by AMP? A buildup of AMP means the rechargeable battery is running low. It's akin to the fuel gauge in your car reading empty. As the needle creeps toward the *E*, what do you do? Add more fuel. But instead of having an extra gas can in your trunk, you may have junk in the trunk—fat stores on your body. So that's what AMPK does: It flips the switch in your body from storing fat to burning fat. That's why AMPK is not only known as the *master energy sensor*²⁵⁸⁴ in our bodies but also the *fat controller*.²⁵⁸⁵

The discovery of AMPK is considered one of the most important biomedical breakthroughs in the last few decades.²⁵⁸⁶ But can it be used to lose weight? If we could find a way to boost its activity, our bodies would burn more fat. The two obvious ways to deplete our energy stores to activate AMPK are exercise and fasting. Put people on a bike and start taking muscle biopsies while they cycle, and you can detect a near tripling of AMPK activity within twenty minutes.²⁵⁸⁷ That makes sense. The muscles use up the ATP to contract, so AMP builds up and AMPK is activated. That's one of the ways exercise leads to weight loss.

AMPK activation also leads to mitochondrial biogenesis, meaning the formation of extra mitochondria, the power plants within our cells where fat is burned and ATP is created.²⁵⁸⁸ So AMPK doesn't just cause more fat to be shoveled into the furnace—it also causes more furnaces to be built. In this way, AMPK helps explain why endurance training eventually enables us to run faster and farther. So might an AMPK activator be like the fabled exercise in a pill? Indeed, an AMPK-activator drug given to sedentary mice for a month boosted their running endurance by 44 percent.²⁵⁸⁹ After one such drug was discovered at the famed Tour de France,²⁵⁹⁰ AMPK activators were banned by the World Anti-Doping Agency.²⁵⁹¹

Even more so than performance boosters, Big Pharma has interest in the obesity market. Obese individuals are often “unwilling to perform even a minimum of physical activity,” wrote a group of pharmacologists, “thus, indicating that drugs mimicking endurance exercise are highly desirable.”²⁵⁹² The thought is that AMPK activation could mimic caloric restriction, effectively fasting in a pill.²⁵⁹³ When we stop eating, our energy gets depleted, so AMPK is activated and switches us over to start burning through our own fat stores. Might AMPK activation thereby allow us to reap the fat-burning benefits of exercise and fasting without the sweat and hunger?

Losing weight through AMPK activation is not that simple, since in our brains it revs up our appetites, which makes sense. Our fat stores can't last forever, so, in addition to tapping into our tummy fat, AMPK drives us to eat more to make up for the energy deficit. AMPK is one of the reasons we get hungry after a workout (or when we starve ourselves). That's the way the antipsychotic drug Zyprexa makes people gain weight—by boosting AMPK activity in the brain.²⁵⁹⁴ So, for weight control, we'd ideally suppress the activity of

AMPK in the brain but ramp it up throughout the rest of our bodies,²⁵⁹⁵ which is exactly how nicotine appears to work.

Pepper Uppers

Smoking cigarettes may be one of the worst things you can do your body, but it's also one of the most reliable ways to lose weight.²⁵⁹⁶ This is thought to be due to the contrasting effects nicotine has on AMPK activation in the brain and body.²⁵⁹⁷ Randomized, double-blind, placebo-controlled studies show that nicotine reduces appetite²⁵⁹⁸ and caloric intake.²⁵⁹⁹ At the same time, fat biopsies taken from smokers show more than five times the AMPK activation compared to fat taken from nonsmokers.²⁶⁰⁰ No wonder people tend to gain weight when they quit smoking,²⁶⁰¹ a phenomenon that can be blunted with nicotine gum.²⁶⁰²

Is there any way to get the weight-loss benefits of smoking without having to worry about the whole dying-a-horrific-death-from-lung-cancer thing? If you may remember from my Parkinson's disease chapter in *How Not to Die*, tobacco isn't the only plant with nicotine. Tobacco is a member of the nightshade family, along with tomatoes, potatoes, eggplants, and bell peppers, and they all contain nicotine as well.²⁶⁰³ This is why smokers can't be identified just by looking for the presence of nicotine in their toenail clippings. Because nicotine is in the food supply, nonsmokers grow out some nicotine into their nails too.²⁶⁰⁴

The total amount of nicotine we eat in our daily diets is hundreds of times less than we would get from a single cigarette, though. So while we've known for at least twenty years that there's nicotine in ketchup, it's been dismissed as insignificant.²⁶⁰⁵ We then learned that just one or two puffs of a cigarette could saturate half of our brains' primary nicotine receptors.²⁶⁰⁶ Even the minuscule nicotine exposure from secondhand smoke may protect against Parkinson's,²⁶⁰⁷ and we can get about the same nicotine exposure eating some vegetables in a nonsmoking restaurant that we'd get working in a smoky one.²⁶⁰⁸

Researchers have found that consumption of nightshade vegetables, particularly peppers and maybe tomatoes and potatoes²⁶⁰⁹ as well, is associated with a significantly lower risk of Parkinson's disease among nonsmokers.²⁶¹⁰ If there is enough nicotine in these vegetables to affect Parkinson's risk, might there be enough to tweak AMPK activation? In other words, might a peck of peppers make Peter Piper less peckish?

Green pepper juice does have anti-obesity effects on mice,²⁶¹¹ and a sweet pepper extract was shown to have an appetite-suppressing ²⁶¹² and abdominal fat-reducing effect on human subjects.²⁶¹³ Though there has yet to be an interventional study with actual foods to see if nightshade vegetables have a particular benefit, why not give them a try? Nonsmokers using nicotine gum can risk long-term addiction,²⁶¹⁴ but I've never heard of anyone becoming a stuffed pepper addict.

Raising the Barberries

More than one hundred plant products have been found to activate AMPK. Nicotine is one, and berberine, which can be found in barberries, is another.²⁶¹⁵ In *How Not to Die*, barberries held the distinction of making it onto two of my favorites lists, as one of my top picks for berries and also for herbs and spices.

Barberries first came across my radar as the single most antioxidant-packed dried fruit I could find. There are some exotic fruits that beat them (with Dr. Seussian names like *whortleberries*), but in terms of what I could find in stores, barberries trumped dried pomegranate seeds and goji berries, two other top contenders.²⁶¹⁶ Barberries are readily and inexpensively found at Middle Eastern groceries, as they're used to make a signature Persian rice dish.

Their taste is described in the medical literature as “pleasantly acidulous,”²⁶¹⁷ which is doctor-speak for *sour*. I had just been sprinkling them on my oatmeal because they’re so tasty, but evidently they’ve played a prominent role in traditional systems of healing around the world for thousands of years. In fact, one pharmacology journal flamboyantly described barberries as an “herbal remedy that has no match in serving [the] human race.”²⁶¹⁸ And I thought they were just kind of tangy.

A common problem with the herbal medicine literature is that there is often a long, impressive list of traditional uses but little or no science to back up the claims.²⁶¹⁹ The science that does exist is often either petri dish or lab animal data with questionable clinical applicability. Who cares if barberries have a “menstruation induction effect in guinea pig”²⁶²⁰ (except maybe the guinea pig)? You end up with scientists injecting herbs into the penises of rabbits in hopes of coming up with the next Viagra,²⁶²¹ but few human studies.

That changed recently. I produced a video for NutritionFacts.org that discussed a clinical trial of barberries for acne. Teenagers randomized to take about a teaspoon of dried barberries, roughly eight cents’ worth, three times a day for a month experienced a dramatic 45 percent drop in inflamed pimples compared to the placebo control group.²⁶²² That’s great news for zits, but what about barberries for weight loss?

Purified berberine, the purported active ingredient in barberries, has been shown successfully to induce weight loss in randomized controlled studies,^{2623,2624,2625} earning it a patent as a “weight-loss agent.”²⁶²⁶ But because the supplement industry is so poorly regulated, you never know what’s in the bottle. An analysis of fifteen berberine supplements on the market found that 60 percent failed to match what was claimed on their labels.²⁶²⁷

The closest we have to a whole-food barberry intervention for weight loss is a trial from 2018. Diabetics randomized to drink about a cup of barberry juice each day for two months lost about six pounds more than those in the control group (and also had better blood sugars and pressures). Unfortunately, the researchers didn’t use a placebo, like barberry-flavored Kool-Aid. The control group didn’t get any intervention at all, which is problematic because we know that anytime doing *something* is compared to doing *nothing*, the placebo effect can come into play. At the same time, the barberry group received an extra ninety calories every day through the juice, yet still ended up losing more weight than the no-juice group.²⁶²⁸

A note of caution: Barberries are classified as unsafe to eat during pregnancy and are not recommended for consumption while breastfeeding.²⁶²⁹ The reason so many different plants produce compounds that end up activating AMPK may be because they are trying to fend off nibbling herbivores by producing compounds that impair animal metabolism. Cyanide, for example, is an AMPK activator too. Cyanide can kill by completely blocking energy production, whereas compounds like berberine are thought to just impair our mitochondrial function, making energy production less efficient.²⁶³⁰ It’s this inefficiency that may be what’s driving the weight loss.

Is there any way to activate AMPK without mucking with our mitochondria? Alcohol is another plant product that shouldn’t be used during pregnancy and activates AMPK, but by a totally different mechanism. Alcohol is detoxified in the body into acetic acid, which our bodies have to use ATP to metabolize.²⁶³¹ AMPK is therefore activated naturally in response to the energy expenditure.²⁶³² The problem is that before alcohol gets fully converted into acetic acid, there’s a toxic intermediate called *acetaldehyde*, which is a known carcinogen. That may be why alcohol consumption is understood to increase the risk of at least a half dozen different cancers,²⁶³³ including breast cancer, even among light drinkers.²⁶³⁴

If only there were a way to skip the toxic step and take in acetic acid directly.

Take an Acid Trip

In a review on the role of AMPK in burning off excess body fat, an investigator concluded that “it is crucial that oral compounds with high bioavailability are developed to safely induce chronic AMPK activation ... [for] long-term weight loss and maintenance.”²⁶³⁵ There is no need to develop such a compound, though, since you can already buy it any grocery store in the form of vinegar.

Acetic is derived from the Latin word *acetum*, meaning *vinegar*. By definition, vinegar is just a dilute solution of acetic acid in water.²⁶³⁶ The acetic acid is absorbed and metabolized with ATP, and we get a natural AMPK boost. Enough of a boost to lose weight at the typical dose you might get dressing a salad? Evidently, vinegar has been used to treat obesity for centuries,²⁶³⁷ but only recently has it been put to the test.

Researchers in Japan performed a randomized, double-blind, placebo-controlled trial on the effects of vinegar intake on the reduction of body fat in 155 overweight men and women. The subjects were randomly split into one of three groups: a high-dose vinegar group drinking a beverage containing two tablespoons of apple cider vinegar a day, a low-dose group drinking a beverage with one tablespoon of apple cider vinegar a day, or a placebo control group drinking an acidic beverage developed to taste the same as the vinegar drink but prepared with a different kind of acid so it didn't have any *acetic* acid. The researchers monitored the subjects' diets and gave each of them a pedometer to make sure the only significant difference among the three groups was the amount and type of vinegar they were getting every day.²⁶³⁸

By the end of the first month, there was already a significant drop in weight in both the high-dose and low-dose vinegar groups compared to placebo, with the high-dose group doing better than the low-dose one, and both vinegar groups continued to lose weight each month. In contrast, by month three, the do-nothing placebo group had gained weight (as overweight people tend to do), whereas the vinegar groups had dropped weight significantly. Like any weight-loss strategy, it only works if you do it. A month after the vinegar was stopped, the weight crept right back, but that's just additional evidence that the vinegar was working.²⁶³⁹

Was the weight loss simply statistically significant or actually significant? That's for you to decide. During the three-month trial, compared to the placebo group, the group taking one daily tablespoon of vinegar steadily lost about a pound a month and the group taking two daily tablespoons were down a total of about five pounds. Five pounds may not sound like a lot, but that weight loss was achieved for just pennies a day without removing anything from their diets.²⁶⁴⁰

The vinegar groups also got slimmer, losing about an inch off their waistlines compared to placebo, suggesting they were burning abdominal fat. The researchers went the extra mile by putting the subjects through a CT scanner. That way, they could directly measure the amount of fat before and after the trial, both the superficial fat under the skin that makes for flabby arms and contributes to cellulite, and the visceral fat, which is the fat that builds up around our internal organs and bulges out our bellies. Visceral fat is the killer fat, which is what the placebo group was putting on. Both vinegar groups, however, experienced a *drop* in visceral fat, removing about a square inch off the CT scan slice.²⁶⁴¹

Perhaps, a competing research group suggested,²⁶⁴² the vinegar drinks were just so unappealing they were ruining the subjects' appetites, while somehow the placebo drink wasn't (despite being developed to taste similarly). The diets of all three groups were analyzed, and there were no significant changes in the caloric intakes of any of the groups. So same diets, yet more weight loss in the vinegar groups. That sounds like AMPK activation ignited the fat stores, but you don't know until you put it to the test.

Experiments in a petri dish on human cells (from umbilical cords, a convenient source of human tissue) show that acetic acid can amp up AMPK,²⁶⁴³ but there's only one way to find out if that's what is happening in our bodies. Another randomized, double-blind, placebo-

controlled trial of vinegar was performed by a research group in Korea (this time using pomegranate vinegar). The researchers found the same visceral fat loss on CT scan but took the further step of taking abdominal fat biopsies from study subjects. The fat in those on the vinegar drink was found to have nearly three times the AMPK activation compared to fat taken from those on the placebo drinks, confirming the suspected mechanism.²⁶⁴⁴

The CT scan and biopsies make for very expensive studies, so I was not surprised to learn that they were funded by companies that sell vinegars. On the one hand, that's good, since, otherwise, studies like this might not be performed, but on the other hand, financial conflicts of interest always raise the concern as to whether the funding source somehow manipulated the results. The nice thing about companies funding studies about *healthy* foods, though, is that there's less of a downside. I mean, what's the worst that can happen? Even if we discover one day there was vinegar company meddling and all the findings extolling the virtues of vinegar turn out to be bogus, worse comes to worst, you just would have been eating tastier salads.

Optimal Vinegar Dosing

Treating obesity wasn't the only old-fashioned medicinal use for vinegar. Before the advent of blood sugar-lowering medications, vinegar was used as a folk remedy for diabetes.²⁶⁴⁵ Nobody bothered to formally test this, though, until 1988.²⁶⁴⁶ After all, how much money can be made from vinegar? Apparently, millions of dollars, according to the Vinegar Institute,²⁶⁴⁷ but a single diabetes drug can pull in billions, like Rezulin did before it was pulled from the market for killing too many people, that is (by causing liver failure).²⁶⁴⁸ The pharmaceutical company Pfizer still made out like a bandit, though, having to pay out less than a billion dollars to the grieving families for covering up the hazards of its drug.²⁶⁴⁹

In a study refreshingly *not* funded by a vinegar company, two daily tablespoons of apple cider vinegar mixed into a drink reduced fasting blood sugars in prediabetics an average of sixteen points within one week, which is better than what you'd tend to see with antidiabetic drugs like Glucophage or Avandia.²⁶⁵⁰ The vinegar was found to be safer, cheaper, and more effective. No wonder vinegar has been used medicinally since antiquity.

Adding just two teaspoons of vinegar to a high-glycemic meal (a bagel and juice) reduces the blood sugar spike by 23 percent.²⁶⁵¹ A meta-analysis of eleven such studies found that vinegar taken with a meal significantly improves both blood sugar and insulin responses, and it didn't seem to matter what kind of vinegar was used.²⁶⁵² Originally, we thought this was because vinegar may be delaying the stomach-emptying rate,²⁶⁵³ but subsequent evidence revealed that taking vinegar at bedtime results in lower blood sugars the next morning,²⁶⁵⁴ so it can't just be some stomach-slowng effect. The mystery was solved when a research team in Greece demonstrated that vinegar consumption improves the uptake of blood sugar by our muscles,²⁶⁵⁵ an AMPK effect also seen with exercise.²⁶⁵⁶

Adding vinegar to white bread doesn't only lower blood sugar and insulin spikes—it also increases satiety, the feeling of being full after a meal.²⁶⁵⁷ When study subjects ate about four slices of white bread, they rated their satiety a three on a scale of one to ten, so they were just a little full. Two hours later, however, they ended up hungrier than even before they had eaten the four slices. When they ate that same amount of bread with some vinegar, though, they felt twice as full, with a satiety rating of around six out of ten, and, even two hours later, still felt nearly as full as they had when they had just eaten the four pieces of bread plain.²⁶⁵⁸

Many cultures have taken advantage of this synergy. Vinegar is mixed with high-glycemic foods like white rice in Japan, for example, to make sushi. Sourdough breads may lower blood sugar and insulin spikes²⁶⁵⁹ by the same mechanism.²⁶⁶⁰ You do the same thing when you add vinegar to white potatoes to make potato salad.²⁶⁶¹ So if you are going to eat a high-glycemic food like white bread, dip that baguette in some balsamic.

There are some important caveats when it comes to vinegar, though. First, never drink it straight. It can cause intractable hiccups²⁶⁶² and burn your esophagus,²⁶⁶³ as can apple cider vinegar tablets if they get lodged in your throat.²⁶⁶⁴ There's another reason not to take apple cider vinegar tablets: They may not actually contain any apple cider vinegar, as was the case when eight different brands were tested.²⁶⁶⁵ Vinegar should also never be left on skin, soaked on a bandage, for example, as it can result in third-degree burns.²⁶⁶⁶

How much vinegar should we take? Though as many as a total of six tablespoons a day were not associated with any short-term side effects, until we know more, I'd recommend sticking with more common culinary-type doses, like two tablespoons a day, which is considered safe.²⁶⁶⁷ Acetic acid is metabolized quickly in the body,²⁶⁶⁸ so I'd recommend splitting up the daily dose to activate AMPK throughout the day, rather than taking it all at once. Given the additional mealtime benefits on blood sugars, insulin, and satiety, I'd recommend taking it with food. In the clinical trials, the belly fat-burning dose was two tablespoons a day. Splitting that over three meals would be two teaspoons a meal.

Syrupy Sweet

Acetic acid is a type of short-chain fatty acid. Where have we heard that term before? You read about it in the High in Fiber-Rich Foods section earlier in the book. That's what our good bacteria make with the fiber and resistant starch we eat. When we eat whole plant foods, our gut flora can make acetic acid from scratch in our colons by fermenting the fiber. The acetic acid can then get absorbed back into our bloodstreams, so we can use the top-down approach to activate AMPK by consuming vinegar, or the bottoms-up approach by eating fiber.²⁶⁶⁹

Most studies on isolated prebiotic supplements and extracts for weight loss have been disappointing, with one "extreme"²⁶⁷⁰ exception, a study on yacon syrup. Fiber and resistant starch aren't the only prebiotics. Our good bacteria also eat fructans, and a syrup made from roots of the yacon plant is a concentrated source. Yacon syrup has a caramel taste and is about half as sweet as honey²⁶⁷¹ but with only one-third the calories²⁶⁷² since most of the sugars are strung in the form of fructans, which we can't digest, but our friendly flora can.²⁶⁷³

A randomized, double-blind, placebo-controlled trial was performed to see if treating our flora to this bounty would help with weight loss, and the results seem too good to be true. Obese individuals randomized to just about four teaspoons of yacon syrup a day for 120 days lost nearly four inches off their waists and more than thirty pounds, whereas those on the placebo syrup gained weight.²⁶⁷⁴

With such extraordinary results, you'd think half the foods at the grocery store would be boasting "Now Made with Yacon!" on their labels by now. Presumably, the reason that isn't the case is that it doesn't take much to go overboard. The original study had a third part to it: People were randomized into the placebo syrup group, the four or so teaspoons of yacon syrup group, or a third group getting closer to nine daily teaspoons of yacon syrup. That larger dose group never made it into the study. That much yacon syrup may have excited their gut bacteria a little too much, resulting in such severe bloating, diarrhea, flatulence, and nausea that the entire group was excluded.²⁶⁷⁵

Fructans are one of the FODMAPs, which are fermentable sugars like lactose that can cause problems for some people. Those with irritable bowel syndrome, for example, who are placed on low-FODMAP diets tend to feel better. Much of this improvement may just be the placebo effect,²⁶⁷⁶ which can run as high as 91 percent in irritable bowel syndrome (meaning just giving IBS sufferers a sugar pill can sometimes make up to nine out of ten patients feel better).²⁶⁷⁷ The downside of giving it a try for IBS is that restricting healthy, high-FODMAP foods like apples and onions can deplete our microbiomes. FODMAP restriction has been found to result in a large reduction in beneficial *Bifidobacteria* within a matter of weeks.²⁶⁷⁸ That's why even the research group who had come up with the FODMAP-restriction diet only recommends doing it for four weeks before starting to reincorporate the restricted foods back into the diet.²⁶⁷⁹

If a spoonful or two of yacon syrup doesn't cause gastrointestinal upset for you, though, then, from a weight-loss standpoint, it could be a good replacement for something like honey, which, metabolically, was found to have the same effects as table sugar and high-fructose corn syrup.²⁶⁸⁰

FOOD FOR THOUGHT

To amp AMPK, I recommend trying two teaspoons of vinegar with each meal. You might be thinking, *Wait—vinegar for breakfast?* Those aghast at the thought of drizzling vinegar on their oatmeal may have never heard of chocolate vinegar, strawberry vinegar, or any of the dozens of other exotic flavors out there.

See if there's a vinegar store near you where you can sample some of the more interesting varieties. That's one of the fun things I do when I'm on the road. If I'm ever in your city, stake out the vinegar store closest to my hotel and odds are we'll end up going tasting together. Unfortunately, TSA won't let me take them back on the plane in my carry-on, but most stores have an online presence and offer mail order. There are savory varieties like hickory

smoke, garlic, and herb vinegars for main dishes and sweet selections like apricot and blackberry ginger—and those are just the ones I happen to have in my kitchen right now!

You can also incorporate vinegar into your meals by always having a side salad or even adding it to tea with some lemon juice. For a bonus, you can slice some bell peppers and sprinkle some barberries on your salad, and, if you sweeten your tea with honey or sugar, try yacon syrup instead.

APPETITE SUPPRESSION

Ch-Ch-Ch-Chia

Not only the name of novelty terra-cotta planter pets that sprout “hair,” chia is also the edible seed of a flowering plant in the mint family. It’s been eaten for thousands of years,²⁶⁸¹ which suggests it’s at least safe to consume,²⁶⁸² but does it have any special benefits? It’s certainly nutritious, providing a good source of fiber, plant protein, niacin, minerals, and antioxidants—black chia seeds perhaps more so than white²⁶⁸³—but that could describe a whole host of whole plant foods. Do chia seeds have any unique properties? Though chia seed hawkers make all sorts of claims, a recent review concluded we need to stick to the science rather than rely on cultural traditions, personal belief, or “inaccurate advertising”²⁶⁸⁴ (as redundant a term as the cynic in me has ever heard).

There are, for example, more than fifty thousand videos on YouTube on chia seeds and belly fat, but what does the science say? Eating chia seeds does reduce belly fat—in rats²⁶⁸⁵ and perhaps chickens.²⁶⁸⁶ Evidently, people don’t like smelling or tasting fishy chicken, so by feeding chickens chia seeds instead of fishmeal, you can boost omega-3 levels without it turning into funky chicken, but what happens if you cut out the middlemen and eat chia yourself?

In 2017, a research team in Turkey published a study investigating what happens if two or three teaspoons of chia seeds are added to a yogurt snack.²⁶⁸⁷ After eating yogurt with chia, participants reported significantly less hunger compared to those who had had plain yogurt, which then translated into eating fewer calories a couple of hours later at lunch. When I first heard about this study, my initial thought was a bit dismissive: *Give people more food by adding chia to whatever they were eating and they’re less hungry? Obviously.* But no. The researchers made sure that each snack had the same number of calories by giving people *less* yogurt to compensate for the added chia seeds. Given that, we can at least say that chia seeds are more satiating than plain yogurt. But hours later at lunch, the yogurt-and-chia group didn’t just eat a little less food—they ate about 25 percent fewer calories than the group with chia-free yogurt.

Two teaspoons of chia seeds, which have around thirty-five calories, seemed to work as well as three teaspoons. The yogurt-and-chia subjects, however, ended up eating nearly three hundred fewer calories at lunch, so in effect, the chia could be thought as having “negative” calories. We don’t know if the subjects somehow compensated later on by eating more at dinner, but if adding chia to your diet means eating hundreds fewer calories day after day due to their satiating effects, you’d expect to lose weight over time. You don’t know, though, until you put it to the test.

Researchers at Appalachian State University’s Department of Health, Leisure, and Exercise Science (who knew you could major in leisure science?) randomized overweight individuals to two tablespoons of whole chia seeds before the first and last meals of the day for twelve weeks and found no weight-loss benefit at all over placebo.²⁶⁸⁸ What happened? We know from the flaxseed literature that people eating muffins made with whole flaxseeds don’t seem to absorb all the benefit compared to when they eat muffins made with ground flaxseeds.²⁶⁸⁹ Why? The seed’s hard natural hull that enables flaxseeds to last for nearly a year at room temperature in an airtight container may work a little too

well to protect the seed inside. If a whole flaxseed misses your teeth, it'll pass right through you.²⁶⁹⁰ That's why I recommend grinding them up (or buying them preground).

Chia seeds, in comparison, seem so delicate that I was surprised to learn that, ideally, we should also grind them up to get the most out of them. For example, eating whole chia seeds doesn't appear to bump up our omega-3 levels, but eating ground chia does.²⁶⁹¹ Might that explain why the Appalachian study failed to find an effect? A group of Canadian researchers decided to put ground chia to the test for weight loss in a randomized, double-blind, placebo-controlled trial of about two tablespoons a day versus a fiber-matched control made mostly of oat bran. (This study design helps let us know it wasn't funded by a chia seed company, because the researchers put it head-to-head against an active control, not just a sugar pill placebo.) In this way, they could tell if there was some distinct benefit to chia beyond its fiber content.

All study subjects in both groups were put on a relatively low-calorie diet, so even the control group lost weight, but the chia group lost significantly more. The effect was slight, though: only about three pounds better than placebo after six months and only about an extra inch off the waist.²⁶⁹² What's more, the effects in most shorter duration studies didn't even reach statistical significance.²⁶⁹³

Fortunately, the flaxseed evidence for weight loss is stronger.²⁶⁹⁴

Just the Flax, Ma'am

Like chia seeds, flaxseeds have been shown to cause appetite suppression,²⁶⁹⁵ perhaps in part due to their large soluble fiber content, but does this translate into weight loss? One of the most extraordinary studies on flax was published in 2016. Overweight individuals were randomly assigned to receive either daily ground flaxseeds and lifestyle advice for weight loss, or just lifestyle advice alone. Since simply being enrolled in a study and knowing you'll be weighed repeatedly can get people to lose weight,²⁶⁹⁶ it wasn't a surprise that body weight, waist circumference, and body mass index decreased significantly in both groups. There was, however, a significantly greater reduction in the flaxseed group, and not just by a little.²⁶⁹⁷

Over the twelve-week study, the control group who had only gotten lifestyle advice lost nearly seven pounds and about an inch off their waists, while the group who had gotten the same advice along with spoonfuls of flaxseeds a day lost more than twenty pounds on average²⁶⁹⁸ and nearly four inches off their waists despite being given, in effect, more food to eat. Those are astonishing numbers for an intervention that added, rather than actively removed, calories from the diet. Was this study just some crazy flax fluke?

Another study pitted flaxseeds against nonalcoholic fatty liver disease. Thanks to the obesity epidemic, that's now the most common liver disease, recognized as a major public health problem around the world. A high-fat diet may be the "most common cause,"²⁶⁹⁹ but the fat in flaxseeds (flaxseed oil), compared to lard, was found to be better for the liver—in rats.²⁷⁰⁰ That's not particularly helpful. What about using whole flaxseeds in people?

Fatty liver patients were randomized using the same setup: lifestyle modification advice with or without flaxseeds. The flaxseed group was instructed to mix their daily ounce or so of ground flaxseeds with water or juice and to drink it after breakfast. Body weight dropped in both groups, along with liver fat, inflammation, and scarring, but significantly more so in the flaxseed group. Again, approximately twenty pounds were lost in three months after telling people to add something to their diets.²⁷⁰¹ Perhaps that first study wasn't just a fluke—or maybe they both were.

There have been more than a dozen randomized controlled trials of flaxseeds and weight loss, and when stacked up next to one another, the two twenty-pound weight-loss studies do appear to be the outliers.²⁷⁰² Still, when all the studies are combined together in a meta-analysis, there was a significant reduction in body weight, BMI, and waist circumference

following flaxseed supplementation. No benefit was found for flaxseed oil or flaxseed extract supplements, but randomized controlled trials of the *whole food* do show significant weight loss, though you should expect to drop closer to four pounds over a few months rather than twenty.

What About the Cyanide?

How Not to Die has been translated into thirty-four languages so far. Most of the time, all I have to do is just sit back and admire the creative new cover art, but some countries make publication contingent on a set of demands. The Japanese publisher, for example, wouldn't release the book until I added an extra chapter on how not to die from stomach cancer, a leading killer in Japan. Understandable. The proviso from the Swedish publisher surprised me, though. Given my Daily Dozen recommendation to eat at least a tablespoon of ground flaxseed a day, I was asked to add a section on flaxseed safety.

The Swedish National Food Agency's official website features a page warning people to stay away from ground flaxseed for fear of cyanide toxicity,²⁷⁰³ which helps explain why that was the subject of the first question I was asked when I gave a lecture in Stockholm. Was the Swedish government on to something? Had I been duped by Big Flax-funded researchers who claimed you could literally eat *pounds* of ground flaxseeds a day—more than 150 tablespoons daily—without worrying?²⁷⁰⁴

First, some background. As many as one in five of the plants we eat produces cyanide. In fact, if you look at the major food crops in the world, more than half are cyanogenic, meaning *cyanide-producing*.²⁷⁰⁵ Unlike toxins such as lead, mercury, and arsenic, which are chemical elements that can't be broken down, cyanide is an organic molecule made up of one carbon atom attached to one nitrogen atom. In that configuration, the molecule is indeed potentially poisonous, but it can instantly lose its toxicity when it's broken down or complexed into something else. That's the reason we have a cyanide-detoxifying enzyme in our bodies that does just that.²⁷⁰⁶ Cyanide is a common defense used by plants to fend off herbivores, so our bodies evolved not one—but five—different ways to get rid of it.²⁷⁰⁷

There is a rare genetic condition, though, called *Leber's disease*, where you're born without the ability to detoxify cyanide and can go blind drinking something like apple cider, for example. Other than that, our bodies evolved to be cyanide-detoxifying machines,²⁷⁰⁸ but there's obviously a limit. There have been cases, for instance, of cyanide poisoning after bitter almond ingestion.²⁷⁰⁹ Regular almonds, the kind you buy at the store, produce about forty times less cyanide than bitter almonds,²⁷¹⁰ which are used in flavor manufacturing. If you did manage to get your hands on some, though, eating fifty bitter almonds could kill you. So, doing the math, presumably eating two thousand regular almonds at one sitting would also not be a good idea.

You may not be able to readily buy bitter almonds, but you can easily get apricots, and the apricot kernels—the seeds inside the stone—have cyanide levels high enough to present a threat. So when it comes to the Swedish authorities, I am completely sympathetic to regulators wanting to take a precautionary approach, but are flaxseeds like bitter almonds, where just a few ounces could kill you, or are they more like regular almonds where typical dietary intake wouldn't even come close to being harmful?

The claim from flax industry-funded scientists that we can eat literally pounds of ground flaxseeds a day without running into trouble is a back-of-the-envelope type of calculation based on the fact we can detoxify “up to 100 mg of cyanide/day.”²⁷¹¹ I'm not interested in how much we can detoxify “up to,” though. From a safety standpoint, you want to know about the worst-case scenario, not the best-case scenario. Can't someone please just give people different doses of flaxseeds and simply measure how much cyanide ends up in their blood? Surprisingly, that wasn't done until 2016.

Researchers finally put flaxseeds to the test under conditions expected to maximize cyanide exposure. They examined more than a dozen different sources of flaxseed and used the one with the single highest levels of cyanide they could find.²⁷¹² Making sure to use raw flaxseeds, since cooking often wipes out all the cyanide,²⁷¹³ the researchers also used a 20,000 rpm laboratory grinder to ensure maximal mechanical breakdown to maximize absorption. They then gave the subjects a higher-than-typical dose, four and a half tablespoons, and had them eat it all at once on an empty stomach.²⁷¹⁴ So what did they find?

The range of cyanide blood levels one could estimate to possibly be associated with clinical symptoms of intoxication might be around 20–40 micromoles.²⁷¹⁵ Four and a half tablespoons of the highest cyanide-containing ultraground raw flaxseeds eaten on an empty stomach only raised average cyanide blood levels to 6 micromoles before rapidly coming back down, with the highest individual reading coming in at under 14.

There has to be some amount of flax that takes you over the limit, though, so the researchers tested nine tablespoons and then fifteen tablespoons. Nine tablespoons skirted blood levels right up to 20 micromoles, and fifteen tablespoons, practically a whole cup, put the study subject into the potential toxicity zone for more than three hours.²⁷¹⁶ (So much for the industry's claim that eight cups at a time are safe!²⁷¹⁷) Yet even in that worst-case scenario of one cup of ultraground raw flaxseeds at the highest available cyanide concentration on an empty stomach, there still were no actual symptoms of toxicity.²⁷¹⁸ This is consistent with the fact that there's not a single published report of cyanide toxicity after consumption of flaxseeds anywhere in the medical literature, even in Swedish health spas, where individuals are given up to twelve tablespoons as a “fibre shock.”²⁷¹⁹

Cumin

Used in cuisines around the world from Tex-Mex to South Asian, cumin is the second most popular spice on Earth after black pepper.²⁷²⁰ It is one of the oldest cultivated plants and has a range of purported medicinal uses, including appetite suppression,²⁷²¹ but it wasn't put to the test for weight loss until 2015. A randomized, double-blind, placebo-controlled trial pitted cumin versus placebo versus the "fecal spotting" obesity drug orlistat. The cumin appeared to work as well as the drug, and they both beat out placebo, but only by a few pounds over the eight-week trial.²⁷²² I'd take cumin over anal leakage any day, but rather than the whole spice, the researchers used two drops of cumin essential oil hidden in capsules three times a day, which is the equivalent of about two daily teaspoons of cumin.²⁷²³ A follow-up study sought to see how low in dosage they could go.

The next year, the same research team tried going down to as low as half a drop of cumin essential oil twice a day and still found a similar weight-loss benefit over placebo. However, the interpretation was complicated by the fact that they also added half a drop of lime essential oil.²⁷²⁴ A drop or two of cumin oil a day may also improve blood sugar control in diabetics,²⁷²⁵ but it's so hard to trust the accuracy, safety, and purity of extracts and supplements.²⁷²⁶ What about just giving the whole spice—powdered cumin—readily available at any grocery store?

Overweight women were randomized to eat calorie-restricted weight-loss diets with or without a teaspoon of added cumin a day (half a teaspoon at both lunch and dinner). Over the three-month study, those in the cumin group lost about four more pounds and nearly an extra inch off their waists, in addition to significantly dropping their triglycerides and cholesterol.²⁷²⁷ Since cumin can be purchased in bulk for less than a dollar an ounce, a teaspoon would cost less than ten cents a day.

Black Cumin

Black cumin is not actually related to cumin; it's a member of the buttercup rather than carrot family. Also known as *Nigella sativa* or simply "black seed," it's a common spice whose peppery flavor is popular in Indian and Middle Eastern cuisines, but it's also been prized for purported medicinal benefits. Described as a "miracle herb,"²⁷²⁸ with mentions going back to the Old Testament (Isaiah 28:25, 27), black cumin was found cached in King Tut's tomb, and the Prophet Muhammad evidently is quoted as saying it could "heal every disease except death."²⁷²⁹ Only in the last fifty years or so has it been put to the test, though, culminating in more than a thousand papers published in the medical literature.

Typical doses used in studies are just one or two grams a day, which is only about a quarter teaspoon.²⁷³⁰ This enables researchers to perform randomized, double-blind, placebo-controlled trials by stuffing the whole-food spice into capsules rather than using just a component or extract.

Systematic reviews and meta-analyses of randomized controlled trials have found that daily black cumin consumption significantly improves cholesterol, triglycerides,²⁷³¹ blood pressure,²⁷³² and blood sugar control.²⁷³³ Some of the results are quite extraordinary. For example, one study found that menopausal women randomized to a gram a day (less than a quarter teaspoon) of black cumin powder reduced their bad LDL cholesterol by 27 percent within two months.²⁷³⁴ That's the kind of result you'd expect taking a statin drug, but it was achieved with just a sprinkle of a spice. Black cumin may also help with menopausal symptoms themselves.²⁷³⁵

Now, taking black cumin didn't *cure* anything—a month after stopping the spice, cholesterol levels crept back up²⁷³⁶—but it does appear to be a cheap, safe, effective, and tasty (if you like spice) treatment for some of our deadliest risk factors. And the side effects? Loss of appetite and weight loss.²⁷³⁷ Bingo!

A recent systematic review and meta-analysis of randomized, controlled weight-loss trials found that about a quarter teaspoon of black cumin powder every day appears to

reduce body mass index within a span of a couple of months.²⁷³⁸ If it's truly so beneficial to so many facets of health, why don't we hear more about it? Why wasn't I taught about it in medical school? Maybe because there's little profit motive. Black cumin is just a spice. The daily dose used in most of these studies would cost about three cents.

Saffron

Saffron is another spice found to be effective for treating a major cause of suffering—depression in this case—with a side effect of diminished appetite.²⁷³⁹ When put to the test in a randomized, double-blind, placebo-controlled trial, saffron was found to lead to significant weight loss: five pounds more than placebo and nearly an inch off the waist in eight weeks.²⁷⁴⁰ The dose of saffron used in the study was the equivalent of drinking a cup of tea made from a large pinch of saffron threads.²⁷⁴¹

Suspecting the “active ingredient” might be crocin, the pigment in saffron that accounts for its crimson color, researchers also tried giving people just the purified pigment. That also led to weight loss, beating the placebo by two pounds and half an inch off the waist, but it didn't do as well as the full saffron extract. The mechanism appeared to be appetite suppression, as the pigment group ended up averaging about 85 fewer calories a day, while the saffron group consumed 170 fewer daily calories on average.²⁷⁴²

A similar study looked specifically at snacking frequency. The researchers thought perhaps the mood-boosting effects of saffron might cut down on stress-related eating. Eight weeks of a saffron extract did cut snack intake in half compared to placebo and was accompanied by a slight but statistically significant weight loss (about two pounds).²⁷⁴³ The researchers used about half the saffron dose as the other study.²⁷⁴⁴

Even weight loss of just a few pounds is pretty remarkable given the tiny doses utilized, about 100 mg, which is equivalent to around an eighth of a teaspoon of the spice. The problem is that saffron is the most expensive spice in the world. It's composed of delicate threads poking out of the saffron crocus. Each flower produces only a few threads, such that you need fifty thousand flowers—enough flowers to fill a football field—to make a single pound of spice, so that pinch of saffron could cost up to a dollar a day.

FOOD FOR THOUGHT

In my Daily Dozen checklist of recommendations introduced in *How Not to Die* for fitting some of the healthiest of healthy foods into your daily routine, I already push flaxseeds and spices in general (though I focus on turmeric). For those interested in maximizing weight loss, try expanding your repertoire. Add cumin to hummus and baked beans. Why not enjoy a saffron-infused paella sprinkled with black cumin seeds? An easy way I include black cumin in my family's daily diet is by simply mixing it in with the black peppercorns in the pepper grinder. If you aren't familiar with my chia-based chocolate sauce strawberry dip recipe in *How Not to Die*, don't miss out. It's definitely a tastier alternative than nibbling on your chia pet.

CHRONOBIOLOGY

Is Breakfast Really the Most Important Meal of the Day?

Chronobiology is the study of how our bodies' natural cycles—mental, physical, and emotional—are affected by the rhythms of the sun, moon, and seasons. What does this have to do with losing weight? Consider the question of breakfast. It is widely touted as not only the most important meal of the day in general but specifically in relation to weight loss.²⁷⁴⁵ This is not just a pop-culture prescription from checkout aisle magazines but an idea put forward by such prestigious institutions as Johns Hopkins²⁷⁴⁶ and NYU.²⁷⁴⁷ “Want to trim your waist?” read a headline from the American Dietetic Association. “Try eating breakfast!”²⁷⁴⁸ referring to breakfast as perhaps the “best kept waist-trimming secret.”²⁷⁴⁹

But is it true? The Duke University School of Medicine's health newsletter claimed: "It's always been billed as the most important meal of the day—until now."²⁷⁵⁰

While it is widely presumed that eating breakfast protects against obesity, the belief is held up as a poster child of biased distortion of the scientific record.²⁷⁵¹ No one can argue there isn't an association between body weight and breakfast. Studies have shown that obesity and skipping breakfast tend to go together beyond a shadow of a doubt, in fact, gratuitously so. A meta-analysis found that by 2011, the combined P value had reached 10^{-42} .²⁷⁵² In science, *P value* refers to the chance of getting a result that extreme, if in fact there really was no such effect. In other words, the probability that the association found between obesity and breakfast-skipping was just a fluke is lower than the chances of winning the lottery not once but five times—and then getting struck and killed by lightning.²⁷⁵³ The question is whether the relationship between skipping breakfast and obesity is cause and effect.

To illustrate the difference between correlation and causation, let me share an example of the manipulation of science by the candy industry. The National Confectioners Association has the gall to warn parents that *restricting* candy may make their children fat.²⁷⁵⁴ Candy hawkers justify this outlandish claim with a study (that they funded themselves, of course) that showed that candy-consuming children and adolescents were significantly less likely to be overweight and obese.²⁷⁵⁵ The industry-funded researchers went on to imply this exonerates candy, but what's more likely? Cutting down on candy led to obesity, or obesity led to cutting down on candy? In other words, the lower candy consumption may reflect the *consequences* of obesity, not the *cause* of obesity, as parents of obese children may try to restrict treats.

Similarly, the finding that those who skip breakfast tend to be heavier can be equally interpreted as saying those who are heavier tend to skip breakfast. Doesn't it seem more likely that overweight individuals might be skipping breakfast in an effort to eat less, rather than eating fewer meals somehow leads to weight gain? On the other hand, maybe skipping breakfast somehow slows your metabolism or causes you to overeat so much later in the day that you end up gaining weight. You can't know for certain which direction the causality goes until you put it to the test.

Sometimes randomized controlled trials are impossible.²⁷⁵⁶ To test whether parachutes save lives, you can't exactly boot half the people off a plane without them. However, you could easily randomize people to eat breakfast or skip it to see what happens. It turns out eating breakfast doesn't seem to affect our metabolic rates,²⁷⁵⁷ nor does it sufficiently suppress our appetites. Most studies have found that eating breakfast leads to the same, or even greater, caloric intake over the day.²⁷⁵⁸ Even when people ate more at lunch after skipping breakfast, they didn't tend to eat an entire breakfast's worth of calories more, so they ended up eating fewer calories overall.²⁷⁵⁹ For example, people fed about a 500-calorie breakfast may eat about 150 fewer calories at lunch, compared with those randomized to skip breakfast, but they would still end up with that surplus of around 350 calories over the breakfast skippers.²⁷⁶⁰ Does eating breakfast then translate into weight gain over time?

Researchers at Brigham Young University randomized forty-nine women who habitually skipped breakfast to either start eating breakfast or continue skipping it. If breakfast somehow magically leads to weight loss, then the group who renewed breakfast eating should benefit. But, no. Compared to those who continued to skip breakfast, adding the extra meal led to hundreds more daily calories consumed and about a third of a pound of weight gain a week.²⁷⁶¹

Breakfast of Champions?

Of course, breakfast composition matters. Though a bagel,²⁷⁶² cereal,²⁷⁶³ or eggs²⁷⁶⁴ may not sufficiently affect lunch intake, oatmeal might. Researchers at Columbia University randomized individuals into one of three breakfast conditions: oatmeal made from quick oats, the same number of calories of Frosted Flakes, or just plain water. They then measured how many calories people took in at lunch three hours later. Not only did those who ate the oatmeal feel significantly fuller and less hungry, some then went on to consume significantly less at lunch. Overweight participants who had eaten oatmeal for breakfast consumed less than half as many calories at lunch, about four hundred fewer calories, which is more than the oatmeal itself had contained.²⁷⁶⁵ So in effect, the oatmeal provided “negative” calories. In contrast, the Frosted Flakes was so *unsatiating* that the cereal group ate as much at lunch as the breakfast-skipping, water-only group.²⁷⁶⁶ It’s as if the cereal group hadn’t eaten breakfast at all!

Sadly, only about 6 percent of Americans are eating oatmeal on any given day.²⁷⁶⁷ Not only is oatmeal healthier, it’s cheaper too. Some high-end breakfast cereals price out closer to steaks than flakes at eight dollars a pound, whereas that same pound of rolled oats from your market’s bulk section may be less than a dollar (and would make ten servings).

A nutritional downside of skipping the morning meal is that breakfast may be the only time Americans consume any whole grains,²⁷⁶⁸ which are associated with a lower risk of dying prematurely from cancer, heart disease, and all causes put together.²⁷⁶⁹ A Harvard study following hundreds of thousands of individuals for more than a decade found that those consuming breakfast cereals tend to live longer, presumably because of their higher fiber intake (and perhaps fewer bacon-and-egg breakfasts),²⁷⁷⁰ though this benefit may be limited to whole-grain cereals.²⁷⁷¹

And we know that children’s cereals are the worst. Breakfast cereals marketed to American kids have been found to contain 85 percent more sugar, 65 percent less fiber, and 60 percent more sodium than those marketed to adults.²⁷⁷² Sugary cereals are the number one food advertised to kids,²⁷⁷³ with the average American child exposed to as many as 750 ads for cereal on TV every year.²⁷⁷⁴

Nutrients are added to breakfast cereals as a marketing gimmick in an attempt to create an aura of healthfulness.²⁷⁷⁵ Plastering nutrient claims on the box can create a “nutritional façade,” acting to distract attention away from unsavory qualities such as excess sugar content.²⁷⁷⁶ If those same nutrients were added to soda, would we feed our kids Coke for breakfast? We might as well spray cotton candy with vitamins too. As one medical journal editorial read, “Adding vitamins and minerals to sugary cereals ... is worse than useless. The subtle message ... is that it is safe to eat more.”²⁷⁷⁷ It’s been estimated that a child eating one serving per day of the average children’s cereal would consume more than ten pounds of sugar in a year, nearly a thousand spoonfuls of sugar, just from breakfast cereal alone.²⁷⁷⁸

General Mills argues it’s those spoonfuls of sugar that can help the medicine go down,²⁷⁷⁹ explaining that “if sugar is removed from bran cereal, it would have the consistency of sawdust.”²⁷⁸⁰ If sugar weren’t added, General Mills said its cereals could become “unpalatable.”²⁷⁸¹ If you have to add sugar to a product to make it edible, maybe that should tell you something. A characteristic of so-called ultraprocessed foods is this necessity to pack them full of salt, sugar, flavorings, and the like since they have their natural intrinsic flavors processed out and you have to mask any unpleasant tastes introduced during manufacturing.²⁷⁸²

The president of the Cereal Institute has argued that without sugary cereals, kids might not eat breakfast at all,²⁷⁸³ similar to dairy industry arguments that removing chocolate milk from school cafeterias would risk kids skipping lunch.²⁷⁸⁴ He also stressed we must consider the alternatives.²⁷⁸⁵ As Kellogg’s director of nutrition once put it: “I would suggest that Fruit [*sic*] Loops as a snack are much better than potato chips or a sweet roll.”²⁷⁸⁶ You know there’s a problem when the only way to make your product look good is to compare it to Pringles and Cinnabon.

To Skip or Not to Skip

Where did this idea of breakfast as “the most important meal of the day” come from? Edward Bernays, the so-called father of public relations infamous for his “Torches of Freedom” campaign to get women to start smoking back in the 1920s, was paid by a pork company to design and popularize the emblematic bacon-and-eggs breakfast.²⁷⁸⁷ The role of PR specialists, he wrote in his book *Propaganda*, is the “conscious and intelligent manipulation of the organized habits and opinions of the masses.”²⁷⁸⁸

Breakfast is big business. Powerful commercial interests such as the breakfast cereal lobby are blamed for perpetuating myths about the importance of that morning meal.²⁷⁸⁹ In an editorial about the breakfast controversy published in *The American Journal of Clinical Nutrition*, nutrition scientists are urged to speak truth to power and challenge conventional wisdom when necessary “even when it looks like we are taking away motherhood and apple pie.” (The editorial went on to conclude, “Actually, reducing the portion size of apple pie might not be a bad idea, either.”²⁷⁹⁰)

To lose weight, should we therefore *not* break the fast and instead skip breakfast? Though advice to eliminate breakfast “will surely pit ... nutritional scientists ... against the

very strong and powerful food industry,” skipping breakfast has been described as a “straightforward and feasible strategy” to reduce daily calorie consumption.²⁷⁹¹

Unfortunately, skipping breakfast doesn’t seem to work.

Most randomized controlled studies of skipping breakfast found no weight-loss benefit.²⁷⁹² How is that possible if skipping breakfast means skipping calories? The Bath Breakfast Project, a famous series of experiments run not out of a tub but at the University of Bath, discovered a key to the mystery. Men and women were randomized either to fast until noon every day or to eat breakfast, which was defined as taking in at least seven hundred calories before 11:00 a.m. As in other similar trials, the group eating breakfast ate a little less throughout the rest of the day but still ended up with hundreds of excess daily calories over those who had skipped breakfast. Yet after six weeks, both groups ended up with the exact same change in body fat.²⁷⁹³ How could hundreds of calories a day just effectively disappear?

If more calories were going in with no change in weight, then there must have been more calories going out. Indeed, the breakfast group was found to be engaging spontaneously in more light-intensity physical activity in the mornings than the breakfast-skipping group.²⁷⁹⁴ Light-intensity activities include things like casual walking or light housecleaning, not structured exercise per se, but apparently enough extra activity to use up the bulk of those excess breakfast calories. There’s a popular misconception that our bodies go into energy conservation mode when we skip breakfast by slowing our metabolic rates. That doesn’t appear to be true, but maybe our bodies do intuitively slow us down in other ways.²⁷⁹⁵

The extra activity didn’t completely make up for the added breakfast calories, though, suggesting there may be another factor to account for the mystery of the missing morning calories.^{2796,2797} Recent breakthroughs in the field of chronobiology—the study of our bodies’ natural rhythms—have upended another key piece of nutrition dogma: the concept that a calorie is a calorie. As it turns out, it’s not just what we eat but *when* we eat. Because of our circadian rhythms—*circadian* coming from the Latin words for *about* and *day*—morning calories don’t appear to count as much as evening calories.²⁷⁹⁸

Slave to the Rhythm

The 2017 Nobel Prize in Medicine was awarded for elucidating the molecular mechanisms of our internal circadian clocks.²⁷⁹⁹ For billions of years, life on Earth evolved to the twenty-four-hour cycle of light and dark, so it’s no surprise our bodies are finely tuned to that pattern. When people are in total darkness without any external time cues, our bodies still continue to cycle in about a twenty-four-hour circadian rhythm.²⁸⁰⁰ In fact, you can even take tissue biopsies from people and show the cells continue to cycle outside the body in a petri dish.²⁸⁰¹ Nearly every tissue and organ in our bodies has its own internal clock.²⁸⁰²

An intricate system of intrinsic clocks drives not only some of our behavioral patterns, such as eating, fasting, sleeping, and wakefulness,²⁸⁰³ but also our internal physiology, including our digestion, body temperature, blood pressure, hormone production, and immune activity.²⁸⁰⁴ Most of our genes exhibit daily fluctuations in expression, making the circadian rhythm the largest known regulatory system in our bodies.²⁸⁰⁵ This cycling is thought to allow for a level of predictability and functional division of labor so each of our body processes can run at the best time.²⁸⁰⁶ At night while we’re sleeping, a whole array of internal housekeeping activities can be switched on, such as clearing accumulated waste products from the brain, for example, and as dawn approaches, our bodies can shift back into activity mode.

Anyone who’s ever had jet lag knows what throwing off our cycles by even a few hours can do, but now we know our circadian rhythms can literally be the difference between life and death. A study of more than fourteen thousand suicide attempts using poison (such as

drinking pesticides) found that those who tried killing themselves in the late morning were more than twice as likely to die than those who ingested a similar dose in the evening.²⁸⁰⁷ In the same vein, properly timed chemotherapy can not only end up being five times less toxic but twice as effective against cancer.²⁸⁰⁸ The same drugs, at the same doses, but with different effects depending on the time they're given. Our bodies absorb, distribute, metabolize, and detoxify what we ingest differently depending on when the processes are occurring during the twenty-four-hour cycle.

We're just beginning to figure out the optimal timing for different medications. Randomize people suffering from hypertension into taking their blood pressure pills at bedtime instead of the morning, and not only does the bedtime group achieve better blood pressure control and suffer fewer heart attacks and strokes, but they also cut their risk of death in half.²⁸⁰⁹ (Sadly, most physicians and pharmacists still tell patients to take their blood pressure meds in the morning.²⁸¹⁰)

If chronotherapy—the optimal timing of drugs—can have such an impact, it may come as no surprise that chronoprevention—the scheduling of lifestyle interventions like mealtimes—can also make a difference.²⁸¹¹

No Time to Lose

In the official Academy of Nutrition and Dietetics position paper on effective treatments for obesity, importance is placed on both the quantity and the timing of caloric intake. “Potentially consuming more energy earlier in the day, rather than later in the day,” the paper concluded, “can assist with weight management.”²⁸¹² Some have gone further and even characterized obesity as a “chronobiological disease.”²⁸¹³ What evidence do we have to back up these types of claims?

The timing of caloric intake may have shifted slightly over recent decades toward a greater proportion of food later in the day,²⁸¹⁴ which raised the question about a possible role in the rise in obesity. Middle-aged men and women who eat a greater share of daily calories in the morning do seem to gain less weight over time.²⁸¹⁵ A study entitled “Timing of Food Intake Predicts Weight Loss Effectiveness” found that dieters eating their main meal earlier in the day seemed to steadily lose more weight than those eating their main meal at a later time. An obvious explanation for this finding would be those who eat later also tend to eat more. But is that really what's going on?

There does seem to be a relationship between when people eat most of their calories and how many calories they end up eating over the entire day, with those eating a greater proportion in the morning eating less overall.²⁸¹⁶ Could it be that later eaters are just overeating junk on the couch while watching prime-time TV?²⁸¹⁷ A tendency has been found for night owls to consume more fast food and soda, and fewer fruits and vegetables.²⁸¹⁸ In the field of social psychology, there's a controversial concept called *ego depletion*, where self-control is viewed as a limited resource, like a muscle that can become fatigued from overuse. As the day wears on, the ability to resist unhealthy food choices may decline, leaving one vulnerable to temptation.²⁸¹⁹ So is it just a matter of later eating leading to greater eating?

To the surprise of the investigators in the study that showed earlier eaters steadily lost more weight, the early eaters seemed to be eating as much as the later eaters. Despite that, the early eaters ended up about five pounds lighter than the later eaters by the end of the twenty-week study, even though they were apparently eating the same amount of food.²⁸²⁰ There didn't seem to be any difference in physical activity between the two groups either. Could it be that the *timing* of caloric intake matters? Scientists decided to put it to the test.

Like Night and Day

Mice are nocturnal creatures. They eat during the night and sleep during the day. If, however, you just feed mice during the day, they gain more weight than if you feed them a similar number of calories at night.²⁸²¹ Same food and about the same amount of food, but different weight outcomes, suggesting that eating at the “wrong” time may lead to disproportionate weight gain. In humans, the wrong time would presumably mean eating at night.

Weight management recommendations often include advice to limit nighttime food consumption, but this was largely anecdotal since it wasn’t studied experimentally until 2013. Researchers instructed a group of young men not to eat after 7:00 p.m. for two weeks. Compared to a control period where they continued their regular habits, after the night-eating restriction, they ended up about two pounds lighter. This is not surprising, given dietary records showing they inadvertently ate fewer calories during that period.²⁸²² To see if timing has metabolic effects beyond just foreclosing eating opportunities, you’d have to force people to eat the same amount of the same food, but just at different times of the day. The U.S. Army stepped forward to carry out just such an investigation.

In the first set of experiments, Army researchers had people eat a single meal a day, either within an hour of waking or after twelve hours of waking, so they each had just one meal as either breakfast or dinner. The breakfast-only group lost about two pounds a week compared to the dinner-only group.²⁸²³ As with the night-eating restriction study, this is to be expected, given that people tend to be hungrier in the evening. Think about it. If you went nine hours without eating during the day, you’d be famished, but people go nine hours overnight without a meal all the time yet don’t wake up ravenous. There is a natural circadian rhythm to hunger that peaks at about 8:00 p.m. and drops to its lowest level at around 8:00 a.m.²⁸²⁴ That may be why breakfast is typically the smallest meal of the day.

The circadian rhythms of our appetites aren’t just behavioral—they’re biological. It’s not just that we’re hungrier in the evening because we’ve been running around all day. If you stayed up all night and slept through the day, you’d still be hungriest when you woke up that evening. To untangle the factors, scientists use what’s called *forced desynchrony* protocols where they confine people in a room without windows in constant, unchanging, dim light and make them sleep in twenty- or twenty-eight-hour cycles to totally scramble them up.²⁸²⁵ This goes on for more than a week so the study subjects end up eating and sleeping at different times through all phases of the day. It’s then possible to see if the cyclical phenomenon is based on internal clocks or is just a consequence of what you happen to be doing at the time.

There’s a daily swing in our blood pressures, hormone production, digestion, immune activity, and almost everything else,²⁸²⁶ but let’s look at body temperature for an example. Our core body temperatures usually bottom out around 4:00 a.m., dropping from 98.6°F down to around 97.6°F.²⁸²⁷ Is this just because our bodies cool down as we’re sleeping? No. It can be shown experimentally that it happens at about the same time no matter what; it’s part of our circadian rhythms just like our appetites. It makes sense then that if you are only eating one meal a day and want to lose weight, you’d want to eat in the morning when your “hunger hormones” may be less active.²⁸²⁸

Okay, but then it just gets weirder.

The Army scientists repeated the experiment, but this time had the participants eat exactly two thousand calories, either for breakfast or dinner, taking appetite out of the equation. (They were also not allowed to exercise.) Same number of calories, so same change in weight, right? No, the breakfast-only group *still* lost about two pounds a week compared to the dinner-only group.²⁸²⁹ Two pounds of weight loss eating the same number of calories.

Breakfast Like a King, Lunch Like a Prince, Dine Like a Pauper

What about just shifting our daily distribution of calories to earlier in the day? Israeli researchers randomized overweight and obese women into one of two isocaloric groups, meaning each group was given the same number of total calories. One group was given a seven-hundred-calorie breakfast, a five-hundred-calorie lunch, and a two-hundred-calorie dinner, and the other group was given the opposite—two hundred for breakfast, five hundred for lunch, and seven hundred for dinner. Since they were all eating the same number of calories overall, the king-prince-pauper group should have lost the same amount of weight as the pauper-prince-king group, right? But no; the group who ate the most at breakfast lost more than twice as much weight as the group eating the most at the dinner meal. In addition to slimming nearly an extra two inches off their waistlines, by the end of the twelve-week study, the king-prince-pauper group lost nineteen pounds compared to only eight lost by the pauper-prince-king group despite eating the same number of calories.²⁸³⁰ Eleven additional pounds lost eating the same number of calories. That's the power of chronobiology.

700/500/200 is 50 percent of calories at breakfast, 36 percent of calories at lunch, and only 14 percent at dinner. What about 20 percent of calories for dinner? How would a calorie percentage spread of 50/30/20 compare to eating 20 percent of calories at breakfast, 30 percent at lunch, and 50 percent at dinner? Again, the bigger-breakfast group experienced “dramatically increased” weight loss, about nine pounds difference in just eight weeks with no significant difference in overall caloric intake or physical activity between the groups.²⁸³¹

Instead of eating more than 80 percent of calories at breakfast and lunch, what about just consuming 70 percent compared to 55 percent? Overweight homemakers were randomized to eat either 70 percent of their calories at breakfast, a morning snack, and lunch, leaving 30 percent for an afternoon snack and dinner, or a more balanced 55 percent up through and including lunch. In both cases, only a minority of calories was eaten for dinner. Would it matter if it were 55 percent of calories eaten up through lunch or 70 percent? Yes, there was significantly more weight loss and slimming in the dietary pattern that was more slanted toward the morning. The researchers concluded that one clear communication physicians could give is: “If you want to lose weight, eat more in the morning than in the evening.”²⁸³²

Simply telling people to eat their main meal at lunch rather than dinner may help. Despite comparable caloric intakes, participants in a weight-loss program randomized to get advice to make their main meal lunch beat out those who were instead told to make dinner their primary meal.²⁸³³ The evidence isn't completely consistent, though. A review of meal pattern studies questioned the role that reducing evening intake would facilitate weight loss, citing a study that showed the evening-weighted group did *better* than the heavy-morning-meal group.²⁸³⁴ Perhaps that was because the morning meal group was given “chocolate, cookies, cake, ice cream, chocolate mousse or donuts” for breakfast.²⁸³⁵

Overall, the *what* is still more important than the *when*. Like each of the other Weight-Loss Boosters in part IV, you can use chronobiology to expedite weight loss, but caloric timing can't substitute for a healthy diet. When he said there was “a time for every purpose under heaven,” Ecclesiastes probably wasn't talking about donuts.

Burning the Morning Oil

Why do calories eaten in the morning seem to be less fattening than calories eaten in the evening? One reason is that more calories are burned off in the morning due to diet-induced thermogenesis, the amount of energy the body takes to digest and process a meal, given off in part as waste heat. When people are given the exact same meal in the morning, afternoon, and at night, their body uses up about 25 percent more calories to process the meal in the afternoon than at night and about 50 percent more calories to

digest it in the morning.²⁸³⁶ That leaves fewer net calories in the morning to be stored as fat.

Let's put some actual numbers to this. A group of Italian researchers randomized twenty people to eat the same standardized meal at either 8:00 a.m. or 8:00 p.m. After a week, the subjects returned, this time eating the same meal at the opposite time. So each person had a chance to eat the very same meal for breakfast and for dinner. After each meal, the subjects were placed in a "calorimeter" contraption to precisely measure how many calories they were burning over the next three hours. The researchers calculated that the meal given in the morning took about 300 calories to digest, whereas the exact same meal given at night used only about 200 calories to process. The meal itself was about 1,200 calories, so, when given in the morning, it ended up providing only about 900 calories compared to around 1,000 calories at night.²⁸³⁷ Same meal, same food, same amount of food, but effectively 100 fewer calories when consumed in the morning. So a calorie is not just a calorie. It depends on when it's eaten.

But why do we burn more calories eating a morning meal? Is it behavioral or biological? If you started working the graveyard shift, sleeping during the day and working all night, which meal would net you fewer calories? Would it be the "breakfast" you had at night before you went to work, or the "dinner" you had in the morning before you went to bed? In other words, is there something about eating before we go to sleep that causes our bodies to hold on to more calories, or is it built into our circadian rhythms such that we store more calories at night regardless of what we're doing? Harvard researchers decided to find out.

People were randomized to eat identical meals at 8:00 a.m. versus at 8:00 p.m. while under simulated night shifts or day shifts. Regardless of activity level or sleeping cycle, the calories burned while processing the morning meals were 50 percent higher than the evening meals.²⁸³⁸ So the difference is explained by chronobiology; it's just part of our circadian rhythms to burn more meal calories in the morning.

How does it make sense for our bodies to race through calories in the morning when we have the whole day ahead of us? Perhaps our bodies aren't so much *wasting* calories as *investing* them. When we eat in the morning, our bodies bulk up our muscles with glycogen, which is the primary energy reserve we use to fuel our muscles. That takes energy, though. In the evening, our bodies expect to be sleeping for much of the next twelve hours, so rather than storing blood sugar as extra glycogen in our muscles, the body preferentially uses it as an energy source, which may end up meaning we burn less of our body fat.²⁸³⁹ In the morning, however, our bodies expect to be running around all day, so instead of just burning off breakfast, our bodies continue to dip into our fat stores while we use breakfast calories to stuff our muscles full of the energy reserves we need to move around over the course of the day.

This is where the "inefficiency" may come from.²⁸⁴⁰ Why does it cost more calories to process a morning meal? Instead of just burning glucose (blood sugar) directly, our bodies are using up energy to string together glucose molecules into chains of glycogen in our muscles, which are then broken back down into glucose later in the day. That extra assembly/disassembly step takes energy, energy that our bodies take from the meal, leaving us with fewer calories.²⁸⁴¹

So in the morning, our muscles are especially sensitive to insulin, rapidly pulling blood sugar out of our bloodstreams to build up glycogen reserves. At night, though, our muscles become relatively insulin-resistant and resist the signal to take in extra blood sugar. Does this mean we get higher blood sugar and insulin spikes in the evening compared to when we eat the exact same meal in the morning? Yes! In that hundred-calorie difference study, for example, blood sugars rose about twice as high after the 8:00 p.m. meal compared to the same meal eaten at 8:00 a.m.²⁸⁴² So shifting the bulk of our caloric intake toward the

morning would appear to have the dual benefit of more weight loss and better blood sugar control.

Time Heals Some Wounds

We've known for more than a half century that our bodies' ability to keep blood sugars under control, known as *glucose tolerance*, declines as the day goes on.²⁸⁴³ If you hook yourself up to an IV and just steadily drip sugar water into your vein throughout the day, your blood sugars start to go up around 8:00 p.m. even though you haven't eaten anything and the infusion rate didn't change.²⁸⁴⁴ The same amount of sugar is going into your system every minute, but your ability to handle it deteriorates in the evening before bouncing right back again in the morning. A meal eaten at 8:00 p.m. can cause twice the blood sugar response as an identical meal eaten at 8:00 a.m.²⁸⁴⁵—as if we had eaten twice as much! Our bodies just aren't expecting us to be eating when it's dark outside. Our species may have only discovered how to make fire about a quarter million years ago.²⁸⁴⁶ We just weren't built for twenty-four-hour diners.

One of the tests for diabetes is the glucose tolerance test, which measures how fast your body can clear sugar from the bloodstream. You drink a cup of water mixed with about four and a half tablespoons of regular corn syrup and then have your blood sugar measured two hours later. By that point, your blood sugar should be under 140 mg/dL. Between 140 and 199 is considered prediabetic, and 200 and higher is a sign of full-blown diabetes.²⁸⁴⁷ The circadian rhythm of glucose tolerance is so powerful that a person can test normal in the morning but prediabetic later in the day.²⁸⁴⁸ Prediabetics who average 163 at 7:00 a.m. test as frank diabetics by 7:00 p.m. at over 200.²⁸⁴⁹

In the Low Glycemic Load section, I talked about the importance of choosing lower-glycemic foods for weight loss. Timing is critical, though. Because of our circadian pattern of glucose tolerance,²⁸⁵⁰ eating a low-glycemic food at night can cause a higher blood sugar spike than consuming a high-glycemic food in the morning. We're so metabolically crippled at night that researchers found that eating a bowl of All-Bran at 8:00 p.m. caused as high a blood sugar spike as eating Rice Krispies at 8:00 a.m.²⁸⁵¹ High-glycemic foods at night would seem to represent the worst-case scenario.²⁸⁵² So if you can't resist eating refined grains and sugary junk, they might be less detrimental in the morning.²⁸⁵³

This drop in glucose tolerance over the day may help explain the weight-loss benefits of frontloading calories toward the beginning of the day beyond just the diet-induced thermogenesis effects.²⁸⁵⁴ Simply eating an earlier, rather than later, lunch may make a difference. People randomized to eat a large lunch at 4:30 p.m. suffered a 46 percent greater blood sugar response compared to an identical meal eaten just a few hours earlier at 1:00 p.m.²⁸⁵⁵ Breakfast versus lunch also seems to make a difference. A meal eaten at 7:00 a.m. can cause 37 percent lower blood sugars than an identical meal taken at 1:00 p.m.²⁸⁵⁶ There doesn't seem to be any difference between a meal at 8:00 p.m. and one at midnight,²⁸⁵⁷ but eating *that* late can disrupt our circadian rhythms so much that it can mess up our metabolisms the next morning, resulting in significantly higher blood sugars after breakfast.²⁸⁵⁸

The revelations of chronobiology bring the breakfast debate full circle. Skipping breakfast not only generally fails to cause weight loss, but it worsens overall daily blood sugar control in both diabetic²⁸⁵⁹ and nondiabetic individuals.²⁸⁶⁰ This may explain why those who skip breakfast appear to be at higher risk of developing type 2 diabetes in the first place.²⁸⁶¹

Breakfast skippers also tend to have higher rates of heart disease²⁸⁶² and atherosclerosis in general.²⁸⁶³ Is this just because skipping breakfast tends to cluster with other unhealthy choices, such as smoking and sicker eating habits overall?²⁸⁶⁴ The link between skipping breakfast and heart disease—even premature death in general²⁸⁶⁵—seems to survive

attempts to control for these confounding factors, but you don't really know until you put it to the test.

Does skipping breakfast lead to higher cholesterol, for example? Yes, within just two weeks, there was a significant rise in bad LDL cholesterol in those randomized to skip breakfast.²⁸⁶⁶ The Israeli 700/500/200 study found that the triglycerides of the king-prince-pauper group got significantly better, dropping 60 points, while those of the pauper-prince-king group got significantly worse, rising 26 points.²⁸⁶⁷

So consuming more calories in the morning relative to the evening may actually have the *triple* benefit of more weight loss, better blood sugar control, and lower heart disease risk.

Chronodisruption

One of the most important breakthroughs in recent years has been the discovery of peripheral clocks.²⁸⁶⁸ We've known about the central clock, the so-called suprachiasmatic nucleus, for nearly a half century.²⁸⁶⁹ It sits in the middle of our brains right above where our optic nerves cross, allowing it to respond to night and day. We now know there are semiautonomous clocks in nearly every organ of our bodies.²⁸⁷⁰ Our hearts run on a clock, our lungs run on a clock, our kidneys run on a clock. Up to 80 percent of the genes in our livers are expressed in a circadian rhythm,²⁸⁷¹ and our entire digestive tracts are too.

The rate at which our stomachs empty, the secretion of digestive enzymes, and the expression of transporters in our intestinal linings for absorbing sugar and fat—these all cycle around the clock. So, too, does the ability of our body fat to sop up extra calories.²⁸⁷² The way we know these cycles are driven by local clocks rather than being controlled by our brains is that we can take surgical biopsies of fat, put them in a petri dish, and still observe their natural rhythm.²⁸⁷³

All this clock talk is not just biological curiosity. Our health may depend on keeping these clocks in sync. Think of it like a child playing on a swing. Imagine you're pushing the child, but become distracted by other goings-on in the playground. You stop paying attention to your timing, so you push too early, push too late, or forget to push altogether. What happens? Out of sync, the swinging becomes erratic, slows, or even stops. That is what happens when we travel across multiple time zones or have to work the night shift.²⁸⁷⁴

The pusher in this case is the light cue falling on our eyes. Our circadian rhythms are meant to get a bright light push every morning at dawn, but if the sun rises at a different time or we're exposed to bright light in the middle of the night, this can push our cycles out of sync and leave us feeling out of sorts. That's an example of a mismatch between the external environment and our central clocks. Problems can also arise from a misalignment between the central clock in our brains with all the other organ clocks throughout our bodies. An extreme illustration of this is a remarkable set of experiments suggesting even our poop can get jet lag.

Our microbiomes seem to have their own circadian rhythms. Even though our friendly flora are down where the sun don't shine, there's a daily oscillation in both bacterial abundance and activity in our colons.

Check this out: If you put people on a plane and fly them halfway around the world, then feed their poop to mice, those mice grow fatter than mice fed their preflight feces.²⁸⁷⁵ Though it may have just been bad airline food or something, the researchers suggest the fattening flora were a consequence of circadian misalignment.²⁸⁷⁶ Indeed, several lines of evidence now implicate chronodisruption—the state in which our central and peripheral clocks diverge out of sync—as playing a role in conditions ranging from premature aging and cancer²⁸⁷⁷ to mood disorders and obesity.²⁸⁷⁸

Bright light exposure is the synchronizing swing-pusher for our central clocks. What helps drive our internal organ clocks that aren't exposed to daylight? Food intake.²⁸⁷⁹ That's

why the timing of our meals may be so important. Removing all external timing cues by locking people away under constant, dim light, researchers showed you could effectively decouple central from peripheral rhythms just by shifting mealtimes. They took blood draws every hour and even took biopsies of the subjects' fat every six hours to demonstrate the resulting metabolic disarray.²⁸⁸⁰

Just as morning light can help sync our central clocks, morning meals can help sync our peripheral clocks. Skipping breakfast disrupts the normal expression and rhythm of the clock genes themselves, which coincide with the adverse metabolic effects.²⁸⁸¹ Thankfully, much of this can be reversed. Take a group of habitual breakfast skippers and have them eat meals at 8:00 a.m., 1:00 p.m., and 6:00 p.m., and their cholesterol and triglycerides improve compared to taking those three meals five hours later, at 1:00 p.m., 6:00 p.m., and 11:00 p.m.²⁸⁸² There's a circadian rhythm to cholesterol synthesis in the body as well, which is also strongly influenced by food intake, as evidenced by the fact that cholesterol production drops 95 percent in response to a single day of fasting.²⁸⁸³

Working Against the Clock

Night-shift workers have higher rates of obesity, as well as diabetes, cardiovascular disease, and cancer²⁸⁸⁴—graveyard shift indeed!—but is it because they tend to eat out of vending machines or simply because they don't get enough sleep? Highly controlled studies have attempted recently to tease out these factors by putting people on the same diets with the same sleep, but at the wrong time of day.²⁸⁸⁵ Redistributing eating to the nighttime not only resulted in elevated blood pressure, inflammation, and cholesterol,^{2886,2887,2888} but shifting meals to the evening in a simulated night-shift protocol turned about one-third of the subjects effectively prediabetic in only ten days.²⁸⁸⁹ Our bodies just weren't designed to handle food at night.²⁸⁹⁰

Just as avoiding bright light at night can prevent circadian misalignment, so can avoiding eating at night. We may have no control over the lighting at our workplaces, but we can try to minimize overnight food intake, which has been shown to help limit the negative metabolic consequences of shift work.²⁸⁹¹ When we do finally get home in the morning, though, we may disproportionately crave unhealthy foods. In one experiment, 81 percent of participants in a night-shift scenario chose high-fat foods such as croissants off a breakfast buffet, compared to just 43 percent of the same subjects during a control period on a normal schedule.²⁸⁹²

Shift work may leave people too fatigued to exercise, but even at the same physical activity levels, chronodisruption can affect energy expenditure. Researchers at the Sleep and Chronobiology Laboratory at the University of Colorado found that we burn 12–16 percent fewer calories while sleeping during the daytime compared to at night.²⁸⁹³ Just a single improperly timed snack can affect how much fat we burn every day. Study subjects eating a specified snack at 10:00 a.m. burned about six more grams of fat from their bodies than on the days they ate the same snack at 11:00 p.m.²⁸⁹⁴ While that's only about a pat and half of butter's worth,²⁸⁹⁵ it's astounding that eating an identical snack just given at a different time can make such a difference. What's more, the evening snack group also suffered about a 9 percent bump in their LDL cholesterol within two weeks.

Only a Matter of Time

Social jet lag is the discrepancy in sleep timing between the days we work and the days we're off.²⁸⁹⁶ From a circadian rhythm standpoint, when we go to bed late and sleep in on the weekends, it's as if we flew a few time zones west on Friday evening and flew back east on Monday morning.²⁸⁹⁷ Travel-induced jet lag goes away in a few days, but what might be the consequences of constantly shifting our schedules every week over our entire working career? To my knowledge, no interventional studies have tested this yet, but population

studies suggest those who have at least an hour of social jet lag a week (which may describe more than two-thirds of people²⁸⁹⁸) have twice the odds of being overweight.²⁸⁹⁹

If sleep regularity is important, what about meal regularity? Evidently, the importance of regular meals at roughly the same time every day was emphasized by such luminaries as Hippocrates and Florence Nightingale,²⁹⁰⁰ but it wasn't put to the test until the twenty-first century. A few population studies have suggested that those eating meals irregularly were at a metabolic disadvantage, including heavier body weight and wider waistlines,²⁹⁰¹ but the first interventional trials weren't published until 2004. Subjects were randomized to eat their regular diets split up into either six regular eating occasions a day or three to nine daily eating occasions, but in an irregular manner. Researchers found that eating an irregular pattern of meals every day can cause drops in insulin sensitivity²⁹⁰² and diet-induced thermogenesis,²⁹⁰³ as well as cause cholesterol levels to rise.²⁹⁰⁴ Obese participants ended up eating more, though, on the irregular meals, so it's difficult to disentangle circadian effects. The fact that overweight individuals may overeat on an irregular pattern may be telling in and of itself, but it would be useful if such a study were repeated using identical diets to see if irregularity on its own has metabolic effects. And, indeed, just such a study was published in 2016.

During two periods, people were randomized to eat identical foods in either a regular or irregular meal pattern. During the irregular period, people had impaired glucose tolerance and lower diet-induced thermogenesis, meaning they had higher blood sugar responses to the same food and burned fewer calories to process each meal. The difference in thermogenesis only came out to be about ten calories per meal, though, and there was no difference in weight changes over the two-week periods.²⁹⁰⁵ However, diet-induced thermogenesis can act as a satiety signal.²⁹⁰⁶ The extra work put into processing a meal can help with slaking one's appetite, and, indeed, the lower hunger and higher fullness ratings during the regular meal pattern could potentially translate into better weight control if they were maintained over the long term, but this has yet to be tested.²⁹⁰⁷

Keeping Yourself in the Dark

If weakening our circadian rhythms can cause weight gain, might strengthening them facilitate weight loss? Regular morning meals can give our circadian cycles a little daily push,²⁹⁰⁸ but the biggest shove comes from our exposure to bright midmorning light (8:00 a.m.-11:00 a.m.). Similarly, exposure to light at night would be analogous to nighttime eating.²⁹⁰⁹ Yes, we've had candles to illuminate the darkness for five thousand years, but flames from candles, campfires, and oil lamps are skewed toward the red end of the light spectrum, and the shorter blue wavelengths are the ones that specially set our circadian clocks. Even incandescent electric lighting, which only started a little over a century ago, consisted of mainly low-level yellow wavelengths, but they've been replaced over just the last few decades with fluorescents and LED lights that now contain extra blue wavelengths,²⁹¹⁰ which are more similar to morning sunlight.²⁹¹¹

Using wrist meters to measure ambient light exposure, researchers found that increased evening and nighttime light exposure correlated with a subsequent increased risk of developing obesity over time.²⁹¹² This was presumed to be due to circadian misalignment, but is it possible it may instead be a sign they're not sleeping as much, and that's the real reason they grew heavier?

A study of more than one hundred thousand women controlled for this and found that the odds of obesity trended with higher nighttime light exposure independent of sleep duration.²⁹¹³ Compared to women who reported their bedrooms at night were either too dark to see their hands in front of their faces or at least too dark to see across the room, those who reported it was light enough to see across their bedrooms were significantly heavier on average.²⁹¹⁴ And it isn't as though they were sleeping with night-lights. Without

blackout curtains on the windows, many neighborhoods may be bright enough to cause circadian disruption. Using satellite imagery, scientists have even been able to correlate higher obesity rates with brighter communities.²⁹¹⁵ There's so much light at night these days that, outside of a blackout, the only Milky Way many of our children will likely ever see is inside a candy wrapper.

Begin to See the Light

Insufficient morning light may be the circadian equivalent of skipping breakfast. Indoor lighting is too bright at night, but it may also be too dim to robustly boost our daily rhythm.²⁹¹⁶ Light exposure from getting outdoors in the morning even on an overcast day is correlated to lower body weight compared to typical office lighting,²⁹¹⁷ so some doctors started trying phototherapy to treat obesity. The first case reports began being published back in the 1990s. Three out of four women lost an average of about four pounds over six weeks of morning bright light exposure, but there was no control group to confirm the effect.²⁹¹⁸

Ten years later, the first randomized controlled trial was published. Overweight individuals were randomized to an exercise intervention with or without an hour a day of bright morning light. Compared to normal indoor lighting, the bright light group lost more body fat,²⁹¹⁹ but it's possible the light just stimulated them to exercise harder. Studies show that bright light exposure even the day prior to exercise may boost performance. In a handgrip endurance test, exposure to hours of bright light increased the number of contractions until exhaustion from about 770 to 860 the next day.²⁹²⁰ While light-induced improvements in activity or mood can be helpful in their own right, it would be years more before we finally learned whether the light exposure itself could boost weight loss.

Following unpublished data purporting to show a twelve-and-a-half-pound weight-loss advantage from eight weeks of thirty minutes of daily daylight compared to indoor lighting, researchers in Norway tried three weeks of forty-five minutes of bright morning light compared to a placebo: the same time sitting in front of an ion generator that appeared to turn on but was secretly deactivated. The three weeks of light beat out the placebo, but the average difference in body-fat reduction was only about a pound.²⁹²¹ This slight edge didn't seem to correlate with mood changes, but bright light alone can stimulate serotonin production in the human brain²⁹²² and cause the release of adrenaline-type hormones,²⁹²³ both of which could benefit body fat aside from any circadian effects.²⁹²⁴ Regardless of the mechanism, bright morning daylight exposure could present a novel weight-loss strategy straight out of the clear blue sky.

Winter Never Comes

SAD doesn't just stand for the *Standard American Diet*. There's a condition known as *seasonal affective disorder* that's characterized by increased appetite and cravings, along with increased sleepiness and lethargy, beginning in autumn when light exposure starts to dwindle. This now appears to simply represent the far end of a normal spectrum of human behavior. We all appear to eat more as the days get shorter. There is a marked seasonal rhythm to caloric intake, with greater meal size, eating rate, hunger, and overall caloric consumption in the fall.²⁹²⁵

During the winter, some animals hibernate and, in preparation, double their fat stores with autumn's abundance to deal with the subsequent scarcity of winter.²⁹²⁶ Genes have been identified in humans that are similar to hibernation genes,²⁹²⁷ which may help explain why we exhibit some of the same behaviors. The autumnal effect isn't subtle. Researchers have calculated an average difference of 222 calories per day between caloric intake in the fall versus spring, and this isn't just because it's colder, since we eat more in the fall than the winter.²⁹²⁸ It appears we are just genetically programmed to prep for the deprivation of winter that no longer comes.

It's remarkable in this day and age of modern lighting and heating that our bodies would still pick up on the environmental cues of the changing seasons enough to affect such a major influence on our eating patterns. Unsurprisingly, bright light therapy is used to treat seasonal affective disorder, nearly tripling the likelihood of remission compared to placebo.²⁹²⁹ Though it's never been tested directly, it can't hurt to take the dog for some extra morning walks each fall to help fend off some of the coming holiday season weight gain.

Resetting the Clock

There are many ways we can preserve, sync, and strengthen our circadian rhythms. We can eat breakfast and get some sun in the morning, and at night, try to avoid eating and exposing ourselves to bright light. But because it is evidently “highly unlikely” that people will change their lifestyles, concludes a review on chronobiology approaches to obesity, “pharmacological modulation of circadian clock function ... might offer an easier alternative.”²⁹³⁰ One such approach might be melatonin, the so-called darkness hormone.

Melatonin is secreted by a little gland in the center of our heads as soon as it gets dark and shuts off when the sun comes up in the morning. Its rise and fall overnight in the bloodstream helps sync all the circadian clocks throughout the body. Appropriately timed and dosed, melatonin, which is available over the counter, has been found to effectively decrease jet lag symptoms after long flights.²⁹³¹ What about taking it before bedtime to reinforce our rhythm for weight loss? It works for rats²⁹³² and mice,²⁹³³ but what about people?

There are certain antipsychotic drugs notorious for causing weight gain. Melatonin was put to the test as an adjunct treatment to try to forestall this effect and, in some cases, was able to improve weight outcomes compared to placebo in patients with bipolar disorder²⁹³⁴ and schizophrenia.²⁹³⁵ These particular mental illnesses are known to have a chronodisruption component, though, so the melatonin findings can’t necessarily be generalized to others.²⁹³⁶ Combined with Prozac, melatonin was found to have an extraordinary effect on body weight, resulting in about a four-and-a-half-point drop in BMI over twenty-four weeks compared to Prozac plus placebo. At average height, that’s a difference of twenty-seven pounds.²⁹³⁷ Again, though, one can’t extrapolate to the general population since Prozac itself appears to interact with melatonin secretion.

There was a study of the effect of melatonin on migraine sufferers, and the melatonin group lost slightly more weight than those who were instead given a placebo or a conventional migraine medication.²⁹³⁸ However, a trial in which otherwise healthy obese individuals were given 6 mg a day of melatonin or placebo failed to provide evidence of a weight-loss benefit.²⁹³⁹ Given how poorly regulated the supplement industry is, there are troubling issues with the strength and purity of over-the-counter melatonin, so I recommend that you *not* use melatonin supplements to regulate your sleep schedule.

First of all, the doses found in melatonin supplements are massive. Even just taking a 3 mg dose produces levels in the bloodstream that can be fifty times higher than normal nightly levels,²⁹⁴⁰ which raises safety concerns.²⁹⁴¹ After all, melatonin used to be known as an *anti-gonad hormone*, with human-equivalent doses of just a milligram or two reducing the size of sex organs and impairing fertility in laboratory animals.²⁹⁴² Obviously, rats aren’t people, but considering the pronounced effects of melatonin on reproduction in other mammals, commentators have suggested it might be naïve to assume melatonin wouldn’t have some effects on human sexuality. Some have even speculated it may have a role one day as some sort of a contraceptive agent.²⁹⁴³

Wouldn’t we know about these effects, though? Not necessarily, since there isn’t any post-marketing surveillance of dietary supplements for side effects as there is with drugs.²⁹⁴⁴ There also isn’t the same guarantee of authenticity with dietary supplements. Based on an analysis of thirty-one different brands, the actual melatonin content varied by up to nearly 500 percent compared to what was listed on the bottle.²⁹⁴⁵

Then there are the contaminants.

Two-thirds of melatonin products tested from health food stores were found to contain unidentified impurities.²⁹⁴⁶ With no exclusive patent, companies appear unwilling to invest in ensuring purity since the pills are sold so incredibly cheaply.²⁹⁴⁷ The concerns raised are not just theoretical. Contaminants present in tryptophan supplements, for example, were thought responsible for a disease outbreak that affected more than a thousand people and

resulted in dozens of deaths.²⁹⁴⁸ Given the structural similarities between the melatonin impurities and the implicated tryptophan contaminants, melatonin supplements may just be another accident waiting to happen.²⁹⁴⁹ Because of all these reasons, melatonin supplements cannot be recommended.²⁹⁵⁰

Dietary Melatonin

It's a shame there's no way we could get the purported benefits of melatonin without the risks—*unless* melatonin were somehow found naturally in certain foods you could eat. And sure enough, melatonin was first discovered in plants in 1995 and has since been found throughout the plant kingdom.²⁹⁵¹ Randomize people to eat more or less vegetables, and you can demonstrate an effect on melatonin levels within the body.²⁹⁵²

Eat two bananas or drink the juice of about two pounds of oranges or pineapple, and you can also get a significant bump, and the melatonin levels found in those fruits are pretty modest compared to some other foods.²⁹⁵³ Cranberries appear to be the most melatonin-rich fruit.²⁹⁵⁴ Consume just a single ounce, about a third of a cup, and it's like you took a melatonin supplement with only good side effects.²⁹⁵⁵ Unfortunately, Craisins, or dried cranberries, may not have the same affect.

A study of various tart cherry products suggests that the drying process wipes out their melatonin, so there isn't any melatonin in dried cherries and presumably not in dried cranberries either.²⁹⁵⁶ The same appears to be the case with juice. The level of melatonin in cherry juice concentrate was also found to be nondetectable, so drinking cranberry juice would presumably also be a wash.

That brings us to pistachios.

Pistachios are not just the most melatonin-rich nut, they are off the charts as the most melatonin-rich food ever recorded.²⁹⁵⁷ To get a physiological dose of melatonin, all you have to eat is two. Two cups? Two handfuls? No, just two pistachios. Pistachio nuts were found to contain 0.2 mg of melatonin per gram.²⁹⁵⁸ It only takes 0.3 mg of melatonin to cause the normal daily spike our brains give us, so just two nuts would presumably do the trick.²⁹⁵⁹ So the best food for jet lag would appear to be appropriately timed pistachios. Sound too good to be true? It may be. A second lab failed to replicate the findings using a different batch of pistachios,²⁹⁶⁰ but it can't hurt to give it a try.

FOOD FOR THOUGHT

The proverb "Eat breakfast like a king, lunch like a prince, and dinner like a pauper" evidently has another variant: "Eat breakfast yourself, share lunch with a friend, and give dinner away to your enemy."²⁹⁶¹ I wouldn't go that far, but there does appear to be metabolic benefit to frontloading the bulk of calories earlier in the day. And certainly, if you're going to regularly skip a meal—for example, those practicing intermittent fasting or trying to fit all their food into a certain window through time-restricted feeding—it would probably be safer and more effective to skip dinner rather than breakfast.

Other "recommendations for the prevention of obesity ... by improving the circadian system,"²⁹⁶² based on varying degrees of evidence, include:

- Sleep during the night and be active during the day
- Sleep enough (seven to eight hours a night)
- Early to bed, early to rise
- Avoid bright light exposure at night
- Sleep in total darkness when possible
- Eat dinner at least two and a half hours before going to bed
- Avoid eating at night

I also talked about the potential for shedding light on shedding pounds through bright morning daylight exposure, especially in the fall, and eating regular meals at the same time every day. Any other ways to lose weight like clockwork? You could try eating two pistachios two to three hours before bedtime. Will that help? There's only one way to find out.

EATING RATE

A Solid Grip on Satiety

As I discussed in the Rich in Fruits and Vegetables section, the human body doesn't seem to register calories from liquids as well as it does calories from solid foods for some reason. Take, for example, the famous study of soda versus jelly beans. Researchers had people add twenty-eight extra spoonfuls of sugar to their daily diets in the form of jelly beans or soda and then measured how many calories the study participants ate over the rest of the day to see if their bodies would compensate for all that extra sugar. In the jelly bean group, their bodies registered the extra calories from the handfuls of candy, and the subjects ended up eating less of everything else throughout the day. In the end, they ate pretty much the same number of calories before and after adding the jelly beans to their diets. In the soda group, however, despite all the added calories from the cans of pop they drank every day, they continued to eat about the same amount of the rest of their diets. No wonder they gained weight after a month of drinking soda.²⁹⁶³ Their bodies didn't seem to fully recognize the extra calories when they were in liquid form and, therefore, didn't compensate by reducing their appetites for the rest of the day. Of course, when it comes to deciding which is a better dietary choice—soda versus jelly beans—the answer is *neither*. When I encourage people to eat beans every day, I'm decidedly not talking about the Jelly Belly variety.

What about solid-versus-liquid *healthy* foods? What if you drink a smoothie for breakfast instead of eating a solid meal? Will your body mistakenly think you effectively skipped breakfast and lead you to eat more later in the day? To answer this, we first have to make sure this solid-versus-liquid-calorie effect is real. Soda and jelly beans don't just differ by physical form; they have different ingredients.

To truly test for a solid-versus-liquid effect, you'd have to use the exact same foods in two different forms. Finally, a study did just that. Researchers looked at what happens if you eat a fruit salad of raw apples, apricots, and bananas and drink three cups of water or, instead, blend the fruit with two cups of water to make a smoothie and drink the third cup of water.²⁹⁶⁴ The meals are identical except one is in solid form and the other is in smoothie form. What happened? People felt significantly less full after the smoothie, even though it was the same type and amount of food. In smoothie form, it didn't fill people up as much as eating fruit *au naturel*.

Originally, we thought it was due to the lack of chewing. The act of chewing itself may send "I've eaten enough" signals that you don't get just by drinking.²⁹⁶⁵ In one experiment, people were asked to eat pasta, chewing either ten or thirty-five times per mouthful, until they felt comfortably full.²⁹⁶⁶ Those who chewed thirty-five times per bite ended up eating about a third of a cup less pasta than those who had only chewed ten times per bite. So there we have it: not only proof of a solid-versus-liquid effect from the smoothie study but the actual mechanism. As so often happens in science, however, just when you think everything is neatly wrapped up with a bow, a paradox arises.

The Great Soup Paradox

Puréed, blended soup—essentially a warm smoothie of blended vegetables—was sometimes found to be *more* satiating than the same veggies in solid form.²⁹⁶⁷ Since the meal in liquid form was more filling than the same meal in solid form, it can't be due to the amount of chewing. How can cold smoothies be less filling than the constituent ingredients eaten in solid form, but warm smoothies are more filling? So filling, in fact, that when people have soup as a first course, they may end up eating so much less of the main

course that they eat fewer calories overall, even when the added soup calories are taken into account.²⁹⁶⁸ How can we explain this paradox?

Might puréed fruits be less filling than solid fruits, but puréed vegetables more filling than solid vegetables? To test this, Purdue University researchers gave subjects three apples to eat, three cups of apple juice to drink, or a warm, blended apple soup made from a cup of apple juice with two cups of applesauce liquefied in a blender and heated up. Within fifteen minutes of eating the three actual apples, the subjects reported feeling pretty full. Drinking three cups of apple juice, on the other hand, didn't cut hunger much at all. What about the apple soup, which was pretty much just apple juice mixed with applesauce and warmed? The apple soup cut hunger almost as much as the whole apples, even more than an hour later, and in fact beat out whole apples for decreasing overall caloric intake for the day.²⁹⁶⁹

What's so special about soup? What does eating soup have in common with prolonged chewing that differentiates it from drinking a smoothie? Time. It took people about twice as long to eat when they chewed each bite of pasta thirty-five times rather than ten in that previous study.²⁹⁷⁰ Now think about how long it takes to eat a bowl of soup compared to drinking a smoothie. Could eating more slowly reduce caloric intake?

Alternatively, maybe we just think of soup as a filling food so the added satiety is more like a placebo effect. Feelings like hunger and fullness are subjective. People tend to report hunger more in accordance with how many calories they think something has rather than the actual caloric content.²⁹⁷¹ Remember that movie *Memento* about a guy who can't form short-term memories? That's actually a real disorder in which people can't remember what had just happened more than a few moments earlier. Tragically, sufferers of anterograde amnesia can overeat to the point of vomiting because they forgot they had just eaten, which shows what poor judges we are of our own hunger.²⁹⁷²

The effects of thoughts about foods can extend beyond the subjective. In a famous study entitled "Mind Over Milkshakes," people were offered two different shakes: one described as indulgent, "decadence you deserve," and another labeled as sensible, "guilt-free satisfaction." People had different hormonal responses to the two options even though they were being fooled and given the exact same milkshake.²⁹⁷³ Just the *thought* of them being different was enough to affect how their bodies responded based on objective blood tests.

Or could it be as simple as soup is most often served hot and warmer foods are more satiating?²⁹⁷⁴ How could we figure out if the answer to the soup paradox was time, thought, or temperature? If only that blended fruit salad and water study had a third group in which the smoothie was just eaten cold out of a bowl with a spoon. That would solve the mystery. If it were just preconceived notions about the comforts of soup or its warmth, then fullness ratings would fall down around that of the smoothie. It turns out that the study did include just such a third group, and the participants felt just as full sipping the smoothie with a spoon as they did eating the whole fruit—so the answer is *time*.²⁹⁷⁵ The only real reason smoothies aren't as filling is that we gulp them down. If we sip them slowly over time, they can be just as filling as if we had eaten the fruits and veggies whole.

The Twenty-Minute Rule

Schoolchildren have been timed consuming lunch in an average of seven to ten minutes.²⁹⁷⁶ Children are often scolded not to wolf down their food, but does it really matter how fast we eat? More than you may realize. People were given soup, but half were given small spoons and told to eat slowly, and the other half were given big spoons and told to eat quickly, and an amazing thing happened: The slow-eating group not only ended up feeling more satiated, but they did so after eating less soup.²⁹⁷⁷ They felt fuller eating less food.

Prolonged meal duration can allow more time for our bodies' own "I'm full" satiety signals to develop before too many calories have been consumed.²⁹⁷⁸ The slower we eat, the more time our bodies have to catch up. As Harvard's Healthy Weight Checklist puts it: "Slowing down at meals ... can help avoid overeating by giving the brain time to tell the stomach when it's had enough food."²⁹⁷⁹ We evolved for millions of years trying to extract calories from undomesticated fruits and vegetables, which were much tougher and fibrous than produce today. This was long before hot dog-eating contests enabled the human frame to inhale twenty thousand calories in ten minutes.²⁹⁸⁰ Our bodies are built to expect us to take our time when eating.

When we eat, anorexigenic hormones such as GLP-1 and PYY, which I discussed in the High in Fiber-Rich Foods section, are released from cells lining our intestines into our bloodstreams. These hormones then have to travel to our brains to flick on the satiety switch to get us to slow down, but this process takes time. Preload studies, where people are fed a first course one, five, fifteen, twenty, thirty, or sixty minutes before the main meal, show that this fullness feedback loop may take about twenty minutes to fully tamp down our appetites.²⁹⁸¹ This, then, explains the soup study results. The fast-soup-eating group was done in fewer than nine minutes, while the slow-soup-eating group stopped after twenty-nine minutes.²⁹⁸² Even though the group eating more slowly and with smaller spoons ended up having less soup overall, their brains had time to fully process the meal and were able to give them a stronger sense of satiety.

In smoothie form, you can drink fruits and vegetables at about two cups a minute—ten times faster than it might take to eat fruits and vegetables in solid form.²⁹⁸³ Liquid calories can be consumed so quickly they can undermine our bodies' ability to regulate food intake at healthy levels. It's not the liquid texture per se but the high rate of consumption at which liquids are normally consumed. Blend all the smoothies you want, but sip them slowly for a half hour or so rather than gulping them down.

Every one of a dozen population studies found that those who eat faster are at higher risk of obesity, approximately doubling their odds.²⁹⁸⁴ In a behavioral treatment program for obesity, those who were able to slow their average meal length by just four minutes, from fourteen to eighteen minutes, lost more weight over a seven-month period.²⁹⁸⁵ There are lots of ways to extend meal duration, like putting down your utensil between bites, chewing longer, taking smaller bites, or choosing foods that simply take longer to eat.

Merely inserting enforced breaks while eating doesn't appear to work, however. One experiment in which people were interrupted with a buzzer every minute or so and asked to pause eating for up to sixty seconds ended up eating more,²⁹⁸⁶ seemingly out of sheer frustration.²⁹⁸⁷ Prolonged chewing shows more promise.

Chewing the Fat Away

An obituary from 1919 about health food enthusiast Horace Fletcher proclaimed that he "taught the world to chew."²⁹⁸⁸ Also known as the Great Masticator, Fletcher was a health reformer who popularized the idea of chewing each mouthful more than thirty-two times, a chew for every tooth.²⁹⁸⁹ That practice wasn't put to the test until nearly a century later in that pasta study when chewing a bite thirty-five times was shown to beat out chewing only ten times and resulted in 12 percent fewer calories eaten at a meal.²⁹⁹⁰ A similar study found a similar result, comparing forty versus fifteen chews.²⁹⁹¹ This is not surprising given the twenty-minute rule—the fewer-chews group finished in fifteen minutes, whereas the greater-chews group took nearly a half hour before they felt satisfied, allowing their natural satiety feedback loop time to kick in. The investigators concluded that public health messages to promote "slower eating" are vague, whereas a recommendation to chew food more thoroughly may be more actionable advice.²⁹⁹²

Do people who chew less weigh more? One study sent people home with a chew-recording device—a headband with electrodes placed over their jaw muscles—and found that those scoring fewer chews had up to nine times the odds of gaining more than twenty pounds over the subsequent decades.²⁹⁹³ Of course, the obvious confounding factor to *how* they were eating was *what* they eating. Maybe the high-chew group gained less weight because they were eating lots of fiber-rich foods like vegetables, while the low-chew group was slurping down more calories from Slurpees. Eating an apple may take an average of 186 chews, whereas the same weight in Jell-O may only take 23.²⁹⁹⁴

If you seat people in a room and watch them eat the same food, overweight and obese individuals do seem to chew fewer times per mouthful than those who are normal weight, resulting in a faster eating rate.²⁹⁹⁵ If you ask people to double their baseline number of chews per bite, they end up eating about 15 percent less pizza, feeling just as full eating more than one hundred fewer calories.²⁹⁹⁶ Even just asking them to chew 50 percent more times than normal may cut their consumption by nearly 10 percent.²⁹⁹⁷

More thorough chewing leads to a slower eating rate, which leads to fewer calories consumed.²⁹⁹⁸ In other words, the same fullness with less food. If you have people eat the same amount but chew more, they end up less hungry,²⁹⁹⁹ but does that appetite suppression translate into less food eaten hours later? Researchers gave people a fixed amount for lunch and told some to chew as they normally would and the others to chew each bite for thirty seconds. Later that afternoon, the subjects were presented with a snack (essentially Skittles and M&M's) and those who, hours earlier, had chewed each mouthful of lunch for thirty seconds ended up eating only half as much candy.³⁰⁰⁰

But just when we think we have the mechanism figured out, a new enigma arises. The candy study also involved a third group instructed to chew lunch normally but with a ten-second break between each mouthful, which resulted in approximately the same meal duration as the chew-each-bite-for-thirty-seconds group. So the same slowed eating rate would presumably result in the same drop in snack intake hours later, right? No. Only the prolonged-chewing group sufficiently suppressed appetites enough to significantly cut down on snack intake later on, even though both of the slowed eating groups ate lunch over about the same protracted period.³⁰⁰¹ There must be more to the story than just allowing time for our brains to recognize the release in satiety hormones from the digestive tract.

Oral Stimulation

The cephalic phase of digestion starts before food even hits our stomachs. *Cephalic* means *in the head*. There are nerves traveling straight from our brains to our mouths. This is how even the thought of food can get us salivating. And the nerves are a two-way street. Signals coming from our mouths can tip off our brains to what's coming down the pike.³⁰⁰²

To test the effect of this mind-to-mouth connection on appetite, you can insert a tube down someone's throat to compare regular eating to slipping the same amount of food directly into their stomachs. Removing the experience of the taste, smell, and texture of the food left people feeling significantly less full even though they ended up with the exact same amount of food in their stomachs.³⁰⁰³ This wasn't just a psychological effect. Objective measures, such as slowed stomach emptying times, prove that sensations from the mouth translate into physical fullness.³⁰⁰⁴

Another way to study the cephalic phase response is to use sham feeding, known less delicately as the *chew-and-spit technique*. The insulin levels in our blood can be doubled within fifteen minutes just by chewing on some pizza, even though none of it is swallowed.³⁰⁰⁵ Based on the signals coming from the mouth, our brains seem to anticipate how much insulin is going to be needed to handle the incoming load and try to get a head start. Incidentally, the mismatch between the sweetness on the tongue and the lack of

calories flooding in when drinking diet soda may actually help explain some of the metabolic disruption associated with the consumption of artificial sweeteners.³⁰⁰⁶

In regard to appetite control, the cephalic phase response can be so powerful that fake eating can even trump actual eating. Consider this ingenious study: Subjects were split into two groups—one who chewed and spat out cake for one minute, and another who chewed and spat out cake for eight minutes, the “long oral stimulation” group. Meanwhile, within each group, half had about one hundred calories of “cake-solution” pumped into their stomachs with a tube and the other half had eight hundred calories pumped in. Then, thirty minutes later, everyone was offered a meal to see what effect each manipulation had on appetite. Remarkably, the long-chewing group getting the smaller, hundred-calorie preload ate less than the short-chewing group getting the larger, eight-hundred-calorie preload.³⁰⁰⁷ So eight times the oral exposure more mightily tamped down their hunger than getting eight times more actual food in the stomach. Amazing!

You can see how the cephalic phase response would work in concert with the digestive hormone feedback loop. It would take the average person about twenty minutes to eat nine cups of apple slices, whereas drinking the same number of calories of apple juice would take less than two minutes.^{3008,3009,3010} Not only would that twenty minutes allow time for our “stop-eating” hormones to make it up to our brains, but the apples offer eighteen more minutes of oral exposure and ten times the number of oral-stimulation signals racing from the mouth to the brain, letting it know we’re chowing down.

Slow Burn

The cephalic phase response also plays a role in diet-induced thermogenesis, the calories your body burns just to process the food you eat. As soon as food hits your mouth, your brain starts priming the pump. You’ve got to spend money to make money, and it costs the body roughly 10 percent of the calories you eat to get at the other 90 percent. That could add up to hundreds of calories a day, and about half of them are due just to the signals to the brain that arise from contact between food and the inside of your mouth. We know this because if people are tube-fed, diet-induced thermogenesis gets cut by 53 percent^{3011,3012} or more.³⁰¹³

Half of just 10 percent of the calories you eat may not sound like a lot, but it could add up to thousands of calories a month.³⁰¹⁴ What are the practical implications of this, though? It’s not as if you wake up every morning and have to decide whether or not to tube feed. You can, however, increase oral exposure time by slowing down at mealtime. If you have people eat especially fast (consuming in five minutes what would normally take them fifteen), diet-induced thermogenesis gets cut by nearly a third within fifteen minutes, so you don’t get to take full advantage of the effect for weight loss.³⁰¹⁵ In contrast, having people slow down by chewing each bite “until no lumps remain” significantly boosts thermogenesis compared to a rapid-eating group. Using Doppler ultrasound, the researchers were able to correlate these differences to the changes in abdominal blood flow.³⁰¹⁶ As soon as our brains detect food in our mouths, they start rerouting blood to the intestines to deal with the coming influx.

Another study compared chewing thirty times per mouthful versus not chewing at all (effectively drinking the same meal blenderized into a purée). The researchers found the same 50 percent difference in thermogenesis uncovered in the tube-feeding studies. So eating without chewing seemed to register as little as not eating at all. It’s almost as if the mouth had been bypassed entirely. The researchers concluded that “thorough mastication [chewing] before swallowing ... may be useful for preventing obesity.”³⁰¹⁷ But was it the act of chewing itself or just the extra time the food was present in the mouth?

Bite-Sized

How could you design an experiment to differentiate among prolonged chewing, oral exposure, and meal duration? A research group in the Netherlands came up with an elegant solution. They had people effectively take either a teaspoon of tomato soup every five seconds or a tablespoonful every fifteen seconds until they were full. Because a tablespoon is three times bigger than a teaspoon, the eating rate was exactly the same at a quarter cup per minute. Note, though, the oral exposure time was completely different. Even though the tablespoon of soup lasted slightly longer in the mouth (three seconds versus two seconds with the teaspoonful), because the tablespoon group was only getting four spoonfuls a minute, the total oral exposure time every minute was only half that of the teaspoon group (twelve seconds versus twenty-four seconds). So it was the same eating rate, but the soup was only in the mouths of the tablespoon group one-fifth of the time and in the mouths of the teaspoon group nearly half the time.³⁰¹⁸ Who ended up eating more soup?

If chewing were the critical factor, then both groups would have presumably eaten the same amount of soup since there was no chewing in either group. (It was creamy tomato.) Similarly, since their stomachs were filling up at the same rate, if it were just the length of the meal, then both groups would get full around the same time. But if the results came down to the amount of time food is physically in our mouths, then the teaspoon group would get fuller faster and end up eating significantly less—and that’s exactly what happened. The teaspoon group felt full after about four minutes, but the tablespoon group ate for closer to six minutes and ended up consuming a third more soup.³⁰¹⁹

The same thing happens when you replicate this experiment with drinks. Researchers had people swallow teaspoon-sized sips of orangeade every other second versus a larger four-teaspoon swallow every eight seconds. Same minute-by-minute drink rate, but twice the oral exposure in the teaspoon-sip group. Again, the smaller-sip group won out, feeling satiated after about one-and-a-half cups compared to the two cups it took when taking larger sips.³⁰²⁰ Experiments simultaneously varying bite size and oral exposure time with solid food found the same phenomenon: It’s better to nibble and savor than chomp and gulp.³⁰²¹

What About Chewing Gum?

If prolonged oral exposure can cause appetite suppression, what about chewing gum as a weight-loss strategy? An article entitled “Benefits of Chewing Gum” suggested as much, but it was written by—no joke—the executive director of the Wrigley Science Institute.³⁰²² Big Gum likes to point to a letter published in 1999 in *The New England Journal of Medicine*,³⁰²³ where Mayo Clinic researchers claimed chewing gum could burn eleven calories an hour. Critics pointed to the fact that this was based on having people chewing the equivalent of four sticks of gum at a “very rapid cadence”³⁰²⁴ (“precisely 100 Hz”³⁰²⁵) for twelve minutes. That seemed to burn two and two-tenths calories, hence potentially eleven calories an hour.

One might have more confidence in the Mayo scientists’ conclusion had they not lacked a fundamental understanding of basic units: 100 hertz would mean one hundred chews per second, which *would* be very rapid indeed!³⁰²⁶ If the eleven calories an hour is true, though, that might mean you could burn more calories actively chewing gum while sitting in a chair than you would *not* chewing gum while upright at a standing desk.³⁰²⁷ The calorie expenditure isn’t only due to our little jaw muscles at work. For some reason, chewing gum revs up our heart rates—as much as an extra twelve beats per minute after chewing two sticks of gum for just five minutes at rest³⁰²⁸ or three more beats per minute while walking³⁰²⁹ (proving scientifically that people *can* indeed walk and chew gum at the same time).

Chewing one small piece of gum at your own pace may only burn about three calories an hour,³⁰³⁰ which would approximate the calorie content of sugar-free gums (typically two to three calories per piece). Chewing off the calories of sugar-sweetened gum, however, which are typically twenty to twenty-five calories each, might take all day.³⁰³¹ There’s more to the energy balance of gum, though, than just all the chewing.

If the oral exposure of chewing a meal can increase diet-induced thermogenesis, how about effectively extending this period by chewing gum immediately after a meal? Will that trick the body into thinking it’s still eating? Chewing a single, three-calorie piece of gum for fifteen minutes after a meal does appear to burn off six to eight calories in extra thermogenesis.³⁰³² A few calories here and there would be nothing, though, compared to any effect chewing gum might have on portion size if it affected our appetites. So does it?

The results from studies on the effects of chewing gum on hunger are all over the place. Some studies show decreased appetite ratings,^{3033,3034} others show no effect,^{3035,3036} and one even shows significantly *increased* hunger after chewing gum.³⁰³⁷ The more important question is whether there are any changes in subsequent caloric intake. Again, the findings are mixed.^{3038,3039} One study even found that while chewing gum didn't impact consumption of M&M's, it did appear to decrease the consumption of healthy snacks.³⁰⁴⁰ The chewing gum was mint and the healthy snacks included mandarin orange slices, though, so this may have just been an orange-juice-after-tooth-brushing effect.

It can take an hour before the residual taste effect of mint toothpaste dissipates.³⁰⁴¹ This is bad if it cuts our fruit intake, but what about harnessing this power against Pringles? An international group of researchers had people eat Pringles potato chips for twelve minutes, interrupting them every three minutes to swish with a menthol mouthwash. Compared to those in the control group swishing with plain water, the minty mouthwash group cut their consumption of chips by 29 percent. The researchers concluded that "if a consumer finds themselves snacking on too many [potato chip] crisps during a given eating occasion, one potential strategy could be intervening by having a peppermint tea, menthol flavoured chewing gum, or brushing their teeth, to slow down or stop snacking."³⁰⁴²

What really matters, though, is weight loss. Even if some little modification like chewing gum can affect the consumption of a single snack, our bodies could just compensate later in the day. The only way to know for certain whether chewing gum can be used as a weight-loss hack is to put it to the test.

Researchers at the University of Buffalo randomized study participants to either not chew any gum at all or chew gum before every single eating occasion, which meant they didn't just have to chew gum before each meal but also before each snack or even before each drink if the beverage had calories. This may have been too much for folks, so they actually ended up eating on fewer occasions, switching from eating four times a day on average down to around three. However, they ended up consuming more calories at each of those fewer eating occasions, so they had no overall change in caloric intake and no change in weight.³⁰⁴³

University of Alabama researchers tried a different tack, randomizing people to chew gum after and between meals. After two months, compared to those randomized to avoid gum entirely, no improvements were noted in weight, BMI, or waist circumference.³⁰⁴⁴ What about those few studies that did show immediate hunger suppression with chewing gum? In one study, for example, people ate sixty-eight fewer calories of pasta at lunch after chewing gum for twenty minutes.³⁰⁴⁵ Okay, but other studies showed otherwise.

Different types of gum using different sweeteners could have contributed to the diversity of findings. The study showing chewing gum actually increased appetite, for example, was done with gum sweetened with aspartame. People reported feeling hungrier after chewing the sweetened gum—not only compared to no gum but also compared to chewing the same gum with no added aspartame. True, not a single randomized controlled trial has ever shown a benefit to chewing gum, but they've all used gum containing artificial sweeteners.

Remember that orangeade study demonstrating that sip size matters? The one where subjects taking smaller sips felt satiated drinking less than those taking larger sips of the same beverage? Using an artificially sweetened orange drink instead appeared to blunt the effect.³⁰⁴⁶ Since getting repeated pulses of a calorie-free flavor didn't appear to be an appetite suppressant, is it possible a different type of gum, perhaps with a different sweetener, would have a different effect? In that study where people ate fewer calories of pasta at lunch after chewing gum for twenty minutes, the gum used was largely sweetened with sorbitol,³⁰⁴⁷ a sweet compound found naturally in foods like prunes.³⁰⁴⁸ Like prunes, though, it can have a laxative effect.

Case reports with names like "An Air Stewardess with Puzzling Diarrhoea" unveil what can happen when you eat sixty sticks of sorbitol-sweetened, sugar-free gum a day.³⁰⁴⁹ Another was entitled "Severe Weight Loss Caused by Chewing Gum," but not in a good way: A twenty-one-year-old woman ended up malnourished after suffering up to a dozen bouts of diarrhea a day for eight months due to the twenty daily grams of sorbitol she was getting from chewing sugar-free gum.³⁰⁵⁰ Most people suffer gas and bloating at ten grams of sorbitol a day, which is about eight sticks of sorbitol-sweetened gum, and at twenty grams, most get cramps and diarrhea.³⁰⁵¹ So be careful how much sorbitol you eat.

The bottom line is that we have no good science showing that chewing gum results in weight loss. Could that be because the studies tended to use gum with artificial sweeteners that may have counteracted any benefits? That's a possibility. The most obvious conclusion from the results to date, however, according even to gum company-funded researchers, "is that chewing gum simply is not an efficacious weight-loss strategy."³⁰⁵²

Hard Feelings

We've talked about some of the ways to increase the time food stays in our mouths so we can take better advantage of the cephalic phase response. Whatever you're eating, you can take smaller bites, eat slower, or chew longer. Another strategy is to choose different foods entirely. The *texture* of foods can make a difference. By default, harder foods are consumed in smaller bites, eaten more slowly, and with longer chewing. If you feed people a soft rice salad made with creamy risotto rice and boiled vegetables, they end up eating 17 percent more calories than when given the same salad made with regular rice and raw vegetables. Even just swapping a hard hamburger bun for a soft one can make a difference.³⁰⁵³ However, this is the opposite of what Big Food tends to dish us. The food

industry processes products for maximum consumption rate.³⁰⁵⁴ They don't call it *fast food* for nothing.

People overeat more liquid yogurt when presented with a straw versus a spoon because we can gulp faster than we can spoon.³⁰⁵⁵ For the same reason, if people are given chocolate milk versus pudding made from nearly identical ingredients but fine-tuned with different thickeners to change the physical state, they will consume more of the liquid than the semisolid food. If the eating speed is standardized, though—for example, if the products are pumped directly into their mouths at the same rate—people can end up feeling just as full either way.³⁰⁵⁶ Some studies still suggest a satiety benefit of more solid foods, however, even at the same rate of consumption.³⁰⁵⁷ This may be due in part to differences in stomach-emptying rates.

If you put people in an MRI machine to measure how quickly food is draining from their stomachs, you can see that thicker foods tend to drain more slowly. In fact, one hundred calories of a thick milkshake can end up being more satiating than five hundred calories of a thin shake.³⁰⁵⁸ Presented with thick or thin porridge, people feel just as satisfied eating about fifty fewer calories of the thick porridge.³⁰⁵⁹ So, when making oatmeal, remember that thicker and chewier may be more filling.

Adding dried fruits and nuts can create textural complexity, which has also been found to suppress appetite, based on studies of retro Jell-O salad-like concoctions that mixed in layers of chewy and crunchy bits. The appetite-lowering benefits over more homogenous foodstuffs are thought to be due to enhanced oral-sensory stimulation.³⁰⁶⁰

The Time-Calorie Displacement Program

Whether through increasing viscosity or the number of chews, or decreasing bite size and eating rate, dozens of studies have demonstrated that regardless of how we boost the amount of time food is in our mouths, it can result in lower caloric intake.³⁰⁶¹ Some approaches may be more viable than others. For example, in that study where people had to chew each mouthful for thirty seconds before swallowing, they went on to eat less candy hours later—but they weren't happy about it. The prolonged-chewing group reported enjoying their meal significantly less,³⁰⁶² calling long-term amenability into question.³⁰⁶³ My favorite method for increasing oral exposure time is to choose healthier foods.

As opposed to those made in a factory, foods that *grow* tend to be slow. Thanks in part to the fiber content of whole, healthy plant foods, the default eating rate of more healthful foods just tends to be slower naturally.³⁰⁶⁴ Though there are certainly exceptions, like caramel toffee, highly processed foods tend to be consumed quicker. There can be a hundredfold difference in consumption between the fastest and the slowest foods. You could consume an entire two-thousand-daily-calorie-allotment's worth of chocolate milk in four minutes, whereas it would take more than six straight hours to chew through that many raw carrots.^{3065,3066,3067}

Even healthy foods can vary drastically. The average eating rate of boiled carrots is ten times that of raw.³⁰⁶⁸ This is not to say cooked carrots aren't super healthy, but the longer something takes to eat, the more time those hunger-squashing hormones have to reach your brain and the more direct mouth-brain nerve stimulation there will be to quell your appetite. So, from a weight-loss standpoint, raw carrots clearly beat out boiled.

Directing people toward more slow-food options was formalized into a weight-loss program known as *Time-Calorie Displacement*, also known as *Time-Energy Displacement*, which sounds like a contraption that belongs in a DeLorean. In the Low in Calorie Density section, I talked about how whole plant foods tend to offer a much greater volume of food for the same number of calories, and more food takes longer to eat, so in effect, healthier foods can often displace less healthy options in both time and space. A greater quantity of

food doesn't just physically fill you up more. All that extra eating can allow other satiety mechanisms beyond just stomach-distension time to kick in.

When people were put on a diet packed with fruits, vegetables, whole grains, and beans and allowed to eat all they wanted, they ended up eating 48 percent fewer calories than they might have otherwise.³⁰⁶⁹ Part of that was due to the lower calorie density of the plant-heavy diet, but people also spent about 40 percent more time chewing, for seventeen minutes per meal compared to twelve minutes. It's one thing for people to feel just as full on half the calories, but can they be kept satisfied on a thousand-calorie diet if they're eating enough whole plant foods? That's what the Time-Calorie Displacement diet was all about.³⁰⁷⁰

Thousands of people went through the official Time-Calorie Displacement Program³⁰⁷¹ (since renamed the EatRight program).³⁰⁷² The weight loss of participants averaged eighteen pounds over six months of active treatment, and body fat was lost while muscle mass was maintained. The critical question, though, is what happened after that? Over an average follow-up of seventeen months post-treatment, 44 percent of patients continued to lose weight, and more than 90 percent stayed under their baseline weights.³⁰⁷³ In designing the diet, the researchers recognized that nearly any diet can cause weight loss at least short term, but the ends don't always justify the means. Their challenge was to design a "nutritionally sound" diet "conducive to a lifelong pattern of healthful eating."³⁰⁷⁴ To that end, the diet encourages people to eat more high-bulk, calorie-dilute foods (vegetables, fruits, whole grains, and beans) and fewer energy-dense foods (meats, cheeses, sugars, and fats).³⁰⁷⁵

In *The Journal of the American College of Nutrition*, a review article was published entitled "Rational Weight Loss Programs: A Clinician's Guide." The Time-Calorie Displacement Program was held up as a prototypical example: safe, effective, health-promoting, and based on sound scientific principles.³⁰⁷⁶

FOOD FOR THOUGHT

A systematic review and meta-analysis of the effects of faster versus slower eating found that no matter how the eating rate was manipulated—whether solid food versus liquid, thick versus thin, spoon versus straw, or just telling people to slow down when they eat—on average, the slower-eating groups had their hunger satiated eating less food.³⁰⁷⁷ So choose foods that take longer to eat, and eat them in a way that prolongs the time they stay in your mouth. Think bulkier, harder, chewier foods, such as apples, carrots, or intact grains, eaten in smaller, thoroughly chewed bites. Snack on raw veggies, and fall in love with soup. If possible, extend meal duration so it lasts at least twenty minutes to allow your natural satiety signals to take full effect.

Try eating with chopsticks. Even in experienced hands, they tend to slow eating rate.³⁰⁷⁸ If you are going to drink your calories, make your smoothies thicker and sip them leisurely through a skinnier straw (preferably reusable, like the glass straws with silicone tips I love). The notion that eating quickly may lead to weight gain used to be considered an old wives' tale.³⁰⁷⁹ As anyone married to one can attest, though, wives—young or old—are most often right in the end.

EXERCISE TWEAKS

The Exercise "Myth"

When trying to lose weight, which is more important: diet or exercise? A national survey found that a "vast majority" of Americans, seven out of ten, believe that food and beverage consumption and physical activity are equally important when it comes to weight loss. About two out of ten favored exercise, and only about one in ten chose diet.³⁰⁸⁰ The vast majority of Americans are wrong.

It's easy to understand how people might think diet and exercise play equal roles. After all, our body fat is determined by the balance of calories in and calories out. What people

may not understand about this energy-balance equation is that we have much more power over the calories-in side. In fact, on a day-to-day basis, we have full control. We could choose to eat zero calories or ten thousand calories. Most of the calories out, however, tend to be outside our control.

Wild animals typically burn most of their calories on activity,³⁰⁸¹ but thanks in part to our energy-intensive brains, most of our daily calories are used just to keep us alive.³⁰⁸² Even if we stayed in bed all day, we'd still burn more than a thousand calories just to fuel our resting metabolic rates—the basics like thinking, breathing, and keeping our hearts pumping. In contrast, even most “active” people exercise less than two hours a week, which may average out to fewer than one hundred calories burned off daily.³⁰⁸³ That's less than 5 percent of the calories-out side of the equation.³⁰⁸⁴ Given that, the two thousand calories we may take in every day can exert twenty times more influence than exercise over our weight destiny.

Though most people believe exercise is a “very effective” way to lose weight,³⁰⁸⁵ that has been referred to as a “myth” in the scientific literature.³⁰⁸⁶ In fact, it's been labeled as one of the most common misconceptions in the field of obesity,³⁰⁸⁷ yet virtually all formal weight-loss guidelines include some sort of exercise recommendation.³⁰⁸⁸ What does the science say?

Population studies certainly have found strong correlations between physical inactivity and obesity, but does a sedentary lifestyle lead to obesity, or does obesity lead to a sedentary lifestyle? It probably works a little in both directions.³⁰⁸⁹ To prove cause and effect and also to quantify the relationship, you really have to put it to the test.

Can You Outrun a Bad Diet?

Dozens of randomized controlled trials involving thousands of participants have been published on the effects of exercise on weight loss.³⁰⁹⁰ How did exercise fare? Surprisingly, physical activity was not found to be an effective strategy.³⁰⁹¹ Think of it this way: A moderately obese person doing moderate-intensity physical activity, like biking or very brisk walking, would burn off approximately 350 calories an hour.³⁰⁹² Most drinks, snacks, and other processed junk are consumed at a rate of about 70 calories a *minute*. Therefore, it only takes five minutes of snacking for someone to wipe out a whole hour of exercise.³⁰⁹³

Looking at the studies that tried to use exercise alone to induce weight loss, for example, people only lost about three pounds over an average of about six months.³⁰⁹⁴ The experiments ranged from two to twelve months in duration, with people exercising under supervision for fifteen to seventy minutes at a time, two to five days a week, with intensities ranging from light to vigorous. Putting all the studies together, it looks like it took an average of around eight weeks of exercising to get people to lose a single pound. That was exercise alone, though. What about exercise as an adjunct to diet?

When people are randomized into diet-and-exercise interventions versus diet alone, the diet-and-exercise groups do better, but the difference in weight loss only averages about two pounds.³⁰⁹⁵ The studies lasted between three and twelve months, and all that extra prescribed exercise seemed to translate into only a few pounds lost. The two-pound difference was *statistically* significant, however, which means we're pretty sure it was a real effect, but losing two pounds over a year's time can hardly be considered *clinically* significant. As a general rule, researchers like to see at least a five- or six-pound drop.³⁰⁹⁶

The longer-term trials performed even worse. In a meta-analysis of eighteen randomized controlled studies lasting a minimum of six months, the diet-plus-exercise group failed to beat out the diet-only group at all.³⁰⁹⁷ There appeared to be no long-term benefit to encouraging people to add exercise to their weight-loss regimens. What is going on? Maybe exercise is better at just preventing people from regaining weight but not losing it to begin

with? The vast majority of randomized controlled trials examining weight-loss maintenance also failed to show an exercise benefit.³⁰⁹⁸

Part of the problem is compliance. It's one thing to tell people (or even ourselves) to adhere to an exercise regimen; it's another thing for them to actually do it. A 2018 review found that, in most cases, the groups of people randomized to work out showed no weight-loss benefit. However, if the people who flouted the instructions are excluded and the analysis is limited just to those who actually put in the time and sweat, a clear advantage to exercising emerges.³⁰⁹⁹ Exercise, like diet, only works if you actually do it. Still, though, people tend to experience less weight loss than one would predict based on the number of calories burned.

Exercise can rev up your baseline metabolic rate. For up to forty-eight hours after a single bout of exercise, you can experience an afterburn effect, known technically as *EPOC*, or *excess post-exercise oxygen consumption*. EPOC can bump up our resting metabolic rates as much as 5–10 percent. That may not seem like much, but it can build up. For example, a brisk half-hour walk may only burn 150 calories,³¹⁰⁰ but if it then boosts our metabolic rates by 7.5 percent over the subsequent thirty-six hours, that EPOC effect alone could burn an additional 170 calories or so—more than was burned during the actual walk. So we should be burning *more* calories than expected by exercising, not less. What's going on?

An Hour a Slice

Our gross overestimation of the capacity of exercise to burn off extra calories may be one reason people can rapidly become disillusioned with their new gym membership.³¹⁰¹ Consider some foods that are CRAP—that is, *calorie-rich and processed*, as I explained [here](#). To walk off the calories found in a single pat of butter, we'd have to add an extra seven hundred yards to our stroll that evening. What about a Snickers bar? We'd need to jog a quarter mile for every single bite. If we eat two chicken legs, we'd better get out on our own two legs and run an extra three miles that day just to outrun the calories—and that's for boiled chicken with the skin removed.

A piece of pizza has about three hundred calories, which converts into an hour of brisk walking per slice. How many kids are jogging two hours a day to burn off their Happy Meals? Who's got time to climb up the Empire State Building's eighty-six flights to burn off a single donut?³¹⁰² That's one reason what we put into our mouths is most important.

Public health researchers have been experimenting with providing this kind of information for public consumption. Labeling fast-food menus with pictograms of exercising stick figures was found to help nudge people toward lower-calorie options. Once they know that supersizing their fries would mean walking about three extra miles that day or that choosing the chicken salad over the garden salad could mean having to run around three miles, people are more likely to make the healthier choice.³¹⁰³

For their calculations, the researchers assumed about 125 calories burned per mile run. We're remarkably efficient animals. It doesn't take much energy for us to move. Take sex, for instance. One of the "Seven Myths About Obesity" identified in *The New England Journal of Medicine* is that a bout of sexual activity burns a few hundred calories.³¹⁰⁴ So you may think, *Hey, I could get a side of fries with that!* But if you hook people up (literally *and* figuratively) and actually measure their oxygen consumption during the act (assuming they don't get too tangled up in all the wires and hoses), having sex only turns out to be the metabolic equivalent of bowling. Given that the average bout of sexual activity may only last about six minutes, a young man might expend approximately twenty-one calories during intercourse. Because of baseline metabolic needs, he would have spent roughly one-third of that just lounging around watching TV, so the incremental benefit is plausibly on the order of fourteen calories.³¹⁰⁵ So maybe he could have *one* fry with that.

Licensed to Eat

Evidently, most overweight individuals choose exercise as their first approach to weight loss.³¹⁰⁶ When unrealistic hopes inevitably clash with reality, the disappointment may lead to abandonment of weight-loss efforts altogether as an exercise in futility. (Pun intended!) Our false expectations may also give us license to overeat. Our pie-in-the-sky notions about the power of exercise may be used to justify an extra slice of pie right here on earth. Some researchers warn that labeling menus with calorie equivalents of exercise could be counterproductive, backfiring if people rationalize their indulgences after a workout.³¹⁰⁷ This concern has actually been put to the test.

Experimental psychologists took a group of men and women, put them on stationary bikes, and had them cycle until they burned either 50 calories or more than 250 calories. Unbeknownst to them, the experimenters effectively manipulated the machines to give false readouts such that, in actuality, both groups burned the same number of calories, about 120; they just thought they had burned more or less than that. The subjects were then offered snacks ten minutes later, ostensibly to measure the “effects of exercise on taste perception and food reward.” The real purpose, however, was to covertly measure how much they ate. Those who falsely believed they had burned off more calories on the stationary bike did seem to demonstrate a greater license to eat, ending up eating significantly more calories—mostly in the form of chocolate chip cookies.³¹⁰⁸

After a workout, people may be tempted to treat themselves for their sweaty sacrifice. To prevent this knee-jerk reaction from undermining our efforts, we should strive to make exercise less of a chore. A paper entitled “Is It Fun or Exercise? The Framing of Physical Activity Biases Subsequent Snacking” described a study in which individuals were randomized to the same amount of physical activity, but with different descriptions. Half were told they were going on a “fun walk,” while the other half were told they were going on an “exercise walk.” Afterward, researchers covertly measured how much dessert everyone took at a subsequent meal. Those in the movement-as-exercise group reportedly served themselves about 35 percent more chocolate pudding than the movement-as-fun group.³¹⁰⁹

This is all the more reason to choose activities that are enjoyable, such as walking with friends or while listening to music or a podcast, or watching a video while on the treadmill. Reframing exercise as play rather than work may not only make for a more sustainable regimen, it may make us less likely to consciously or unconsciously feel the need to reward ourselves later at the buffet line.

Even just thinking about exercise may compel people to eat more food. Those randomized to simply read about physical activity went on to give themselves nearly 60 percent more M&M’s than those in the control group, adding up to hundreds of extra calories. The researchers concluded that “simply imagining exercising leads participants to serve themselves more food.”³¹¹⁰

Working Up an Appetite

Expending energy through exercise may not only predispose us *psychologically* to eat more, it also may make us hungrier *physiologically*. As we’ve discussed, we evolved in the context of scarcity, so our bodies place great value on rapidly replenishing lost fat stores.³¹¹¹ This offers another explanation as to why the average weight loss with exercise training is only 30 percent of that predicted.³¹¹² Calories in versus calories out can be complicated by the fact that changes on one side of the equation can affect the other side too.

Carefully controlled studies show that caloric intake tends to rise over time to match any increase in caloric expenditure, making significant weight loss through exercise alone

remarkably difficult.³¹¹³ This doesn't happen over a day or two, though.³¹¹⁴ After a workout, there may not be an immediate increase in hunger, but averaged over the week³¹¹⁵ or weeks,³¹¹⁶ our appetites do tend to increase. This calorie compensation, this attempt to balance it out, isn't perfect, however, so we can end up with a net loss in body fat, particularly at higher exercise levels.³¹¹⁷

Here's a concrete example: Overweight men and women were randomized to an exercise regimen that consistently burned off 1,500 calories a week, which would be about forty-five minutes of brisk walking every day, for instance. After twelve weeks of all that extra exertion, they didn't lose a significant amount of weight. An analysis of the changes that took place in their diets explains why: Yes, they burned 1,500 more calories a week, but they inadvertently started eating about 950 more calories a week. So, at the end of the three months, they were only down about three pounds.³¹¹⁸

What would happen if they doubled their workouts? Burning 3,000 calories a week is equivalent to walking briskly about ninety minutes a day, every day, seven days a week. On that kind of regimen, how much more did they end up eating? Their appetites increased, but not enough to keep up with the increased caloric expenditure, so they ended up losing about six pounds over that same period. Though the 1,500 calories-out group had started taking in about 950 more calories, the 3,000 calories-out group had boosted their intakes a similar amount—about 1,000 calories a week above baseline—so they ended up with a much greater calorie deficit. Our bodies try to compensate by boosting our appetites, but there is a limit.

The secret to weight loss through exercise may be sheer volume: at least three hundred minutes a week to achieve appreciable fat loss.³¹¹⁹

This regulation of our appetites through activity works in both directions. Just as there exists a higher level of exercise where we can start to outpace our appetites and lose weight, there's a lower level of exercise where our bodies lose the ability to sufficiently downgrade our appetites and we gain weight. This "zone of regulation" where our appetites become uncoupled from our activity levels appears to start at around 7,100 steps a day.³¹²⁰

If you've been a really active person and have to cut back on exercise for whatever reason, you may be surprised that you don't gain much weight, but that's likely because your appetite tends to come down as well. Once you cross that threshold, though, once you dip below logging at least 7,100 steps a day on your pedometer, your appetite doesn't slow much further to match, so the pounds can start to pile on. Your body tries to keep your weight steady by adjusting your appetite, but we just weren't designed to handle such an extremely low level of movement that sadly characterizes about 80 percent of the U.S. population.³¹²¹

Coming In from the Cold

Swimming and aquatic exercise in general are popular alternatives to land-based activities such as walking or biking.³¹²² Buoyancy in water helps take some of the weight-bearing stress off joints, but swimming appears to be less effective for weight loss. Obese women were randomized to an hour a day of walking, cycling, or swimming. Six months later, the walkers lost an average of seventeen pounds, the cyclists lost an average of nineteen pounds, but the swimmers didn't lose an ounce—in fact, they actually gained five pounds. Gauging skin folds to estimate body fat, the measurements slimmed more than 40 percent in the walking and cycling groups, but there was no change at all in the swimming group.³¹²³ What's going on?

Some exercise boosts appetite more than others. In contrast to walking,³¹²⁴ running, or cycling,³¹²⁵ swimming can significantly heighten hunger within hours.³¹²⁶ This may explain why swimmers tend to have more body fat than runners of equal athletic caliber.³¹²⁷ If anything, one might think swimming may lead to even greater weight loss since you lose heat to the water, but swimming didn't seem to work at all.³¹²⁸ The cold, it turns out, may be the culprit.

If you exercise in warm water (about 90°F), it doesn't boost your appetite more than exercising on land. After the same workout in cool water (about 70°F), however, people can end up eating more than twice as many snacks an hour later.³¹²⁹ Maybe they're just burning off extra calories to stay warm? No, even at the same number of calories expended, people eat hundreds more calories after exercising in colder water. When offered a buffet after burning

off about five hundred calories in cool water, people ate nearly nine hundred calories, hundreds more than after exercising in warm water or just resting on dry land.³¹³⁰

Would the same thing happen under different temperatures on land? A team of British researchers sought to find out, randomizing people to walk briskly for forty-five minutes on a treadmill in the cold (at about 46°F) or at closer to room temperature (about 68°F). Participants were then presented with a buffet meal in which their eating was recorded covertly. Caloric intake was significantly greater after exercising in the cold. The researchers concluded that though walking is often prescribed for overweight individuals, “if walking was to take place in a cold environment, such as in winter, then this may stimulate food intake.”³¹³¹ In the warmer months, obesity researchers suggest, exercising outdoors may be preferable to an air-conditioned gym.³¹³²

All studies to date on the effects of hot and cold environments have found that exercising in cool water or under cool conditions on land leads to an increase in post-workout caloric intake.³¹³³ What about a quick dip in the pool after you exercise? Australian researchers found that immersion in water—cool or warm—for fifteen minutes after a running session resulted in increased caloric intake. What is it about getting wet that whets our appetites? Maybe they got a chill after getting wet before they could change into dry clothes? This suggests that although a cool shower after a workout may be invigorating, it might be better to stick to a hot one.

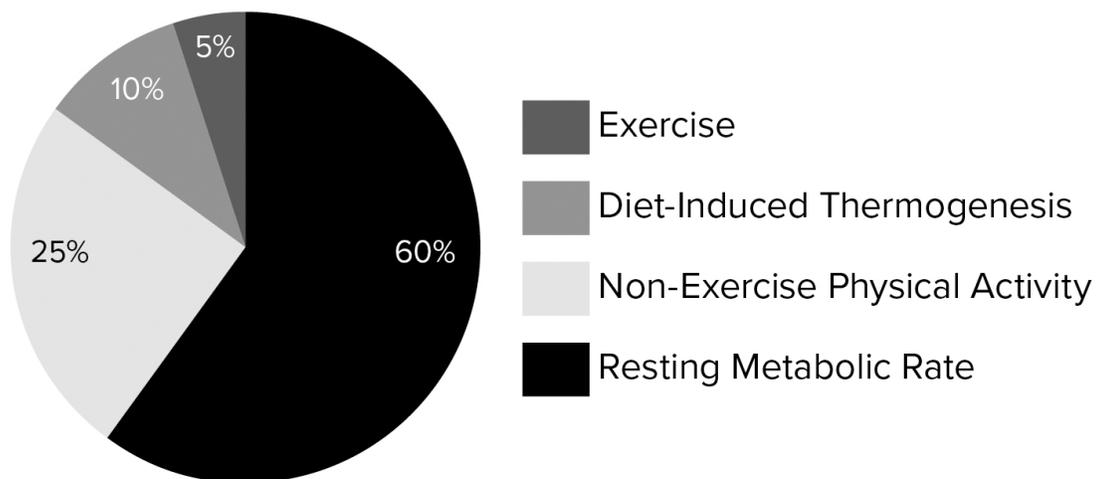
Changing the Equation

Throughout millions of years of our prehistory, starvation was a bigger problem than obesity, so our bodies developed a multitude of ways to fight against weight loss. Let’s look at the energy-balance equation to see how:

Body Fat = Calories In – Calories Out

In this simplified model of weight basically equaling calories in minus calories out, you can see how the only way our bodies can defend themselves against weight loss if the calories-out factor goes up (we start exercising, for example) is to simultaneously ratchet up the calories-in factor (that is, boost our appetites).

Calories Out



Let’s break down the equation further. *Calories In* means food and beverages; *Calories Out* means metabolism and motion. Motion can be further separated into exercise versus nonexercise physical activity, and most of the calories people expend on movement fall into the nonexercise category. (Leisure-time exercise, such as working out at the gym, typically only accounts for about 5 percent of daily energy expenditure.) Our resting metabolic rates use up at least 60 percent of our daily calories. Remember diet-induced thermogenesis from the Chronobiology section? That takes up about 10 percent of our daily calories. Movement takes up the remaining 30 percent, but if only 5 percent is structured

exercise, the other 25 percent is comprised of nonexercise physical activities, such as cleaning the house or caring for children.³¹³⁴ The pie chart above illustrates a typical situation.

Our bodies then have a number of options to offset an increase in exercise:

Body Fat = Food + Beverages – Metabolism – Exercise – Other Movement

Since our metabolisms are already remarkably efficient at baseline, there's limited wiggle room to slow them down much further to prevent us from losing weight. What's more, exercise can end up boosting our metabolic rates, both through that EPOC afterburn and by building muscle mass, which takes more energy to maintain.³¹³⁵ Even if our bodies can't resist exercise-induced weight loss much by slowing our metabolisms, there's another option besides just boosting our appetites. Can you figure it out by looking at the equation?

An increase in exercise can inadvertently result in a decrease in nonexercise physical activity. When overweight adolescents engaged in an hour of moderate-intensity exercise, they burned off a total of 286 calories. Within that same period, they would have burned off 80 calories just existing. So, at the end of the hour, the exercise group had more than a 200-calorie deficit, and that deficit remained at the end of the day. By the end of the week, though, that calorie-expenditure gap had narrowed to less than 100 calories. The kids had been fitted with high-tech accelerometer devices to measure all their movements over the week. What was happening? The exercise group unintentionally moved less over the few days after the single bout of activity. Simple things like sitting instead of standing or fidgeting less can add up over time and eat away at the gains you make exercising.³¹³⁶

Again, this makes total sense evolutionarily. Our bodies are trying to conserve energy. If you spend one day chasing (or being chased by) a woolly mammoth, your body tries to mellow you out over the next few days to make up for it.³¹³⁷ It's like what happens with appetite. You might not feel hungrier the day you exercise, but over the ensuing week, your body tries to fill in the gap.

Let's say that after you wake up tomorrow, you go out and take an hour-long walk in nice weather. (See the Coming In from the Cold box [here](#) to see why this temperature-related caveat is necessary.) Over the rest of the day, you'll likely end up eating and moving just as much as you would have had you slept in instead of gone for a walk. So if you walked off three hundred calories, at the end of the day, you'll be left with a three-hundred-calorie deficit. Your body doesn't like being in the red, though, since millions of years of scarcity-stress has been hardwired into our DNA. As a result, over the next few days, your body starts to chip away at that debt from both directions, nudging you to eat a little more and move a little less such that by the end of the week, all the walked-off calories are back on board. In terms of calorie balance, it's almost as if you hadn't taken that walk at all. This explains why so many exercise interventions fail to result in weight loss over time.³¹³⁸

Over the millennia, those whose bodies failed to defend their fat stores were likely more often felled by famine and long winters. Plopped down into the land of plenty, though, this genetic legacy becomes a handicap. Winners in the ancient fight against famine are today's losers in the battle of the bulge.³¹³⁹ But like most handicaps, that just means we may have to work a little harder.

Consider the same scenario as before, but what if you repeat that morning walk every day? Those calorie deficits would start compounding, and your body would be forced to keep up by starting to make withdrawals from your body fat. Perhaps only significant amounts of exercise can cause significant weight loss.³¹⁴⁰ In a review entitled "Why Do Individuals Not Lose More Weight From an Exercise Intervention...," the investigators suggested it was in part "primarily due to low doses of prescribed exercise."³¹⁴¹

Is there a magic exercise threshold that allows us to overcome our bodies' attempts to undermine our weight loss?

Nearly everyone seems to agree that the current national³¹⁴² and international³¹⁴³ recommendations of 150 minutes a week of moderate-intensity exercise simply aren't enough. That only comes out to be about one hundred calories burned a day, against which our bodies could easily compensate. From an obesity standpoint, this has been considered the "physiological equivalent of bringing a knife to a gunfight."³¹⁴⁴

At the same time, no one disagrees that there isn't at least some level of exertion that works. Just as extreme inactivity, such as twenty-four-hour bed rest, can reliably increase body fat,³¹⁴⁵ extreme activity like military training³¹⁴⁶ or mountain climbing³¹⁴⁷ can reliably decrease body fat. At about ten times the recommendation—a thousand calories of exercise a day—people lose about a pound a week, down eleven pounds within three months.³¹⁴⁸ The question is, what's the minimum amount of extra physical exertion that we should expect to have a non-negligible effect?

Published recommendations range from the American College of Sports Medicine's 250 minutes a week³¹⁴⁹ up to a USDA-funded paper pushing 250 minutes a day.³¹⁵⁰ I checked with the lead author, and, thankfully, the latter was a typo.³¹⁵¹ They also had meant to say *weekly*. That fits the Healthy Lifestyle Institute's "200–300 min per week" minimum,³¹⁵² a level that can at least help keep our weight stable, according to the U.S. Department of Health and Human Services Physical Activity Guidelines Advisory Committee.³¹⁵³ For significant weight loss, however, the committee recommends closer to a minimum of 450 minutes a week, or more than an hour a day. Note that these times are for moderate-intensity activity, such as walking. For vigorous activity like running or rapid cycling, exercise duration can be cut by more than half.

The National Academy of Medicine, arguably the most prestigious medical authority in the United States, recommends an hour a day for everyone based on the exercise habits of normal-weight individuals.³¹⁵⁴ For those who started out obese but slimmed down and are trying to prevent weight regain, one analysis estimated a threshold of eighty minutes a day was necessary.³¹⁵⁵ This falls into the daily sixty-to-ninety minutes range suggested in one systematic review,³¹⁵⁶ which is what an earlier version of the *Dietary Guidelines for Americans* recommended³¹⁵⁷ before it wimped out.³¹⁵⁸ Such levels of exercise had evidently "not proven manageable."³¹⁵⁹

Up to 50 percent of Americans self-report that they reach the 150 minutes a week recommendation, but if people are hooked up to accelerometers and their movement is objectively measured, what do you think the real number is? Not the 50 percent self-reported, but less than 5 percent. Indeed, rather than one in two people meeting the 150 minutes a week recommendation, it was only one in twenty.³¹⁶⁰ Some people can pull it off, though. Those in the National Weight Control Registry who successfully lost lots of weight and kept it off for years evidently average about an hour a day, most commonly in the form of walking. About one in six hardly exercised at all, though, showing it is possible to stay slim without the gym.³¹⁶¹

The bottom line is that exercise for obesity is neither a "myth"³¹⁶² nor a "magic bullet."³¹⁶³ Sufficient, regular exercise can indeed aid in weight loss, just not nearly as much as most people think.³¹⁶⁴ On a population scale, even a 1 percent decrease in body mass index could potentially prevent millions of cases of diabetes and heart disease, and thousands of cases of cancer,³¹⁶⁵ but on an individual level, the weight loss can prove disappointingly small.³¹⁶⁶ We just have so much more control over the calories-in side of the equation than the calories-out. There is, however, a neat trick.

NEAT

Why do some people gain more than others? If you experimentally overfeed a group of people the same amount over the same time period, you might assume there would be *some* variation, but the actual range of variability is truly mind-boggling. In a famous study

out of the Mayo Clinic, subjects ate a thousand extra calories every day for eight weeks with no added exercise. In some people, that extra thousand calories translated into only about a spoonful of added daily body fat, whereas others gained more than a third of a cup of body fat every day. By the end of the eight weeks, there was a tenfold variation in fat gain from under a pound in total to more than nine pounds.³¹⁶⁷

Hold on. Someone ate fifty-six *thousand* extra calories and gained less than a single pound of body fat? There's a law in physics that basically says calories can't just disappear,³¹⁶⁸ so what happened? Let's look at the energy-balance equation again:

$$\text{Body Fat} = \text{Food} + \text{Beverages} - \text{Metabolism} - \text{Exercise} - \text{Other Movement}$$

The exercise level for the study subjects was fixed at a steady, low amount, and it turned out their metabolisms didn't change much. So the only way caloric intake could shoot up without depositing as body fat would be if "other movement" shot up as well. And that's what happened. The secret to eating in excess of fifty thousand calories without gaining weight is NEAT: *nonexercise activity thermogenesis*.

NEAT is the heat given off by our regular activities of daily living, such as standing, moving, and fidgeting. On average, fewer than four hundred of those extra thousand calories consumed each day of the study ended up being stored as fat. The bulk was burned off, particularly from a spontaneous increase in movement. One participant inadvertently started moving so much that an extra 692 calories burned off in a day. That's like spending a quarter of your waking hours in motion.³¹⁶⁹

You'd think overfeeding might lead to the opposite: inactivity. I imagine someone crashed on the couch rubbing their swollen belly. But no—when people are fed a thousand extra calories a day, a strange thing happens. They spontaneously start to move more out of some instinctual drive. This could be in the form of fidgeting or gesticulations, a restlessness leading to frequent standing or pacing,³¹⁷⁰ using up as many as hundreds of extra calories on average over the course of a day.³¹⁷¹ Basically, NEAT is the sum of calories burned by everything we do that is not sleeping, eating, or sports-like exercise.³¹⁷²

So the primary reason some people gain more weight than others despite eating the same amount of food is that they go weak in the NEAT.³¹⁷³ Easy gainers just don't intuitively start moving more to compensate for the extra calories. Indeed, a NEAT deficit has been identified in obesity. Studies show obese individuals tend to remain seated for about two and a half hours longer each day than the average, inactive yet lean, shoestring couch potato.³¹⁷⁴ Normal-weight individuals just tend to get up and move around more.

After fitting "sedentary" people with sensors that tracked their posture and movement, researchers were surprised to find they in fact were walking the equivalent of seven miles a day. That distance was just split up into dozens of stints lasting a few minutes at a time simply ambling around throughout the day.³¹⁷⁵ Remarkably, those small moments of movement can add up to more than two thousand calories a week, which just so happens to be what those overfed study subjects started burning up and about what you'd get from the hour-a-day exercise recommended for weight loss.³¹⁷⁶

Just by subtly moving around more, your body can drain off as many calories as pounding it out an hour a day at the gym. Remember those extra 692 calories a day burned off by the study subject who had inadvertently started moving more? That's more than you might burn rock climbing for an hour. Given its demonstrated power, if our bodies aren't going to move more unconsciously, then maybe we should make a conscious effort to accrete some NEAT.

Staying One Move Ahead

Since prescriptions for structured exercise have so often failed to result in appreciable weight loss, some obesity researchers have turned to trying to enhance NEAT instead.³¹⁷⁷ After all, remember the pie chart? Nonexercise activity typically burns off at least five times more calories a day than an average exercise program. The reason the Amish have some of the lowest rates of obesity is not a high prevalence of gym memberships. They walk an average of eighteen thousand steps a day just living their lives.³¹⁷⁸

You don't have to go full horse-and-buggy to enjoy the benefits of nonexercise activity thermogenesis. NEAT means taking the stairs instead of the escalator and parking at the far end of the lot. It means singing, laughing, cleaning, and doing yard work—any activity that creates muscular contractions. Cooking dinner burns five to ten times more calories than sitting in front of the TV.³¹⁷⁹

Imagine two scenarios of modern life: An office worker drives to work, sits all day at their desk, drives home, and then sits all evening watching television or surfing the internet. If they had gotten home at 5:00 p.m. and went to bed at 11:00 p.m., those six hours of leisure time probably wouldn't expend more than fifty calories, even if they double-thumbed the remote control. What if instead, when our hypothetical office worker got home, they started raking leaves or vacuuming? They would have burned about ten times more calories that same evening³¹⁸⁰ and around twenty times more if they more actively commuted, like biking rather than driving to work.³¹⁸¹

Stand to Lose

In *How Not to Die*, I documented the health risks associated with prolonged sitting. The reason nearly all the studies to date on television viewing and mortality have found an association between screen-based entertainment and premature death is thought to be because screen time tends to equal sitting time.³¹⁸² Sitting more than three hours a day may be responsible for more than four hundred thousand deaths every year worldwide.³¹⁸³ (Sitting, however, is decidedly *not* the new smoking. Tobacco is responsible for up to more than ten times greater shortening of life expectancy.³¹⁸⁴)

What about standing versus sitting for weight loss? Standing burns three times more calories per minute than sitting.³¹⁸⁵ Even if you're standing still, your postural muscles are tensed and stretched to fight gravity,³¹⁸⁶ so anything you usually do while sitting, try doing while standing, like watching TV or reading the newspaper. A sure sign that I'm speaking at a lifestyle medicine conference versus a more traditional medical event is how many more audience members are standing along the back of the lecture hall.

A standing desk can be as simple as a crate on a table you can use when you pay bills or watch cat videos on your computer. Prolonged standing on a hard floor can be hard on our feet, but using cushioned insoles in our shoes or standing on an "anti-fatigue" mat (or maybe a thick or doubled-over yoga mat) has been shown to help relieve discomfort.³¹⁸⁷ Another potential downside of prolonged standing is increased risk of developing varicose veins,³¹⁸⁸ a cosmetic concern hopefully offset by the decreased risk of obesity³¹⁸⁹ and premature death.³¹⁹⁰

There are "sit-stand desks" available now that are height-adjustable so you can alternate between sitting and standing. In the short term, they were found to reduce sitting time at work on average by one hundred minutes per workday, but after three months, people appeared to tire of them and only sat about an hour less a day.³¹⁹¹ Those using sit-stand workstations were also found to compensate a bit at home by sitting down more in their off hours.³¹⁹²

Even without compensation, though, standing for six hours a day rather than sitting may only net about a fifty-calorie deficit daily.³¹⁹³ Walking at a treadmill desk, on the other hand, could wipe out more than seven hundred calories a day. Just moving at a snail's pace at about one mile per hour, people burn an extra two calories a minute over sitting.³¹⁹⁴ That

means you could erase more than one hundred extra calories an hour while you work or two hundred extra calories at 3 mph.³¹⁹⁵ (My treadmill desk is currently set at 1.8 mph.) If you work 250 days a year and stroll while you work for even just half the workday, you could theoretically burn off thirty pounds of fat a year if your body didn't otherwise compensate for the one hundred thousand annual calorie deficit.³¹⁹⁶ No wonder obesity researchers have called for a "moratorium on the chair."³¹⁹⁷

Does productivity suffer using a standing or walking desk? With the exception of high-precision mouse tasks, work performance in general appears to be unaffected,³¹⁹⁸ but one study of transcriptionists on treadmill desks found that their speed slowed by 16 percent, though their accuracy was unchanged.³¹⁹⁹

While I'm a big fan of treadmill desks, I'll admit they can be expensive and noisy. Even if the motor is quiet, the footfalls may be distracting to coworkers. (When I'm on the phone, interviewers sometimes ask me what that "thumping" is.) Stepping devices, also known as *exercise steppers*, are a smaller, cheaper, quieter, and more convenient alternative. They have two pedals you stand on, allowing you to simulate walking up stairs. Steppers appear to burn even more calories in an office setting than walking,³²⁰⁰ and you can simply slide them under a desk when not in use.

Dynamic Sitting

Sedentary comes from the Latin word meaning *to sit*, but just because you're sitting doesn't mean you're sedentary—just ask any cyclist or rower. The problem is sitting *motionlessly*. That causes blood to pool and stagnate in our legs, which can result in arterial dysfunction. Just like our muscles can atrophy from disuse, it may be *use it or lose it* when it comes to artery function as well. Special cells lining our arteries can detect the tugging, sheer force of the blood flowing past and send signals through the artery wall to maintain proper structure and function.

Significant decrements in artery function can be detected within three hours of sitting,³²⁰¹ while three hours of standing, even while motionless, does not produce the same effect. Part of the reason blood flow can be stanchied nearly 40 percent by prolonged sitting³²⁰² is the ninety-degree angle in our knees that kinks our blood vessels.³²⁰³ When that's straightened out by standing, our arteries remain fully functional.

If standing or dynamic workstations are not an option, taking five-minute walking breaks every hour can prevent the stiffening of the arteries that comes with prolonged sitting.³²⁰⁴ Frequent trips to the watercooler (and then subsequently to the restroom) or taking out the trash during commercial breaks can maintain full artery function.

What are your options if you really can't walk away from your workstation? Exercising your legs for forty-five minutes before sitting down can preserve artery function³²⁰⁵—another advantage to an active commute. Researchers concluded that "people should be encouraged to engage in aerobic leg exercise before sitting for extended periods of time and, if this is not possible, sitting should be replaced by standing."³²⁰⁶

Just standing intermittently for a few minutes an hour does not appear sufficient to counteract the adverse effects of sitting, and neither does a few minutes of pedaling under your desk with one of those sit-cycle gadgets.³²⁰⁷ Constant standing works, though, as presumably would constant pedaling, an example of "dynamic sitting." You may have noticed people in an office sitting on large rubber stability balls. That does activate trunk muscles in your core, but it's been found to cause more low-back discomfort and spinal shrinkage,³²⁰⁸ likely due to the absence of a backrest.

What about a fidget chair that allows for a degree of side-to-side lateral movement of your hips?³²⁰⁹ Unfortunately, people tend to move so little while seated in them that they only burn about thirteen more calories an hour compared to sitting in a regular chair.³²¹⁰ A cheaper way to burn comparable calories while sitting is the use of a fidget bar, a device referred to in the medical literature as an "under-the-table leg-movement apparatus."³²¹¹ It's sort of like a balance beam that hangs under your desk that you can put your feet on to fiddle around, burning up an extra twenty-two calories an hour.³²¹² Either fidgety approach could easily add up to burning one hundred calories a day.

Does seated fidgeting protect our arteries, though? Researchers had people intermittently fidget just one leg for one minute out of every five, while keeping their other leg still. While artery function in the resting leg dropped, that of the restless leg experienced a pronounced improvement.³²¹³ This helps explain why frequent fidgeting appears to neutralize the mortality risk of prolonged sitting.³²¹⁴ What I liked most about the one-leg fidget study was that the researchers didn't rely on any fancy gizmos. They simply had people tap their heel by bouncing their knee at their own natural cadence, something we can all try to remember to do. Just try not to annoy the person you're sitting beside on the airplane or at the movies.

The Object of the Exercise

Should word get out that exercise is relatively ineffective for weight loss, it could have negative public health implications. The problem with the prevailing bait and switch of “come for the weight loss and stay for the longevity” is that it could end up being counterproductive, which is why some experts suggest we should promote exercise without any mention of weight loss.³²¹⁵ The fear is that the relatively unchanging number on the bathroom scale will disillusion people out of exercising altogether, and then they really would miss out on exercise’s myriad benefits, which may indeed include living longer. Walking briskly just fifteen minutes a day is associated with a life span gain of about two years, for example, and an hour a day may give us four more years on this earth.³²¹⁶

While the data on exercise for weight loss are relatively weak, the evidence supporting the overall health benefits of physical activity is overwhelming.³²¹⁷ For example, forty minutes a day, four days a week, can improve erectile function in men.³²¹⁸ Being more fit can mean having more fun, all the while reducing risk of breast cancer,³²¹⁹ colon cancer,³²²⁰ diabetes, gallstones, hypertension, heart disease, and stroke.³²²¹ Exercise can also help minimize the bone loss that can accompany weight loss.³²²²

A single exercise session can improve insulin sensitivity for up to seventeen hours³²²³ and may be used to treat prediabetes as effectively as medications.³²²⁴ Exercise *is* medicine. Researchers at Harvard and Stanford found that exercise may work as well as drugs for coronary heart disease patients and even better than some medicines for stroke. They suggested that drug companies should perhaps be required to compare any new chronic disease drugs head-to-head against exercise, as “patients deserve to understand the relative impact that physical activity might have on their condition.”³²²⁵

Visceral Reaction

The number on the scale doesn’t tell the full story. When obese diabetics were put through four months of strength training, they didn’t achieve any significant weight loss, which is typical. They did, however, lose about eight pounds of body fat! The reason that loss didn’t register on the scale is that they *gained* about seven pounds of lean body mass.³²²⁶ They lost fat while gaining muscle, and their blood sugar control improved to reflect that, so it wasn’t a wash at all. Far from it. Aerobic exercise can cause a similar fat loss in thirteen weeks, with no significant difference noted between thirty minutes a day and sixty minutes a day,³²²⁷ though those putting in two-hour bouts do separate out from the pack.³²²⁸

One of the reasons exercise can be such a lifesaver is that, while it may not affect our overall weights, it can help get rid of our most dangerous body fat—that visceral fat slithering around our internal abdominal organs.³²²⁹ A systematic review found that even in the absence of weight loss, exercise may cause a 6 percent drop in visceral fat levels.³²³⁰ Exercise in particular seems to home in and burn off the worst fat first. An average obese person losing about ten pounds through caloric restriction might remove about 13 percent of their visceral fat, but the same amount of weight loss through exercise could wipe out 21 percent.³²³¹

What about doing crunches? Thanks to advertising claims from companies trying to sell people various exercise gadgets and workouts targeting the tummy, there’s a common perception that we can reduce our waistlines solely by doing abdominal exercises. Seven different abdominal exercises were put to the test, including sit-ups, leg lifts, and abdominal crunches, two sets of ten repetitions each for five days a week. After six weeks, there was no effect on abdominal fat.³²³² All that core conditioning only took about ten minutes a day, so that just doesn’t burn enough calories to make a difference. Based on averaging together a dozen or so studies, it may take three months of around three hours of aerobic exercise a week to take an inch off our waists.³²³³ One inch may not seem like a lot, but on a CT scan or MRI cross section of our abdomens, that may mean the removal of

a respectable five square inches of visceral belly fat.³²³⁴ When it comes to the worst of the worst kind of fat, aerobic exercise appears to beat out resistance exercise.³²³⁵

HIIT It Off?

What about interval training? High-intensity interval training (HIIT) involves short bursts of vigorous exercise interspersed with periods of low-intensity activity or rest. The idea is that you could burn the same number of calories in a shorter time, thereby improving compliance for those who don't feel they have the time. When it's put to the test in a real-world setting, though, adherence to even just two unsupervised sessions of HIIT a week declines rapidly to less than 20 percent within twelve months. No surprise then that the HIITers experienced no significant weight or body-fat benefit over the standard recommendation of engaging in moderate-intensity activity for thirty minutes a day most days of the week.³²³⁶

The benefits of HIIT for weight loss appear modest even under more carefully controlled conditions. A meta-analysis of thirty-nine studies found that people only lost about a pound of fat a month,³²³⁷ which is no better than when engaging in continuous, moderate-intensity activity.³²³⁸ The HIIT required about 40 percent less of a time commitment, though, so HIIT participants accomplished in about an hour and a half a week what took the medium-intensity groups closer to two and a half hours—namely, no change in weight, but a loss of a few pounds of body fat over a few months and one inch off the waist.³²³⁹ This suggests that what matters is not the intensity but the total work performed³²⁴⁰—but that's not entirely true.

Does walking a mile or running a mile burn more calories? Running burns more than twice as many calories per minute, but you could finish the mile in less than half the time it would take to walk it. So does it all equal out? No, because we were designed to walk at a speed that minimizes the energy cost of transport.³²⁴¹ Our bodies try to get from A to B using the fewest calories, and peak efficiency is walking about 3 mph. Walking slower burns fewer calories but takes longer. Walking faster gets you there quicker, but you burn more—and that's what we want. Efficiency is good for conserving energy, but if the aim is to lose weight, you don't want to conserve your fat. You want to get rid of it.

Indeed, have people run a mile at a 6 mph pace in ten minutes versus walk a mile at about a 3 mph pace in twenty minutes, and the runners expend about 110 calories compared to 90 calories spent by the walking group. This is then compounded by the afterburn advantage of higher-intensity activity. During the recovery period, the running group burned about an extra 50 calories compared to more like 20 calories in the walking group. So in total, the runners beat out the walkers by about 50 calories and did so in half the time.³²⁴²

In a nutshell, continuous high-intensity activity beats out lower intensity, but shorts bursts of high intensity don't appear to beat out continuous, moderate-intensity exercise.

All Walks of Life

Running isn't for everyone, though. Vigorous activity is warned against in certain heart conditions and can be difficult or uncomfortable for the beginner.³²⁴³ Walking, on the other hand, can be easy, safe, and sociable, and may therefore be "ideal as a gentle start-up for the sedentary."³²⁴⁴ Hippocrates evidently called walking "man's best medicine"³²⁴⁵ (and it works for women too!).

Pooled together, twenty-two studies of walking for weight loss found that an average of forty-five minutes or so of brisk walking about four times a week for three or four months removes nearly six pounds of body fat and takes about an inch off the waist.³²⁴⁶ What's the optimum dose? The more the better. The longer you walk and the faster you walk, the

more calories you burn—though not as many as might be expected due to compliance and compensation.

When doctors prescribed ninety minutes of walking a day as part of a research protocol, within three weeks, accelerometer data showed people were actually only putting in sixty-five minutes a day, and those prescribed sixty minutes were only walking about forty minutes. Those prescribed thirty minutes, however, were keeping up with their full half hour.³²⁴⁷ So, though those prescribed more did walk more, asking people to triple their walking time may only end up doubling it.

All the study subjects were told to add the walking on top of their baseline levels of activity, but that only worked to varying degrees. Adding thirty minutes of walking to their routines didn't affect the rest of their daily activity much, but most of the extra steps in the ninety-minute group were effectively lost since the participants compensated by moving so much less over the remainder of the day. Nearly two-thirds of the added exercise was offset by a reduction of other daily activities. Still, even with the compensation and compliance, those who set out to do more, did more.³²⁴⁸ The optimal duration is as long as possible.

Timing Is Everything ... Right?

What's the best exercise dose for weight loss? The more the better. What about the optimal timing? Is it better to exercise in the morning or the evening? Before or after breakfast? A Nobel Prize-winning exercise physiologist said he always ran a mile every morning before breakfast.³²⁴⁹ Was that prize-winning timing?

More than a dozen experiments have been published comparing the amount of fat burned in a fasted state versus a fed state, and every single one found more fat was burned on an empty stomach. On average, a single bout of low- to moderate-intensity activity before a meal burned off three more grams of fat than the same amount of exercise after a meal.³²⁵⁰ Same amount of exercise, but more fat loss just because of timing.

Simply because you burn more fat while exercising doesn't necessarily mean you end up with less fat at the end of the day. Maybe our bodies offset the extra fat loss that occurs during exercise with a little extra fat storage when you finally do eat, balancing out the equation. Researchers in Japan set out to investigate this possibility by measuring twenty-four-hour fat balance after one hundred minutes of running either before breakfast or after lunch. On the exercise-after-lunch day, subjects burned a total of 608 calories of fat over the course of that day. In contrast, on the exercise-before-breakfast day, in the same twenty-four-hour period, they burned through nearly 90 percent more—1,142 calories of straight fat.³²⁵¹ So the next day, before-breakfast exercisers woke up with about a quarter cup less fat after the same amount of exercise. Remarkable!

Running for one hundred minutes is pretty hard-core no matter whether you do it before or after breakfast. What about something less intense, like walking? Study subjects walked for sixty minutes at different times of the day—before breakfast, after lunch, or after dinner—and also had a control day when they didn't exercise at all. Over twenty-four hours, they burned off 432 fat calories after exercising in the evening and 446 fat calories after walking in the afternoon. On the exercise-free control day, however, they burned through 456 fat calories. It's almost as if the post-lunch and post-dinner walkers hadn't walked at all. What about a pre-breakfast walk? The same amount of exercise before breakfast resulted in 717 calories of fat loss.³²⁵² Over the course of a day, timing truly does matter.

All such similar studies on both men and women show we burn through more fat on the days we exercise before, rather than after, eating.³²⁵³ After reading the Chronobiology section, though, an alternative explanation may spring to mind. Maybe it's just a morning thing. Is it possible it has nothing to do with meals at all and our circadian rhythms are dictating the difference?³²⁵⁴ No. Exercising in the morning after breakfast appears no better

than exercising in the evening after dinner,^{3255,3256} and exercising before breakfast works better than immediately after breakfast, yet both are still in the morning.³²⁵⁷ It really does seem to be a pre- versus post-meal effect—but why?

Skinny Dip

Carbohydrate is the preferred fuel for our bodies. Whenever you eat sugars or starches, they get broken down and converted into blood sugar. After a meal, blood sugars rise, and our muscles are quick to snatch them up for fuel without having to rely much on our energy stores. If you take a siesta after a meal, your muscles have no immediate need for energy, so the excess blood sugar from that meal can be stored for later use in the muscles in the form of glycogen, which is just a bunch of blood sugar molecules strung together into a mass of branches that can be broken off and used for quick bursts of energy anytime you need them.

If you exercise after a meal, your muscles can siphon off some of the extra blood sugar floating around for energy. When you work out before a meal, though, your muscles have to resort to dipping into your energy stores and end up burning mostly a combination of glycogen and fat.³²⁵⁸ That explains why you burn more fat during fasted exercise, but what about all the extra fat burned throughout the rest of the day?

Glycogen is more than a store.³²⁵⁹ It isn't just an energy reserve. Glycogen acts as a sensor capable of activating metabolic pathways. Exercising before breakfast can exhaust as much as 18 percent of your glycogen stores, and that depletion can act as a powerful rallying cry to your fatty tissues to start pulling more of their weight by breaking down more fat. The lower glycogen stores fall, the greater the sustained twenty-four-hour fat loss.³²⁶⁰

How long do you have to go without food in order to trigger this effect? Six hours may be sufficient, so before breakfast isn't the only optimal window.³²⁶¹ If you timed it right, you could exercise midday before a late lunch or, if you had an early enough lunch, before dinner after you got home from work.

If exercise in a fasted state isn't possible, does it matter what you eat? Insulin release after a meal appears to play a critical role in suppressing fat breakdown,³²⁶² which explains why lower-glycemic foods can have less of an effect.³²⁶³ Lentils were identified as a promising option for maintaining athletic endurance,³²⁶⁴ which can take a hit on an empty stomach,³²⁶⁵ while maintaining more of the fat dissolution. They are “unlikely to be consumed by the general population,” though, wrote one research team, “due to low palatability.”³²⁶⁶ (They obviously haven't tried my mom's lentil soup.)

A systematic review and meta-analysis on exercise timing for fat metabolism found that exercising in a completely fasted state may work best.³²⁶⁷ The Japanese team who published some of the seminal work in this area went as far as asserting: “If exercise were a pill to burn body fat, it would be effective only when taken before breakfast.”³²⁶⁸ Surveys show few people exercise before breakfast, though.³²⁶⁹ Before asking people to make the switch, we need to make sure that these tantalizing, twenty-four-hour results translate into weight loss over the long term. There's a solid theoretical basis, but you don't know until you put it to the test.

In a study of experimental weight gain, volunteers were fed up to 4,500 calories a day for six weeks while vigorously exercising a total of three hundred minutes a week, always either after an overnight fast or after a meal. A control group who didn't exercise at all but consumed the same extra calories gained about six and a half pounds, compared to three pounds gained in the exercise-after-a-meal group. The premeal exercise group worked out the same amount and ate the same amount, but they only gained half as much, one and a half pounds.³²⁷⁰ What about weight *loss*, though?

Twenty young women on calorie-restricted diets were randomized to exercise for three hours a week either before or after a meal. Same diets, same amount of exercise, and, disappointingly, about the same amount of weight loss. The premeal exercise group did lose about an extra pound of body fat (total weight loss of three and a half pounds versus two and one-fifth pounds), but this did not reach statistical significance, meaning such a small difference could very well have been due to chance.³²⁷¹ Similarly, a study of six weeks of low-volume, high-intensity interval training before or after meals also failed to show a difference.³²⁷²

One explanation that's been offered for this failure is that the increased fat loss during premeal exercise might be "neutralized" by the lesser diet-induced thermogenesis.³²⁷³ It costs our bodies fewer calories to process food if we eat after physical activity compared to eating before. When we exercise after a meal, our bodies get mixed signals. Exercise is all about mobilizing energy stores for fuel, whereas eating is more about assimilation and storage. So the metabolic challenge presented by the ensuing hormonal "tug-of-war"³²⁷⁴ might be responsible for the 15–40 percent greater calorie cost.³²⁷⁵ This has led some to recommend exercising *after* meals to facilitate weight loss.³²⁷⁶ If you do the math, though, diet-induced thermogenesis makes such a small contribution that this might only come out to be three to twelve calories.³²⁷⁷ Such a slight difference would be easily overwhelmed by the big disparity in fat loss, as confirmed by the twenty-four-hour fat-balance studies.

I would suggest a more reasonable explanation might be that the clear body-fat deficit on premeal exercise days is made up for by extra fat storage on nonexercise days. Our bodies like to hold on to body fat if they can, so, on days you aren't driving it down, it may try to even things out. Both of the failed weight-loss studies had people exercising only three days a week, so their bodies had most of the week to compensate. The study I'd love to see is pre- versus post-meal exercise on all or at least most of the days of the week to see if we can continue to drive down fat stores.

Blood Sugar Taming Through Timing

You can imagine how that siphoning effect muscles have on excess blood sugar during exercise might be great for those suffering from elevated blood sugars. Indeed, exercising after a meal can bring down blood sugars as well as some blood sugar-lowering drugs.³²⁷⁸ Randomize type 2 diabetics to a leisurely twenty-minute stroll (about 2 mph) before dinner or after dinner, and you can show that after-dinner walking can comparatively blunt blood sugar spikes by 30 percent.³²⁷⁹ Same meal, same amount of exercise, same intensity of exercise, but with a significant bonus effect on blood sugar control, thanks to a little tactical timing. Even just a ten-minute walk after a meal may make a difference.³²⁸⁰ So for those with blood sugar problems, it's better to exercise after meals than before them.

Blood sugar from a meal starts appearing in the bloodstream fifteen to twenty minutes after the first bite. It ramps up after thirty minutes to peak around the one-hour mark before declining to premeal levels within a few hours.³²⁸¹ For optimal blood sugar control, prediabetics and diabetics should start exercising thirty minutes after the start of a meal and ideally go for an hour to completely straddle the blood sugar peak.³²⁸² If you had to choose a single meal to exercise after, it would be dinner,³²⁸³ due to the circadian rhythm of blood sugar control that wanes throughout the day. Ideally, though, breakfast would be the largest meal of the day, and you'd exercise after that—or, even better, after every meal.³²⁸⁴

A Walk in the Park

Exercise recommendations for obesity have been referred to as the "mysterious case of the public health guideline that is (almost) entirely ignored." Governmental, scientific, and professional organizations call for at least an hour of exercise a day for weight management, but almost no obese adults meet this target.³²⁸⁵ Surveys suggest Americans watch TV about ten times more than they exercise, and for obese Americans, it may be even worse.³²⁸⁶ Only 2 percent even reach thirty minutes of exercise a day,³²⁸⁷ and the percentage exceeding an hour a day is expected to be close to zero.³²⁸⁸

Why don't obese individuals exercise more? Rather than speculate, why don't we just ask? When questioned, obese adults typically describe exercise as being "unpleasant, uncomfortable and unenjoyable."³²⁸⁹ So how can we break this vicious cycle, where inactivity can lead to weight gain, which can lead to further inactivity and even more weight gain? The first thing to recognize is that it is normal and natural to be physically lazy.³²⁹⁰

Laziness is in our genes. We evolved to instinctually avoid unnecessary exertion to conserve energy for survival and reproduction. These days, there's no shortage of available fuel, yet the hardwired inertia remains. Our ancient ancestors are presumed to have exercised only when it was necessary or when it was fun, as a form of play.³²⁹¹ The only way exercise is going to work long term for weight control is if it becomes a stable, lifelong habit,³²⁹² so you need to restructure your surroundings to require more physical activity (like working at a treadmill desk) and figure out how to make exercise more enjoyable.³²⁹³

Here's a piece of wise advice from a 1925 medical journal entry: "The best prescription to be written for a walk is to take a dog ... and a friend."³²⁹⁴ Listening to your favorite music might also help. Music has been described as a "legal method"³²⁹⁵ for improving peak performance and, more importantly, the enjoyment of high-intensity interval training.³²⁹⁶ During exercise, listening to a preferred playlist can significantly reduce our "rate of perceived exertion," which is how hard you feel your body is working.³²⁹⁷ Put severely obese youth on a treadmill and have them go until exhaustion with or without music, and those listening to their favorite tunes tended to make it about 5 percent longer. This was chalked up to "attentional distraction"—the music may have helped keep their minds off feelings of fatigue.³²⁹⁸ If that's the case, listening to a podcast or audiobook may have a similar effect.

Spin Class

The recommendation to exercise sixty to ninety minutes for weight control has been dismissed as "too ambitious,"³²⁹⁹ "too daunting,"³³⁰⁰ and "too much, too soon," fearing people will feel overwhelmed and not exercise at all.³³⁰¹ In short, America, you can't handle the truth.³³⁰²

Maybe we should just tell it like it is. In a paper titled "Effects of Threatening Communications ... on Weight Change in Obese Children," mothers of obese kids were randomized to receive one of two messages from their pediatrician's clinic. In the "low-threat" group, the message was gentler and more "generic":

There are health problems related to obesity, most of which take years to develop. Being obese can interfere with things that people want to do ... All in all, obese people are more likely to have health problems.

The "high-threat" group got a more blunt, "threatening" message:

The overweight child is likely to become an obese adult ... Heart attacks, strokes, high blood pressure, and diabetes happen a lot more often to obese people—add it all up and you get a shorter life expectancy.

Whose kids do you think consistently lost more weight? Did the stronger message overwhelm the moms into paralysis? No. Their kids lost nearly twice as much weight as the children whose mothers got the milder message.³³⁰³ Ignorance is less blissful when lives are on the line.

Some of the most influential voices in exercise promotion don't think we should focus on health at all. After all, Big Business is smart enough to keep its true goal of profit hidden

from consumers, shrouding its advertising in promises of success and happiness. We should learn from the drug companies, they say. Pharmaceutical ads are less educational than aspirational.³³⁰⁴ If we took a page from Big Pharma’s playbook and listened to those exercise-promoting influencers, we would appeal to emotions, rather than “logical benefits such as better health” to promote exercise and instead prescribe “pleasure and meaning.” We would need to “shift from a medical to a marketing paradigm.”³³⁰⁵

I bristle at the marketing talk, but the nice thing about exercise is that it really can deliver on all those fronts—fostering elixir-of-life feelings of joy and vitality while helping people physically fulfill their goals in life. Frame a walk as exercise, and people report feeling more fatigued and in a worse mood than after going the same distance on a walk framed as fun.³³⁰⁶ And it really can be fun. When sedentary individuals are started on an exercise regimen, they report enjoying it significantly more than they had expected.³³⁰⁷

FOOD FOR THOUGHT

The bottom line with exercise is that any amount is good³³⁰⁸ and the more the better.³³⁰⁹ If, however, you are a man over forty-five, are a woman over fifty-five, have diabetes, or experience symptoms such as chest pain, dizziness, or shortness of breath, I would recommend checking with your health professional before starting a new exercise regimen.³³¹⁰

The evidence for the health benefits of exercise in general is overwhelming. Obesity can exacerbate disabling, painful conditions, such as osteoarthritis of the knees, making exercise more difficult but all the more essential. Losing weight doesn’t just ease pain in the overloaded joints in the lower back, hips, knees, and ankles. The anti-inflammatory effects of exercise can also alleviate headaches and more diffuse, chronic, musculoskeletal aches and pains that disproportionately affect overweight individuals.³³¹¹ However, the efficacy for weight loss is underwhelming for all but the most voluminous regimens. I did offer some suggestions to maximize fat loss, but on the whole, the limitations just make the calories-in side of the equation—that is, the dietary tweaks—all the more important. But overall, exercise is win-win: adding years to your life and life to your years.

FAT BLOCKERS

Eat Your Thylakoids

Turn Over a New Leaf

What on earth is a thylakoid? No big deal, just the source of nearly all known life and the oxygen we breathe. Thylakoids are where photosynthesis, the process by which plants turn light into food, takes place. Microscopic saclike structures composed of chlorophyll-rich membranes concentrated in the leaves of plants, thylakoids are the green engine of life.

When we eat them, when we bite into a leaf of spinach, for instance, the thylakoid membranes are able to resist our digestive enzymes. They can last for hours in our intestines before finally getting broken down,³³¹² and it is in those hours when they work their magic. Thylakoid membranes bind to lipase, the enzyme our bodies make to digest fat, thereby helping to block fat absorption.³³¹³ This mechanism is like a natural version of the fat-blocking drug orlistat, but without the anal leakage.³³¹⁴ Unlike the drug, the thylakoids do finally break down, eventually freeing the lipase enzyme to do its job before fat comes spilling out your other end.³³¹⁵ Ultimately, fat absorption is not so much blocked by thylakoids as it is delayed.

If all the fat is eventually absorbed, what’s the benefit? Location, location, location. Remember that ileal brake effect I described in the High in Fiber-Rich Foods section? By delaying calorie absorption until that tail end of the small intestine, strong satiety signals are sent to our brains saying, in effect, that you are full from stem to stern, thus dialing down your appetite.³³¹⁶ If you feed someone a meal with added thylakoids (by slipping in some powdered spinach, for instance) and measure the level of hormone release into their

bloodstreams over the next six hours, you see a significant rise in a satiety hormone called CCK, as well as a drop in the hunger hormone ghrelin.³³¹⁷ Does this then translate into a drop in appetite? Researchers were eager to find out.

Spinach extracts were disguised in jam³³¹⁸ and juice³³¹⁹ to sneak thylakoids into meals, and those unwittingly eating the equivalent of about a half cup of cooked spinach felt significantly less hungry and more satiated over the next few hours. Give someone the equivalent of a shot of wheatgrass juice or what they might get in a “green drink” or green smoothie, and not only do they feel more satiated, but their cravings for sweet, salty, and fatty snacks, such as potato chips, chocolate, and cinnamon buns, drop by about a third. Feed them candy anyway, and those who unknowingly had been snuck some spinach report liking the sweets significantly less.³³²⁰ The satiating power of greens has been attributed to their high fiber and water contents and low-calorie density,³³²¹ but the thylakoids may be their secret weapon.

The majority of thylakoid trials to date have shown improvements in satiety,³³²² but what about weight loss? Researchers in Sweden randomized overweight women to blended blueberry drinks every morning with or without “green-plant membranes” (powdered spinach). Within twelve weeks, the women who had been slipped spinach lost three pounds more than the control group. The spinach group’s cravings for sweets diminished, and as a bonus, their bad LDL cholesterol dropped, too, even before the weight loss started kicking in.³³²³ If you instead fix their caloric intakes to force the same weight loss, those randomized to the spinach group appeared to have an easier time with eating less. They experienced less hunger after a test meal after weeks of eating green.³³²⁴

Extracts of spinach were used in these studies so the researchers could create convincing placebos, but you can get just as many thylakoids eating about a half cup of cooked greens. Which greens have the most? You can tell just by looking at them.³³²⁵ Because thylakoids are where the chlorophyll is, the greener the leaves, the more potent the effect.³³²⁶ So go for the darkest-green greens you can find. In the store where I shop, that’s the Lacinato (or dinosaur) kale.

What happens when you cook greens? Blanched for fifteen seconds or so in steaming or boiling water, they actually get even brighter green, but if you cook them too long, they eventually turn a drab olive brown. When greens are overcooked, the thylakoids physically degrade, along with their ability to inhibit lipase. Within that first minute when the green gets even more vibrant, though, there’s a slight boost in fat-blocking ability.³³²⁷ So you can gauge thylakoid activity in both the grocery store and the kitchen with your own two eyes.

Which are the best greens, and what is the best cooking method? The best green vegetable and the best way to cook it is whichever, and however, you’ll end up eating the most. We’ve been chewing on leaves for millions of years,³³²⁸ but today, the greenest thing about some people’s diets may be a St. Patrick’s Day pint. Americans average fewer than two grams of spinach a day, not even half a teaspoon.³³²⁹ Our bodies were designed to have thylakoids passing through our systems on a daily basis, so the delay in fat absorption can be thought of as the default, normal state.³³³⁰ It’s only when we eat greens-deficient diets that the accelerated fat digestion undercuts our natural satiety mechanisms. In the *Journal of the Society of Chemical Industry*, a group of food technologists argued that given their fat-blocking benefits, “thylakoid membranes could be incorporated in functional foods as a new promising appetite-reducing ingredient”³³³¹—or you can just get them in the way Mother Nature intended.

Choose Low-Oxalate Greens

Kidney stones affect as many as one in ten people in their lifetime and can cause excruciating pain.³³³² I instinctively cross my legs just thinking about them. Oxalate stones are the most common type,³³³³ forming when the oxalate concentration gets so high in our urine it basically crystallizes out of solution like rock candy. Some

foods, like spinach, have lots of oxalates in them. Should we try to reduce our intakes of oxalates to lower our risk? It turns out that people who get stones don't appear to eat any more oxalates on average than people who don't get stones.³³³⁴ It's less what you eat and more what you absorb. People who are predisposed to kidney stones just appear to be born with a higher intestinal oxalate absorption.³³³⁵ Their guts just really soak it up. So-called super absorbers assimilate up to 50 percent more oxalate than non-stone-formers.³³³⁶

Overall, the impact of typical dietary oxalate on urine levels appears to be small.³³³⁷ Feed people a "massive"³³³⁸ dose of dietary oxalates, and most only experience a relatively mild increase in the amount that makes it into their urine.³³³⁹ Still, until you get your first stone, how do you know if you're a super absorber or not? Is it safer to just generally avoid higher oxalate fruits and vegetables? Well, people who eat more fruits and veggies actually tend to get fewer kidney stones.³³⁴⁰ In fact, when researchers put it to the test and removed produce from people's diets, their kidney stone risk went up.³³⁴¹

Removing fruits and vegetables can make our dietary oxalate intakes go down, but it also impairs our bodies' ability to get rid of the oxalate we produce on our own. Oxalate is formed internally as a waste product, and our bodies have more difficulty getting rid of it without the alkalizing effects of fruits and vegetables on our urine's pH.³³⁴² This may help explain why those eating plant-based diets get fewer kidney stones, though it also may be due to their reduction in meat intake, as meat consumption can have an acid-forming effect in the kidneys.³³⁴³ A single can of tuna a day can increase our risk of forming stones by 250 percent,³³⁴⁴ for example, and just cutting back on animal protein can help cut kidney stone risk in half.³³⁴⁵

Surely, there must be some level of oxalate intake that could put people at risk regardless. The study that showed a "massive" load of dietary oxalate didn't have much of an effect on urine levels used 250 mg of oxalates.³³⁴⁶ That's a massive dose if we were talking about most greens—for example, 25 cups of collard greens, 60 cups of mustard greens, 125 cups of kale, or 250 cups of bok choy—but it's less than a half cup of spinach.³³⁴⁷ Spinach really is an outlier. Even though there are small amounts of oxalates found throughout the food supply, spinach alone may account for 40 percent of oxalate intake in the United States.³³⁴⁸ The Harvard cohorts found that men and older (but not younger) women who ate spinach eight or more times a month had about 30 percent higher risk of developing kidney stones.³³⁴⁹

Oxalates are water-soluble, so blanching collard greens, for example, can reduce oxalate levels by up to a third.³³⁵⁰ (In that case, the oxalate load of those twenty-five cups of raw collards could be bumped up to thirty-three cups of blanched collards!) Steaming spinach reduces oxalate levels by 30 percent, and boiling cuts them by more than half. Boil the three high-oxalate greens—spinach, beet greens, and swiss chard—and up to 60 percent of the oxalates are leached into the cooking water.³³⁵¹ They start out so high, though, that they would still contain hundreds of times more oxalates than low-oxalate greens like kale.

Who may benefit from avoiding the big three high-oxalate greens? Anyone who has a history of kidney stones, is otherwise at high risk (for example, those who take megadoses of vitamin C,³³⁵² have a history of long-term broad-spectrum antibiotic use,³³⁵³ or had Roux-en-Y gastric bypass surgery³³⁵⁴), or who eats cups of greens a day. (I personally try to eat at least a pound of greens a day, which is about three cups cooked or a dozen raw.) This is especially important for those who juice or blend their greens, as oxalates appear to be absorbed more rapidly in liquid than solid form.³³⁵⁵

Other high-oxalate foods that have been associated with kidney problems at high enough doses include chaga mushroom powder (four to five teaspoons a day),³³⁵⁶ rhubarb (four cups a day),³³⁵⁷ almonds³³⁵⁸ or cashews (more than a cup a day),³³⁵⁹ and star fruit (a single dose of one and a quarter cup juice³³⁶⁰ or four to six fruit).³³⁶¹ Excessive tea consumption can also be a problem, especially of instant tea powder, which boosts urine oxalate nearly four times higher than brewed tea.³³⁶² Two cases of kidney damage attributed to drinking sixteen daily glasses of iced tea have been reported.^{3363,3364}

The Calcium Effect

Another reason to give preference to low-oxalate greens is that they are less stingy with their calcium. While less than a third of the calcium in milks (whether from cow³³⁶⁵ or plant³³⁶⁶) may be bioavailable, most of the calcium in low-oxalate greens is absorbed.³³⁶⁷ The bioavailability of some greens is twice that of milks, but the oxalates in spinach, swiss chard, and beet greens bind to the calcium, preventing the absorption. It works both ways, though.³³⁶⁸ The calcium binds to the oxalate too. That's why some gastric bypass surgeries result in enhanced oxalate absorption.³³⁶⁹ The procedures can cause fat malabsorption. The fat steals away the calcium bound to the oxalate to form a type of soap in our intestines,³³⁷⁰ and the oxalate is then freed to be absorbed.

Wait a second. If calcium is so good at grabbing onto fat in the gut, might calcium-rich foods act as fat blockers too? The problem with fat-blocking drugs is that the undigested fat comes out the other end, resulting in fecal leakage. But if calcium turns the fat into a semisolid soap, there's no oily discharge,³³⁷¹ and when we poop out the fat-calcium soap, we poop out all those fat calories contained therein.

The dairy industry was excited to put it to the test. When 1,200 mg or so of calcium in the form of cheese was added to people’s diets, instead of losing about four grams of fat in their stool each day, they excreted closer to six grams of fat.³³⁷² The extra calcium caused the body to absorb two fewer grams of fat. Of course, that much cheese has more than fifty grams of fat,³³⁷³ so it makes no sense to add fifty grams so you can get rid of two. You can imagine, though, how adding a fat-free source of calcium—skim milk, or even healthier, low-oxalate greens—could result in a small, negative fat balance every day. Orlistat can block about sixteen grams of fat a day,³³⁷⁴ whereas a meta-analysis of the calcium fat-blocking studies confirmed only the two-gram difference.³³⁷⁵ But if you absorbed two fewer grams of fat a day, that’s eighteen calories you won’t be holding on to, which, if not compensated for, could add up to a pound of fat loss.³³⁷⁶ (Of course, another way to prevent two grams of fat from being absorbed is just to consume a half-teaspoon less oil every day.)

Nondairy sources of calcium appear to work just as well as dairy sources,³³⁷⁷ and the small fat-blocking effect does not appear to diminish with time.³³⁷⁸ Does this translate into weight loss? When people were randomized to take 1,000 mg of calcium supplements a day, all the extra little bits of daily fat loss added up to about two pounds of body fat lost over six months compared to placebo.³³⁷⁹ Interventions using dairy didn’t show any significant body fat loss,³³⁸⁰ presumably because the added calories from the dairy itself counteracted any fat-blocking effects.³³⁸¹

Caloric-restriction trials in which dairy calories were swapped in rather than added, though, did show an average of about two pounds of fat loss over an average of five months, helping to confirm the calcium effect. Unfortunately, none of the dairy studies lasting a year or longer showed a significant benefit, but they were mostly nonsubstitution trials, so presumably people just weren’t able to compensate for the added dairy calories.³³⁸² Even dairy industry-funded scientists have been forced to conclude that dairy consumption has “no clinically meaningful effect” when it comes to promoting weight loss.³³⁸³ We know the calcium fat-blocking effect *is* real, though. If only it could be provided in a safe, satiating form. It can. That’s why greens—high in fiber, low in calories—may be the perfect delivery vehicle, combining the effects of thylakoids and calcium into one package deal.

Calcium Supplement Safety

In twelve short years, expert panels went from suggesting widespread calcium supplementation to prevent osteoporosis³³⁸⁴ to “do not supplement,”³³⁸⁵ the recommendation that remains for most people to this day.³³⁸⁶ What happened? It all started with a 2008 study in New Zealand.³³⁸⁷

Researchers were hoping to prevent heart attacks by giving people calcium supplements. Short-term studies have shown that calcium supplementation may drop blood pressures by about a point.³³⁸⁸ Though the effect appears to be transient, disappearing after a few months, it’s better than nothing.³³⁸⁹ Further, the fat-blocking effect of calcium could theoretically lower cholesterol levels by preventing a bit of saturated fat from getting into the system.³³⁹⁰ To the researchers’ surprise, however, instead of fewer heart attacks, there appeared to be *more* heart attacks in the calcium-supplement group.³³⁹¹ Was this just a fluke?

All eyes turned to the Women’s Health Initiative, the largest and longest randomized controlled trial of calcium supplementation. If that name sounds familiar, it’s because that’s the very study that uncovered how dangerous hormone replacement therapy was. Would it uncover the same for calcium supplements?

The Women’s Health Initiative reported no adverse effects. However, the majority of the participants were already taking calcium supplements before the study started. So, effectively, the study was just comparing higher versus lower doses of calcium supplementation rather than supplementation versus no supplementation. What if you go back and see what happened to the women who started out not taking supplements and then were randomized to the supplement group? Those who started calcium supplements suffered significantly more heart attacks or strokes.³³⁹² Thus, whether high dose or low dose, any calcium supplementation seemed to increase cardiovascular disease risk.

Researchers went back, digging through other trial data for heart attack and stroke rates in people randomized to calcium supplements, and they confirmed the danger.³³⁹³ Most of the population studies also agreed: Users of calcium supplements tended to have increased rates of heart disease, stroke, and death.³³⁹⁴

The supplement industry was not happy, accusing researchers of relying in part on self-reported data—that is, simply asking if people had had a heart attack or not, rather than verifying it.³³⁹⁵ That’s not as much of a stretch as it may sound. Long-term calcium supplementation can cause all sorts of gastrointestinal distress, including twice the risk of being hospitalized with acute symptoms that may have been confused with a heart attack.³³⁹⁶ However, the increased cardiovascular risk was seen consistently across the trials, regardless of whether the heart attacks were verified or not.³³⁹⁷

The calcium supplementation and heightened cardiovascular risk link continues to be a rising concern.³³⁹⁸ Thankfully, supplementation rates dropped when the news came out, though some doctors continue to prescribe calcium for prevention.³³⁹⁹ This inertia has been attributed to a complex web of industry ties with advocacy organizations and academia to protect the \$6 billion business.³⁴⁰⁰

Why might calcium supplements increase heart attack risk, whereas the same calcium you get in foods does not? When you take calcium pills, you get an unnaturally large, rapid, and sustained spike of calcium in your bloodstream that can last as long as eight hours. This can cause your blood to clot more easily, which could increase the risk of forming clots in the heart or brain.³⁴⁰¹ Of course, if you’re worried about heart attacks, there are risky food sources of calcium too. (I’m looking at you, cheese.)

The best sources of calcium are Green Light foods like leafy greens. In *How Not to Die*, I defined my Green Light category as foods of plant origin to which nothing bad has been added and from which nothing good has been taken away. Green Light whole plant foods, unlike dairy, package calcium with lots of fiber, folate, iron, antioxidants, and thylakoids, instead of the baggage that too often accompanies milk products, such as sodium, cholesterol, and saturated butterfat. Despite the global dairy industry’s campaign to “neutralise the negative image of milkfat among regulators and health professionals as related to heart disease,” the American Heart Association is explicit about our need to cut down on dairy fat (and coconut oil and meat) to reduce the risk of our number one killer.^{3402,3403} The American Heart Association put out a special Presidential Advisory in 2017 to clearly “set the record straight on why well-conducted scientific research overwhelmingly supports limiting saturated fat in the diet.”³⁴⁰⁴

Drink Hibiscus Tea

Flower Power

Hibiscus tea, also known as *roselle* or *Jamaica*, is enjoyed around the world, hot or cold, for its bright red color and tart cranberry-like flavor. It’s the “zing” in Red Zinger tea. I talk about its benefits in the chapter on high blood pressure in *How Not to Die*, working as well as,³⁴⁰⁵ or even beating out, some antihypertensive medications in head-to-head tests.³⁴⁰⁶

Within three hours of drinking hibiscus tea, one hundred different metabolites can be detected in the human bloodstream.³⁴⁰⁷ Alterations in gene expression at the three-hour mark suggest an improvement in metabolism and a downregulation of cholesterol synthesis, but randomized controlled trials have failed to consistently find cholesterol-lowering benefits.³⁴⁰⁸ An interesting side effect did pop up, though: weight loss.³⁴⁰⁹

In Mexico, hibiscus tea has been used traditionally for the treatment of obesity, sparking lots of research interest.³⁴¹⁰ Computer modeling studies have suggested that certain hibiscus compounds might bind to the fat-digesting enzyme lipase like a key in a lock.³⁴¹¹ (Uncreative names of compounds found from the flower include *hibiscin*, *hibiscitrin*, *hibiscetin*, and *hibiscus acid*.³⁴¹²) Test-tube studies screening a variety of medicinal plants did indeed find that hibiscus inhibited lipase more than the others,³⁴¹³ and hibiscus has been found to reduce body fat in hamsters,³⁴¹⁴ mice,³⁴¹⁵ and rats, increasing fecal fat excretion.³⁴¹⁶ However it wasn’t tested in people until recently.

To design a randomized double-blind trial, instead of trying to create an artificially colored and flavored placebo tea, the researchers dried the hibiscus tea into a powder and put it into capsules. After twelve weeks, there was a greater reduction in waistlines and body-fat percentage in the hibiscus group compared to those who got placebo capsules,³⁴¹⁷ but the dose they used was the equivalent of nine cups of hibiscus tea a day.³⁴¹⁸ I recommend people stick to no more than a quart a day on a regular basis due to the high manganese content. (Manganese is an essential trace mineral, but nine cups a day might result in too much of a good thing.³⁴¹⁹)

Finally, in 2018, a study was published using a reasonable dose—the equivalent of about a single twelve-ounce glass of tea a day. The complicating factor is that the researchers

also added lemon verbena to the mix. That's another herbal tea, better known for improving recovery after intense bouts of strength training,³⁴²⁰ but there were some promising in vitro data on effects of lemon verbena on fat cells in a petri dish,³⁴²¹ so they tried a combination. The dose came out to be about a cup and a half of hibiscus tea³⁴²² and a quarter cup of lemon verbena tea³⁴²³ once a day for two months.³⁴²⁴

Both the tea and placebo groups were prescribed diets containing the same number of calories, yet those randomized to the tea group lost significantly more weight—eight pounds compared to five. That's only an extra pound a month, but an extra pound a month on a same-calorie diet.³⁴²⁵ That's the advantage of fat-blocking interventions that actually cause you to lose more calories: Beyond reducing hunger, they can make you feel fuller for longer in hopes that you'll subsequently eat fewer calories.

Why not just pop pills instead of brewing tea? There are all sorts of herbal extract supplements on the market, but do we know enough to extract out the right active ingredients? For example, it does not appear to be the red anthocyanin pigments in hibiscus, since white varieties seemed to have similar effects.³⁴²⁶ When the various compounds in hibiscus tea are isolated out and tested in various combinations, synergistic effects are found, meaning the whole may be greater than the sum of its parts.³⁴²⁷

Other than my manganese caveat, the only potential downside of hibiscus tea is the effect it can have on our tooth enamel if we're not careful. As with any sour food or beverage, like after eating citrus, it's important to wash the natural acids off your teeth by rinsing out your mouth with water to protect your teeth.³⁴²⁸ You also want to wait at least an hour before brushing so as not to erode your enamel when it's in a softened state.³⁴²⁹

FOOD FOR THOUGHT

The best source of the fat-blocking agents thylakoids and calcium is low-oxalate, dark green leafy vegetables, meaning essentially all greens except spinach, beet greens, and swiss chard. To be clear, I encourage everyone to eat huge amounts of dark leafy greens every day, the healthiest food on the planet. Greens answer the question: *What if the food with the lowest calorie content also had the highest nutrient content?* But if you follow this advice (and you should!), then just choose any of the other wonderful greens. If you eat mere-mortal amounts of greens (like a serving a day), then it doesn't matter which type of dark green leafy you choose. I continue to enjoy spinach, beet greens, and chard all the time. It's just that you can overdo those three. To make sure I don't end up consuming more than a serving or two a day of the high-oxalate ones when I'm trying to hit my pound-a-day green leafy quota, I personally do mostly kale, collards, and arugula, which also happen to have the added benefit of being *cruciferocious*. And you can enjoy it with a cup of hibiscus tea for added zing.

FAT BURNERS

Up to BAT

Fat in the Fire

Even if the majority of fat absorption was blocked, we could still accumulate excess body fat in the context of excess calories due to burning less of our own fat stores. Is there any way to ramp up the burn? Let's take a look.

During World War I, it was discovered that some of the ingredients used to make the new explosives had toxic or even lethal effects on the workers in the munitions factories. Chemicals such as dinitrophenol (DNP) can boost metabolism so much that workers were found wandering along the road after work, soaked in sweat with fevers up to 109°F. Then they died. Even after death, their temperatures kept going up as if they were having a total-body meltdown. At lower doses of DNP, workers claimed to have grown thin after several months working with the chemical.³⁴³⁰ That got some Stanford pharmacologists excited about DNP's "promising metabolic applications."³⁴³¹

DNP became the first bona fide fat-burning supplement, boosting resting metabolic rate by 30 percent after a single dose. People started losing weight with no apparent side effects. They felt great.³⁴³² Then thousands of people started going blind, and users started dropping dead from hyperpyrexia (fatal fever) due to the heat created by the burning fat.³⁴³³ Of course, it continued to be sold. The ad copy read:

Here, at last, is a [weight] reducing remedy that will bring you a figure men admire and women envy, without danger to your health or change in your regular mode of living.... No diet, no exercise!

DNP works, but its therapeutic index—the difference between the effective dose and the deadly dose—is razor thin. It was not until thousands suffered irreparable harm that it got pulled from the market.³⁴³⁴ Until, that is, its availability was brought back by the internet.³⁴³⁵ DNP deaths continue to be reported among those dying to be thin.³⁴³⁶

There is, however, a way our bodies naturally burn fat to create heat. When we're born, we go from a balmy, tropical 98.6°F in our mothers' wombs straight out into room temperature, when we're still all wet and slimy. As an adaptive mechanism to maintain warmth, the appearance of a unique organ around 150 million years ago allowed us warm-blooded mammals to maintain our high body temperatures.³⁴³⁷ That unique organ is called *brown adipose tissue*, or *BAT* for short, and its role is to consume fat calories by generating heat in response to cold exposure.

The white fat in our bellies stores fat, but the *brown* fat, located high in our chests, *burns* fat. In newborns, BAT is essential for thermogenesis—the creation of heat—but was considered unnecessary in adults since we have the muscle mass to warm ourselves by shivering. We used to think BAT just shrank away when we grew up, but then an exciting discovery was made.³⁴³⁸

When PET scans were invented to detect metabolically active tissues like cancer, oncologists kept finding hot symmetrical spots in the neck and shoulder regions³⁴³⁹ that were initially dismissed as muscle tension.³⁴⁴⁰ Then, some observant radiologists noticed they appeared in patients mostly during the cold winter months.³⁴⁴¹ When they looked closer at tissue samples taken from people who had undergone neck surgery, they found it: brown fat in adults.³⁴⁴²

Go to BAT Against Fat

By the time a baby is born, brown fat may make up 5 percent of an infant's body weight.³⁴⁴³ As we get older, our brown fat deposits start withering away.³⁴⁴⁴ Some adults are left with more than others, and that may help determine how heavy we may become. The amount of body fat we accumulate as we age is correlated with how much brown fat we lose.³⁴⁴⁵ The more BAT you have and the more active it is, the thinner you tend to be.³⁴⁴⁶ Those who have active BAT have less than half the visceral belly fat³⁴⁴⁷—but which came first: the BAT or the lack of fat? It's possible that underactive brown fat leads to obesity, but maybe obesity leads to underactive brown fat. With all the extra body fat acting as insulation, perhaps our bodies are just able to turn down their internal heaters.³⁴⁴⁸ There is, however, reason to believe that brown fat does play a causal role in regulating our weights.

A hibernoma is a rare, benign tumor of brown fat, so named because it resembled the "hibernating gland" of animals like bears, who utilize brown fat to keep them warm through the winter. This condition allows us the opportunity to see if growing extra brown fat can cause weight loss, and indeed, people with hibernomas can lose as much as thirty-five pounds but then may gain it right back after surgical removal of the tumor.³⁴⁴⁹ Brown fat transplantation studies showing you can reverse obesity in lab animals have even led

scientists to suggest that perhaps we should start harvesting brown fat cells from cadavers.³⁴⁵⁰

Could this explain why some people gain more weight while others seem to be able to overeat and remain slim? Might that just be a consequence of how much brown fat they retained as they grew up? Is it all because of BAT?³⁴⁵¹

Initially, scans of thousands of people revealed active brown fat deposits in fewer than one in ten, raising doubts about BAT's public health significance. But when they were put in a cool room in their undies for an hour or two *before* the scan, more than half of the people started lighting up when they were scanned. Of those who didn't, however, when they were dunked in cold water or made to sit with their bare feet on a slab of ice, their detection rate shot up to 100 percent.³⁴⁵² Given these findings, instead of just a lucky few, it seems nearly everyone retains brown fat, and much more than we used to think.

Initial estimates posited as few as two ounces of brown fat survived into adulthood,³⁴⁵³ but advanced mapping techniques have revealed it's more like a full cup.³⁴⁵⁴ That's still only about 1 percent of our total body mass, though. Is that enough to make a difference? Maximally stimulated, that much brown fat could produce as much heat as a sixty-watt incandescent light bulb.³⁴⁵⁵ Developmentally, brown fat cells may derive from the same precursors that go on to form muscle cells.³⁴⁵⁶ BAT cells are little fat-burning machines. Theoretically, just our BAT alone could burn off fifty pounds of fat a year without us lifting a finger.³⁴⁵⁷ The potential is there, but in most people, their brown fat is just lying dormant. So how can we wake it up?

Turning Up the Heat

Brown fat can be activated rapidly by exposure to cold. There are temperature-sensitive thermoreceptors in our skin connected to nerves that send signals to a special region in our brains that then triggers brown fat activation.³⁴⁵⁸ If you focus an infrared thermography camera on someone's upper chest as they stick their hand into a bowl of ice water, you can see areas above their collarbones light up within minutes,³⁴⁵⁹ indicating the presence of BAT.

Even mild cold exposure, like a few hours spent in a chilly room, can boost our metabolic rates up to 90 percent, thanks in part to brown fat activation.³⁴⁶⁰ Even if that means hundreds more calories burned every day, it only translates into weight loss if there isn't any compensatory increase in appetite.³⁴⁶¹ In the short term, there doesn't seem to be any change in hunger or food intake after a mild cold exposure,³⁴⁶² but you can't know about longer-term impacts until you put it to the test.

In a famous study entitled "Recruited Brown Adipose Tissue as an Antiobesity Agent in Humans," people were randomized to spend two hours a day at 63°F. By the end of six weeks, the cold-exposed group was burning 180 more calories a day and lost significantly more body fat than the control group. At first, only about half the study subjects had detectable brown fat activation in response to the cooler temperatures, but as the weeks went by, BAT hot spots started to ignite.³⁴⁶³

Beige Can Be Slimming

Once cells become specialized, they tend to stay that way. A muscle cell can't just decide one day to turn into a skin cell or a nerve cell. Fat cells, though, are different. They're flexible. In the breast, for example, mature fat cells can morph into gland cells and start producing milk. Imagine if there were a way to reprogram a white fat cell into a brown fat cell, turning it from *fat-storing* to *fat-burning*.

Brown fat is brown because the cells are packed with mitochondria, the little power plants in our cells that burn fat using iron-containing enzymes that give them a deep reddish color.³⁴⁶⁴ Brown fat is also riddled with a dense network of blood vessels to pump in

oxygen and distribute the heat. White fat, on the other hand, is just the regular body fat you can see in a cut of meat. The latest entry in the new color code of fat is beige fat, also known as *brite* (a contraction of *brown in white*).³⁴⁶⁵ Apparently, when we're exposed to cold, not only do we make new brown cells from scratch, but some of our white fat cells also transform into brown fat cells, offering a dual benefit.³⁴⁶⁶ The fat around our middles can become speckled with brown fat cells to start burning off the fat of their neighboring cells. (In fact, that's one of the ways the FTO "fat gene" may work. It was the first obesity-related gene discovered and may increase risk of obesity by decreasing the formation and activity of this beige fat.³⁴⁶⁷)

So the next time you get chilly, look on the "brite" side.

Lose Weight by Chilling Out

Thomas Jefferson purportedly used a cold footbath every morning for most of his life to "maintain his good health."³⁴⁶⁸ Was he on to something? Cold exposure is the most powerful known stimulus for BAT activation.³⁴⁶⁹ Just twenty minutes at cool temperatures can boost metabolism for hours.³⁴⁷⁰ The colder the better, but putting people in a room chilled down into the 50s Fahrenheit is "often not appreciated by [research] subjects."³⁴⁷¹ It's not called a "thermal *comfort zone*" for nothing.

Exposure to cold (or lack thereof) might even help explain the rise in obesity rates. Wintertime bedroom temperatures have been slowly creeping up over the last few decades.³⁴⁷² The U.S. standard for winter comfort evidently increased from 64°F in 1923 to 76°F by 1986. All other things equal, spending just 10 percent of one's life at 72°F instead of 82°F could theoretically result in an eighteen-pound weight loss over a decade.³⁴⁷³

In an extreme example, lumberjacks in Finland who incidentally died in the dead of winter were found to be replete with brown fat on autopsy, but one need not live Beyond the Wall to reap some BAT benefits.³⁴⁷⁴ You burn 164 more calories a day living at 62°F instead of 72°F, about sixteen calories per degree.³⁴⁷⁵ If not otherwise compensated for, this could translate into a pound of fat a year per degree.³⁴⁷⁶ A climate of 62°F is pretty chilly, but simply moving within the range of climate-controlled buildings from 75°F down to 66°F has been proven to boost BAT activation. This resulted in a 5 percent boost in metabolic rate, so about one hundred more calories burned every day or an annual calorie-deficit equivalent of approximately twenty days of fasting.³⁴⁷⁷ So just a slight thermostat shift to a cool-but-not-too-cold ambient temperature may have a significant effect.³⁴⁷⁸

Former NASA scientist Ray Cronise, recognized for helping Penn Jillette lose one hundred pounds,³⁴⁷⁹ advises people to twist their faucet handle to incorporate some twenty-second cold-water blasts while showering. The purported benefits of cold-water immersion remain largely anecdotal, though.³⁴⁸⁰ (Our founding father's footbaths might have worked even better had Jefferson laid off the opium and mercury.³⁴⁸¹) Since BAT burns both fat and sugar to make heat,³⁴⁸² brown fat activation could help with blood sugar control,³⁴⁸³ but as far as I'm aware, there has only been a single study published on the effects of regular cold-water showering on health. Those randomized to even just thirty seconds a day of a cold-water blast ended up taking off fewer sick days from work.³⁴⁸⁴

Foods That Turn On BAT

Metabolic Magic Bullet

Mild cold exposure by "slightly" decreasing home temperatures has been suggested as a "cure for obesity,"³⁴⁸⁵ but the insulating layer of fat worn by obese individuals makes BAT activation harder³⁴⁸⁶—though not impossible.³⁴⁸⁷ Even without cold exposure, however, those who carry active BAT deposits appear to burn off about an extra fifty calories a day

without even trying.³⁴⁸⁸ This has led to brown fat being regarded as a “magic metabolic bullet,”³⁴⁸⁹ with drug companies scrambling to design pills to activate it.³⁴⁹⁰

Fat-burning drugs have a sordid history. When DNP was banned in 1938, amphetamines (speed) took up the slack until they were declared a controlled substance in the 1970s. Then came fenfluramine, followed by dexfenfluramine, and then sibutramine—all of which were later pulled from the market.³⁴⁹¹ Supplements like ephedra also seemed to work, until people started suffering from seizures, strokes, and sudden death, that is.^{3492,3493} Thankfully, there are safer options that don’t involve phrases like *cold shower* or *ice vest*. Brown fat can be activated by certain foods, herbs, spices, and beverages.

Those same thermoreceptors in our skin are also found in our intestines.³⁴⁹⁴ No, you don’t have to eat a brain-freezing Slurpee. There are dietary, as well as temperature, triggers. Unfortunately, most of the studies on food components that can activate brown fat or turn white fat beige were only performed in petri dishes or lab animals. These include studies involving beets,³⁴⁹⁵ broccoli,³⁴⁹⁶ grapes,³⁴⁹⁷ greens,³⁴⁹⁸ olives,³⁴⁹⁹ omega-3s,³⁵⁰⁰ onions,³⁵⁰¹ raspberries,³⁵⁰² rose hips,³⁵⁰³ soybeans,³⁵⁰⁴ and turmeric, but so far, none of these has been shown to activate BAT in humans.³⁵⁰⁵ In ironic contrast to the cold, one of the first foods to pass the test was hot peppers.

Chili Peppers

Capsaicin, the pungent compound in chili peppers that gives them their heat, fits like a lock-and-key into the thermoreceptors that lead to the activation of brown fat.³⁵⁰⁶ Studies have investigated the “antiobesity effects” of “Tabasco hot sauce in rats,”³⁵⁰⁷ and according to some population studies, those who eat spicier foods tend to gain less weight. This has led researchers to conclude that “regular and higher chilli consumption may provide a low cost and simple strategy to reduce the incidence of overweight and obesity.”³⁵⁰⁸ But you don’t *really* know until you start feeding people some peppers.

Remember how you can point a thermography camera at someone and see the area above their collarbones light up when you plunge their extremities into ice water as their brown fat revs up? The same happens if you skip the ice and just feed people a chili pepper extract.³⁵⁰⁹ If you give people 2 mg of purified capsaicin, which is about what you’d find in a jalapeño pepper³⁵¹⁰ or a half teaspoon of red pepper powder,³⁵¹¹ you can potentially increase the rate at which they burn calories by up to 150 calories a day.³⁵¹²

The reason we know this metabolic boost is from the ignition of brown fat is because capsaicin-like compounds only seem to work in people with active BAT deposits.³⁵¹³ Even if yours are lying dormant, cold can not only light up the brown fat you have but also recruit its formation in the first place—and chili peppers appear to do the same thing.³⁵¹⁴ Eight weeks of consuming chili pepper extracts boosted both BAT activity and density by almost 50 percent.³⁵¹⁵ Even just six weeks of taking in chili pepper compounds can so bulk up our BAT that we can get a tenfold increase in cold-induced heat generation.³⁵¹⁶ The researchers concluded that their findings could contribute to “developing practical, easy, and effective antiobesity regimens.”³⁵¹⁷ These studies used straight capsaicin or purified extracts so they could hide it in a pill to pit them head-to-head against sugar pill placebos. What about using the whole pepper?

Normally, diet-induced thermogenesis—the extra calories you burn after a meal to digest it—just bumps up your metabolic rate by about 10 percent. Add some red pepper powder to that meal, however, and you can bump up the rate at which you burn calories immediately afterward by more like 30 percent.³⁵¹⁸ The original pepper powder studies were done in Japan, though, where men³⁵¹⁹ and women³⁵²⁰ happily sprinkled two tablespoons of red pepper powder onto a meal, so people with less affinity for spice might not find it as nice.

Some Like It Hot

Chili pepper may be one of the world's most popular spices, but it's enjoyed more in some places than others.³⁵²¹ In Mexico, for example, studies consider anyone eating less than the equivalent of three jalapeño peppers per day as “low-level consumers,” whereas high consumers averaged nine to twenty-five jalapeño peppers' worth of capsaicin daily.³⁵²² In contrast, in the United States, only about one in ten individuals eats peppers of any kind on a daily basis.³⁵²³ So researchers in Indiana sought to determine if a red pepper dose “hedonically acceptable” to Americans would still have an effect.

Instead of two tablespoons, the researchers tried ten times less—about a half teaspoon of cayenne pepper—and mixed it into tomato soup. Over the next four and a half hours, those who had eaten the spicy tomato soup burned about ten more calories than those who had had the unspiced soup.³⁵²⁴ Since cayenne has essentially zero calories, the spicy group ended up with a relative calorie debt, but ten measly calories is hardly anything to write home about. But that's not the end of the story.

Two years later, a study was published in the Netherlands that reignited interest in the use of chili peppers for weight loss. The researchers started by cutting everyone's caloric intake by 20 percent, which is typical for those on portion-controlled diets. It's the equivalent of removing 500 calories out of a 2,500-calorie day. Your body doesn't like that and tries to compensate, for example, by slowing your sleeping metabolic rate. So, in reality, cutting 20 percent of calories only results in a 16 percent calorie deficit. You may have cut out 500 calories, but since your body is able to make some of that up by slowing your metabolism enough to burn 100 fewer calories, you end up only being down 400 calories by the next morning. The study subjects then were randomized into one of two groups: those who got capsules containing one-half teaspoon of cayenne pepper with each meal or those who got placebos.³⁵²⁵

Both groups had 20 percent of calories cut from their diets, but while the bodies of those in the placebo group successfully compensated that reduction down to only a 16 percent deficit, those who had unknowingly ingested the cayenne experienced the full 20 percent drop. The red pepper powder counteracted the body's attempts to ratchet down the metabolism to slow the weight loss. Indeed, the cayenne group woke up the next morning with nineteen fewer grams of body fat, whereas the placebo group had only lost fourteen.³⁵²⁶ That's about a thick pat of butter's worth of difference, which may not seem like much on any given day, but could add up over time. A study where researchers openly sprinkled red pepper onto people's meals—in tomato juice for breakfast and then in pâté and pizza—experienced a similar benefit.³⁵²⁷

Fire in the Belly

A meta-analysis of studies on capsaicin, whether in extract or pepper form, found that overweight individuals burned, on average, about an extra seventy calories a day compared to those in the control groups.³⁵²⁸ At the same time, taking capsaicin-like compounds before a meal may actually decrease caloric intake, so it may help from both sides of the energy-balance equation.³⁵²⁹ No wonder capsaicin has been referred to in the medical literature as an “anti-obesity drug,”³⁵³⁰ a “spicy solution to the management of obesity.”³⁵³¹ But does it work long term?

The supplement data are mixed. Some randomized, double-blind, placebo-controlled trials using pepper extracts found a benefit in terms of significantly enhanced loss of abdominal fat over time,³⁵³² but others did not.³⁵³³ Even if the extracts the researchers used contained the right mixture of active ingredients, it's possible some of the effect is mediated by nerve signals coming off our tongues or stomachs.³⁵³⁴ This would explain why capsaicin supplements that do not dissolve and open up until they're well into the intestine don't appear to work as well.³⁵³⁵ However, findings from the whole pepper powder studies are inconsistent too.

In an Australian study, where participants were switched between bland and spicy diets, the subjects didn't lose any relative weight in the month they had been adding chili powder to their meals.³⁵³⁶ A subsequent study in Korea, however, did find a benefit. CT scans revealed significant reductions in visceral fat among those randomized to use Korean chili paste (*kochujang*, a signature component of bibimbap) compared to a placebo paste that evidently looked, tasted, and smelled the same, but had no actual peppers. To accomplish this, however, the researchers had to manipulate the ratios of some of the other ingredients in the placebo paste, such as the salt and soybeans, so other factors may have crept in. Study duration may have also played a role. The twelve-week Korean study lasted three times longer than the Australian study, perhaps allowing time for BAT levels to ramp up sufficiently.³⁵³⁷

A nice thing about studies on healthy foods is that even if there are conflicting data about the specific benefits for a particular malady, these foods are by definition healthful. So, with no downsides, I figure you might as well give them a try. But is that the case for chili peppers? Capsaicin has been put to the test as an ergogenic (performance-enhancing) aid and appears to help both with running performance³⁵³⁸ and strength training.³⁵³⁹ but what about effects on chronic disease? Do people who eat red hot chili peppers live longer?

Apparently so. The diets of more than sixteen thousand people across the United States were tracked for nearly twenty years. Over that time, one in three passed away—but they were among those who reported they did *not* eat chili peppers. Over that same period, only one in five chili-pepper eaters died.³⁵⁴⁰ That's significantly lower overall mortality, but it doesn't necessarily mean the peppers had anything to do with it.

Remember the Hispanic paradox³⁵⁴¹ I discussed in the Rich in Legumes section, where despite having on average less education, a higher poverty rate, and worse access to health care,³⁵⁴² Hispanics and Latinos in the United States have a 24 percent lower risk of premature death compared to Caucasians?³⁵⁴³ That translates into Hispanic men and women living about seven years longer than non-Hispanic black Americans and three years longer than non-Hispanic white Americans.³⁵⁴⁴ Latino longevity has been chalked up to their eating up to four to five times more beans,³⁵⁴⁵ which have been a staple among all the longest-living populations in the world³⁵⁴⁶ and have been called “the most important dietary predictor of survival.”³⁵⁴⁷ Is it possible that chilis are just being added more often to beans than burgers, and that explains the apparent pepper protection?

Apparently not. The chili pepper longevity study controlled for race and ethnicity, and adjusted for other dietary factors, such as fruit, vegetable, and meat intake, as well as income, education, alcohol, and exercise.³⁵⁴⁸ A similar study in China that followed hundreds of thousands of individuals confirmed that those who eat spicy food more frequently do appear to lower their risk of premature death, attributed to the “anti-obesity, antioxidant, anti-inflammatory, and antihypertensive effects of spicy foods.”³⁵⁴⁹

As the saying goes, *good peppers burn twice*, but are burning our butts or freezing our bodies our only two options for boosting brown fat? Thankfully, there are a variety of structurally similar flavor molecules in other foods that can go to BAT for us.

Ginger

Ginger has been used in India and China to treat disease for thousands of years,³⁵⁵⁰ but both the Chinese and Indian systems of medicine also prescribed mercury,³⁵⁵¹ so there's only so much that “traditional use” can tell us. That's why we have science.

Randomized, double-blind, placebo-controlled trials have found ginger to be effective for treating morning sickness³⁵⁵² and migraine headaches,³⁵⁵³ as well as reducing cholesterol, triglycerides,³⁵⁵⁴ blood sugars,³⁵⁵⁵ and signs of inflammation.³⁵⁵⁶ What about fat burning? There are weight-loss reviews in the medical literature with titles like “Beneficial Effects of Ginger ... on Obesity...” that sound promising. It's only after you hand over the thirty-eight

dollars to buy access to the paper that you may realize disappointedly they're mostly talking about the effects on fat rats. The authors suggest the lack of clinical studies is due to factors such as "ethical issues [and] limited commercial support."³⁵⁵⁷ The limited commercial support I can see. Ginger is dirt cheap, so who's going to pay for such studies? But ethical issues? We're just talking about feeding people some ginger. Maybe they think it would be unethical to deprive the people in the control group of ginger yumminess.

Cross-sectional studies, where you take a snapshot in time of ginger consumption and body weight within a population, are relatively inexpensive to conduct. One such study in China found that those who are obese do seem to eat less ginger, which the investigators felt "demonstrated that the use of ginger could have relevance for weight management." But maybe ginger consumption is just a marker of a more traditional, less Westernized diet.³⁵⁵⁸

A randomized controlled trial was performed to assess the effects of having a "hot ginger beverage"—two grams of ginger powder stirred into a cup of hot water—with breakfast. That's about a teaspoon of ground ginger, around five cents' worth. Over the next few hours, those in the ginger group reported feeling significantly less hungry than those who had been given plain hot water instead.³⁵⁵⁹ Obviously, the study subjects knew which group they were in, so part of the response may have just been the placebo effect, but not all the effects described were subjective. Four hours after breakfast, the metabolic rate in the ginger group was elevated compared to control.³⁵⁶⁰

What happens when subjects don't know if they're getting a placebo or the real deal? When hidden inside capsules, a half teaspoon's worth of powdered ginger can increase the rate at which our bodies burn fat by about 10 percent two hours after consumption compared to placebo capsules. This only seemed to work in the morning, though. The same amount of ginger given in the afternoon did not appear to have the same effect.³⁵⁶¹ Surprisingly, dried ginger may work better than fresh.³⁵⁶² When ginger is dried, some of the gingerol compounds turn into shogaols (from the Japanese word for *ginger*), which may be even more effective at activating brown fat.³⁵⁶³ Indeed, fresh ginger at breakfast did not appear to affect metabolism at all.³⁵⁶⁴

Human trials with grains of paradise, an African plant in the ginger family, demonstrate that the boost in metabolism is indeed through brown fat activation,³⁵⁶⁵ which can then lead to a drop in visceral body fat.³⁵⁶⁶ We don't have to search for grains of paradise, though, because plain old ginger spice will do.

Bottom line: Putting together all the randomized controlled trials of ginger powder, two to twelve weeks of a quarter teaspoon to one and a half teaspoons a day of ground ginger significantly decreased body weight for just pennies a day.³⁵⁶⁷ And the side effects?

I searched in vain for downsides to ginger consumption and didn't find any, other than "ginger paralysis."³⁵⁶⁸ What?! That doesn't sound good. In 1930, thousands of Americans were poisoned by purportedly drinking ginger extract. First of all, who drinks ginger extract? Well, it was 1930, during Prohibition, so ginger extract was a way to sneak a little alcohol. Little did folks realize that the bootleggers had been taking advantage of the demand by swapping in a ginger substitute, a varnish chemical called *triorthocresyl phosphate*, in order to make greater profits.³⁵⁶⁹ So actual ginger is fine. The moral of the story is don't drink varnish.

Cinnamon

Cinnamon is another spice with some heat that can cause browning of white fat cells in a petri dish and the slimming of mice in a lab,³⁵⁷⁰ but what about in people? Is it all cinnamon bark and no cinnamon bite?

A number of studies have put cinnamon to the test for a variety of maladies. Did the study subjects happen to lose weight in the process? Eight weeks of about a half teaspoon

of cinnamon a day (stuffed into capsules) caused about a pound of weight loss in a group of women suffering from polycystic ovary syndrome.³⁵⁷¹ In a group of type 2 diabetics, just about a third of a teaspoon a day for twelve weeks caused four pounds of weight loss over placebo, and, as a bonus, their blood sugar control and cholesterol also improved.³⁵⁷² Another study on diabetics using triple the dose, however, failed to find a weight-loss benefit.³⁵⁷³ A longer study—sixteen weeks with subjects getting about a teaspoon of cinnamon a day—resulted in about seven pounds of weight loss and a two-inch-slimmer waist, with improvements in blood sugars and pressures, cholesterol, and triglycerides.³⁵⁷⁴ However, at least a half dozen other studies failed to show any significant change in weight with cinnamon supplementation.^{3575,3576,3577,3578,3579,3580}

It's not clear why some studies found a weight-loss benefit and others didn't, but it can't hurt to sprinkle some cinnamon on your oatmeal every morning. Just make sure to choose *real* cinnamon (also known as *Ceylon cinnamon*), not cassia cinnamon (also known as *Chinese cinnamon*). In the United States, if it doesn't specify *Ceylon* on the label, it's probably cassia, which, as I described in *How Not to Die*, has too much coumarin for comfort. A single daily teaspoon of cassia cinnamon could exceed the safety limit for liver toxicity risk in an adult, and even a quarter teaspoon may be too much for a small child.³⁵⁸¹ So make sure it says *Ceylon* on the label, and then sprinkle to your heart's desire.

Peppermint

What about a cooling compound like the menthol in mint? The same receptor in the body that is activated by cold temperatures is also activated by menthol.³⁵⁸² Studies on fat biopsies taken from people during surgery discovered that these cold receptors are found on our fat cells. What's more, when they are activated by menthol, they can be "browned" into burning fat in a petri dish.³⁵⁸³ This discovery led to the 2016 proposition that chronic, menthol-induced browning "could provide a promising novel therapeutic approach for increasing energy expenditure, regulating body weight, and preventing obesity."³⁵⁸⁴

It works in mice.³⁵⁸⁵ Mimicking long-term cold exposure with dietary menthol can prevent obesity in rodents. What about in us? While giving people more than ten cups of peppermint tea's worth of menthol a day didn't appear to significantly raise their metabolic rate, rubbing the same amount on their skin did.³⁵⁸⁶ Our livers rapidly modify the menthol we eat to remove it from the body. The tobacco industry found a not-so-Kool way to skirt the liver by selling menthol cigarettes to provide a purported edge in weight control,³⁵⁸⁷ but topical application may have a similar effect, allowing more menthol to circulate throughout the body before getting metabolized. Research subjects who applied a gel that contained about a half teaspoon of peppermint essential oil's worth of menthol got a significant rise in resting metabolic rate within hours.³⁵⁸⁸

Menthol had been used for medicinal purposes for thousands of years before the menthol receptors in our bodies were discovered.³⁵⁸⁹ The reason sports injuries are often iced is to reduce the swelling by reducing blood flow to the area. When our skin is exposed to cold, our bodies clamp down on blood flow to prevent heat loss, and the same happens when we apply menthol. Researchers found that applying about three-quarters of a teaspoon of a 3.5 percent menthol gel on someone's forearm can reduce blood flow as much as applying a cold pack of crushed ice. Not only was the menthol less uncomfortable than the ice pack,³⁵⁹⁰ it has also been shown to work better in reducing muscle soreness after a tough workout.³⁵⁹¹

Topical menthol has also been found to work for chronic pain (carpal tunnel syndrome in slaughterhouse workers³⁵⁹²) and migraine sufferers (rubbed on the forehead and temple of the affected side³⁵⁹³), but what about weight loss? It works in rats.³⁵⁹⁴ Rub rodents with menthol, and their metabolic rates go up and they gain less weight. Unfortunately, it has never been tested in people. If you want to give it a try, menthol concentrations up to 16

percent are considered safe for topical application.³⁵⁹⁵ Since peppermint essential oil is comprised of one-third to one-half pure menthol,³⁵⁹⁶ you could safely add a tablespoon to a quarter cup of your favorite hand lotion or massage oil. Allergic reactions or skin irritation to menthol is rare,³⁵⁹⁷ and no serious adverse effects have been filed with the FDA.³⁵⁹⁸ However, that is not the case with other “cooling” chemicals such as methyl salicylate (oil of wintergreen) or camphor (found in products like Bengay and Tiger Balm), which can cause serious, even life-threatening, reactions when used improperly.³⁵⁹⁹ So I advise you to stick to menthol-only preparations.

Any other herbs out there with potential?

Cannabis

Pop culture often depicts marijuana users as a “sluggish, lethargic, and unproductive subculture of compulsive snackers,”³⁶⁰⁰ but the majority of large population studies have found that pot smokers actually tend to be thinner.³⁶⁰¹ You might be thinking, *But what about the munchies?* Even a single dose of marijuana has been found to increase food intake.³⁶⁰² In fact, the first documented medical use of cannabis, dating back over a thousand years, was as a treatment for loss of appetite.³⁶⁰³ Today, THC, the main psychoactive component of cannabis, is FDA-approved as an appetite stimulant and has been shown to help slow the wasting syndrome associated with AIDS.³⁶⁰⁴

When young, healthy individuals were put in a live-in laboratory setting with all-you-can-eat cake, cookies, Doritos, and other snacks, they gained as much as six pounds over six days smoking joints four times a day. They then lost that weight after they were switched to placebo joints made with cannabis that had had the THC removed.³⁶⁰⁵ If cannabinoids like THC can cause weight gain, Big Pharma figured cannabinoid-blocking drugs might be able to cause weight loss.

In 1973, scientists discovered that we have specific receptors in our brains for opioid drugs like heroin and morphine.³⁶⁰⁶ Since we didn’t evolve shooting up dope, it stood to reason there were natural compounds produced by our bodies that fit into those receptors. Scientists went looking and discovered we did indeed make endogenous morphines, or *endorphins* for short. In 1990, scientists discovered that we also have specific receptors in our brains for marijuana compounds, cannabinoids like THC.³⁶⁰⁷ Since we didn’t evolve taking up either, it stood to reason there were natural compounds produced by our bodies that fit into *those* receptors. This led to a similar discovery: Our brains make endogenous cannabinoids, or endocannabinoids.

Drug giant Sanofi-Aventis designed a drug called *rimonabant*, which was sold as Acomplia, to block these endocannabinoid receptors to suppress appetite, and it worked. People lost about ten more pounds on the drug compared to placebo over a six- to twelve-month period.³⁶⁰⁸ However, the drug also made some people want to kill themselves, which led to its hasty removal from the market for its serious psychiatric side effects.³⁶⁰⁹ Our bodies make their own endocannabinoids for a reason.

If cannabis is so good at stoking our appetites, why do regular users tend to be skinnier on average? It does not appear to be due just to concurrent tobacco use.³⁶¹⁰ The boost in appetite may be outweighed by the boost in metabolism.³⁶¹¹ We’ve known for more than forty years that our metabolic rates shoot up by about 25 percent within fifteen minutes of lighting up a joint and stay there for at least an hour.³⁶¹² This may be due in part to the activation of endocannabinoid receptors found on brown fat cells.³⁶¹³ Unfortunately, there have yet to be any formal weight-loss trials to put cannabis to the test.

Those considering cannabis for weight loss should familiarize themselves with the balance of risks and benefits. On NutritionFacts.org, I have a twenty-part video series that takes a deep dive into the topic. In short, while there is little evidence to support an association between cannabis use and the two main concerns linked to smoking tobacco—

lung cancer and emphysema³⁶¹⁴—using cannabis can result in addiction, chronic bronchitis, and altered brain development, and may increase the risk of schizophrenia.³⁶¹⁵

Marijuana liberalization has also led to an increase in the incidence of a rare condition known as *cannabinoid hyperemesis syndrome*,³⁶¹⁶ which is believed to be caused by long-term heavy use of high-potency cannabis.³⁶¹⁷ Characterized by intractable vomiting relieved by hot-water immersion, resulting in some sufferers ending up in the shower for hours a day, it's thought to be caused by a numbing of the same thermoreceptors we've been talking about due to an overload of cannabis stimulation.³⁶¹⁸ This realization has led to the successful topical use of a capsaicin cream—in effect, treating fire with fire—to help mediate the debilitating disease. Bottom line? There are safer ways to boost brown fat. If cannabis is not your cup of tea, then next up to BAT? You guessed it: a cup of tea.

Tea

Brewing Evidence

Simply drink a cup of tea, and, within an hour, you may be burning up to 10 percent more calories.³⁶¹⁹ Drink four cups of tea in the twenty-four hours before a thirty-minute walk, and you burn an extra gram of fat during your half-hour stroll.³⁶²⁰ Take about ten cups' worth in the form of green tea extract supplements the day before thirty minutes of cycling, and burn an extra two grams of fat.³⁶²¹ So is this just from the caffeine naturally found in tea, or is something else at work?

Researchers randomized people to one of three groups: getting either the equivalent of a cup of tea with every meal, just the amount of caffeine in the tea, or a placebo with neither tea nor caffeine. The caffeine alone didn't seem to have any effect, but having tea three times a day raised the number of calories burned in that twenty-four-hour period from about 2,280 to 2,360, around 80 calories more.³⁶²² And tea without anything added has practically zero calories, so based on these findings, tea may be thought to have “negative” calories. In effect, each cup of tea swept away about 25 calories.

Interventional studies putting around three to six cups' worth of daily green or oolong tea to the test showed an average metabolic boost of about one hundred calories a day, shaving off three butter pats' worth of extra fat every day.³⁶²³ Tea only seems to work half as well as ephedra,³⁶²⁴ but unlike the drug, tea hasn't chalked up eighteen thousand cases of adverse events or killed any professional baseball players.³⁶²⁵

Although more than two thousand compounds have been identified in tea leaves, most attention has been paid to a family of antioxidants called *catechins*, such as *EGCG*.³⁶²⁶ This is because even straight EGCG has been shown to boost metabolism and the rate at which fat is burned at rest.³⁶²⁷ That is one reason most of the spotlight has been on green, white, and oolong teas, as they have about five times more EGCG than black tea.³⁶²⁸

Originally, we thought this stimulant effect was due to tea compounds keying up our metabolisms by inhibiting an enzyme that degrades adrenaline in the body.³⁶²⁹ This was based largely on test-tube studies, though, using EGCG concentrations higher than what you might expect to reach in your bloodstream.³⁶³⁰ Green tea can boost metabolism without raising heart rate³⁶³¹ and, if anything, reduces blood pressure a bit—both of which are inconsistent with an adrenaline rush.³⁶³² Indeed, when put to the test in people, the adrenaline-eating enzyme wasn't suppressed after all,³⁶³³ calling the whole theory into question.³⁶³⁴ More likely, what's causing this reaction is the BAT signal.

A brown fat effect could help explain the variability in weight-loss responses. In one study, for example, overweight women randomized to about a half teaspoon of green tea powder a day lost an average of twelve pounds more than the placebo group over eight weeks. But, even the twelve-pound difference didn't reach statistical significance because there was such a wide range of responses.³⁶³⁵ Could it be that some individuals started out with more brown fat than others? In a petri dish, tea compounds like EGCG can induce the

browning of white fat cells to beige³⁶³⁶ and green tea extracts have been shown to reduce shivering under cold conditions,³⁶³⁷ but BAT activation from tea wasn't proven until 2016.

Like cold and capsaicin, tea only acutely boosted metabolism in those with active BAT deposits,³⁶³⁸ and furthermore, could recruit the formation³⁶³⁹ and activation of additional brown fat over time.³⁶⁴⁰ It didn't work as well as some of the cold experiments, but drinking tea, the researchers concluded, may be an "easier and more convenient treatment than chronic cold exposure."³⁶⁴¹ But does it get us to lose weight?

Choose Unleaded

China burns about half of the world's coal, spewing toxic heavy metals such as mercury and lead into the atmosphere. Even if you don't live in China or eat any food produced there, you could still be exposed to mercury that settles in the oceans if you eat fish and other seafood, or be exposed to lead if you drink something from China: tea.³⁶⁴²

Beyond the mercury from its coal plants to its tea plants, China didn't ban leaded gasoline until the year 2000, which is reflected in the fact that lead levels on Chinese tea plantations are highest closest to highways.³⁶⁴³ How can you limit your exposure? Just as longer-living fish accumulate more mercury, longer-living leaves accumulate more lead.³⁶⁴⁴

Young tea leaves appear to have two to six times less lead than mature leaves,³⁶⁴⁵ so the younger leaves that are used to make green tea and white tea have significantly less lead than the older leaves used to make black and oolong teas. Furthermore, the lead in black and oolong teas appears to be released much more readily into tea water when brewed. Only 7 percent of the lead in green tea leaves leaches into hot water, compared to more than half in the darker varieties. Combining all these factors, the health risk from heavy metals is approximately one hundred times lower for green tea compared to oolong and black.³⁶⁴⁶

Since certain fungicides may have heavy metal impurities, one might assume organic teas would be less contaminated,³⁶⁴⁷ but in a study of thirty common teas off North American store shelves, there did not seem to be less toxic element contamination in organic versus conventional tea.³⁶⁴⁸ In terms of lead, the country of origin may be the most important factor. Based on the most stringent safety limits in the world,³⁶⁴⁹ such as California's Proposition 65 parameters, and the largest studies of tea leaf contamination in two of the largest tea-exporting countries, this is what I was able to come up with:³⁶⁵⁰

Safe Level of Tea Consumption

	Chinese Green Tea		Chinese Black Tea		Japanese Green Tea	
	Drinking (cups/day)	Eating (teaspoons/day)	Drinking (cups/day)	Eating (teaspoons/day)	Drinking (cups/day)	Eating (teaspoons/day)
Non-Pregnant Adult	>10	3	3	2	>10	(8)
70-Pound Child	(4)	1	1	0	(4)	(2)
During Pregnancy	1	0	0	0	(4)	0

If you're not pregnant and just *drinking* green tea, from a lead standpoint, it doesn't matter where you source your tea. Given the average levels of lead in Chinese black tea samples, however, more than three cups a day would exceed the most conservative daily safety limits for lead. That's if you're just drinking brewed tea and throwing away the tea leaves or tea bag. If you're actually eating the leaves, like drinking powdered green (matcha) tea or throwing tea leaves into your smoothie like I do, I wouldn't use more than two or three heaping teaspoons a day unless your tea is sourced from Japan. The parenthetical numbers in the chart indicate caution only from a standpoint of caffeine limit, rather than that of any sort of contamination.

If you're the weight of an average ten-year-old, lead still isn't a problem when drinking green tea, but the safe caffeine intake for children is more restrictive. I wouldn't add more than two spoonfuls of Japanese green tea to a child's smoothie due to the caffeine or more than one spoonful of Chinese green tea because of the lead. Similarly, I

wouldn't like to see children drinking more than one cup of black tea a day and wouldn't want them eating the leaves at all.

Pregnant women should be able to drink a cup a day of green tea throughout pregnancy, regardless of source, based on average tea lead levels. The cap for Japanese green tea is really just the suggested American College of Obstetrics and Gynecology's 200 mg per day caffeine limit.³⁶⁵¹ I wouldn't recommend drinking black tea during pregnancy at all, though, or eating any kind of tea leaves unless you know you're getting tea from a low-lead source.

Weak Tea

A shallow survey of the medical literature might leave one with the impression that tea is more effective at inducing weight loss than it actually is. Case in point: a study published in the journal *Clinical Nutrition* in 2016. Researchers reported in the abstract that the green tea preparation they used "resulted in significant weight loss" and "reduced waist circumference."³⁶⁵² The abstract of a scientific paper is a concise summary listing all the important findings, and it's often the only part of a study people read since the rest of the paper can be concealed behind a paywall, as it was in this case. Only after shelling out \$35.95 to read the paper in its entirety would you learn the truth: Technically, the green tea supplements did result in significant weight loss and a slimmer waist, but the placebo pills did *better*. Those taking capsules filled with cellulose (essentially purified sawdust) instead of green tea lost more weight and waistline than the green tea group.³⁶⁵³ That's why you always have to read the entire study (or just have me do it for you).

There certainly are studies showing impressive results, like fifteen pounds of weight loss over placebo for about three cups' worth of green tea a day for three months.³⁶⁵⁴ Part of that may be the metabolic boost on the calories-out side of the equation, but improved satiety after a meal with green tea, compared to plain hot water, may also be helping out on the calories-in side.³⁶⁵⁵ If you feed two groups of people the exact same diets, but one gets tea and the other does not, would you still see a benefit? Researchers randomized obese sedentary individuals to two thousand calories a day with either a green tea extract supplement equivalent to about a half cup of tea at each meal or an indistinguishable placebo. Within eight weeks, those in the green tea group were down an average of ten pounds compared to about four pounds in the placebo group. Given the identical diets and no significant change in exercise, this suggests the primary green tea benefit is from burning more calories, which was confirmed by calorimetry. The green tea resulted in a significantly higher resting metabolic rate.³⁶⁵⁶

However, after putting all the weight-loss studies together, meta-analyses seem split between statistically insignificant weight loss³⁶⁵⁷ or clinically insignificant weight loss, an average of about three pounds over twelve weeks.³⁶⁵⁸ Green tea seems less magic bullet and more BB gun pellet, but a pound a month may be worth it for something that's healthy anyway. After nearly five thousand years of tea drinking,³⁶⁵⁹ science has finally caught up and shown green tea can lower cholesterol³⁶⁶⁰ and prevent colon polyps.³⁶⁶¹ You can even gargle with it to help prevent the flu.³⁶⁶² And a meta-analysis of observational studies where tea-drinking populations were followed over time shows consumption of green or black tea is associated with living a significantly longer life.³⁶⁶³

What About Green Tea Extract Supplements?

A head-to-head comparison between brewed green tea and green tea extract supplements found a similar amount of weight loss over the control group over an eight-week period.³⁶⁶⁴ Those randomized to drink the tea lost six pounds, while those randomized to take the supplements lost four pounds, so why not just take the pills? First of all, because the supplement industry is so poorly regulated, you never know what you're getting. There are supplements on the market that list green tea as an ingredient on the label, but when tested, didn't appear to contain any at all.³⁶⁶⁵ Even if supplements are labeled accurately, the fillers may bind to the active components and reduce bioavailability,³⁶⁶⁶ or the capsule shell may not disintegrate properly.³⁶⁶⁷ This may help explain why, in

cholesterol-lowering trials, for example, green tea in beverage form worked, but green tea in supplement form did not.³⁶⁶⁸ More concerning, though, are the side effects.

Twelve years ago, when I first started producing videos about cases of liver toxicity tied to green tea extract supplements, it was thought to be rare, on the order of one in one hundred thousand.³⁶⁶⁹ Now that we have large studies like the Minnesota Green Tea Trial, we realize it may be more like one in twenty. In contrast, not a single liver problem has been reported in any of the trials that used green tea in regular beverage form.³⁶⁷⁰ Even in Japan, where nine cups a day is not uncommon,³⁶⁷¹ adverse effects have not been reported.³⁶⁷² An incredible five billion kilos of tea are produced worldwide annually, enough for more than two trillion cups of tea a year.³⁶⁷³ I think we'd know if just drinking tea could cause liver issues.

Another problem with supplements may be the dose.³⁶⁷⁴ Some studies used extract supplement regimens equivalent to drinking more than forty cups of tea a day.³⁶⁷⁵ To be on the safe side, I recommend enjoying tea in beverage—not pill—form. I encourage people to stay away from green tea extract supplements, but if you do take them, please stick to less than 300 mg EGCG a day³⁶⁷⁶ and stop immediately if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or yellowing of the skin or whites of the eyes (jaundice).³⁶⁷⁷

Not Milk?

Both green and black teas have been shown to improve artery function within hours of consumption.³⁶⁷⁸ Why then in population studies is green tea consumption associated with lower heart disease risk than black tea?³⁶⁷⁹ In two British studies, in fact, tea consumption was associated with an *increased* risk of coronary artery disease.^{3680,3681} Is it because Brits tend to drink their tea with milk, whereas green tea is typically taken straight? If only there were a country that drank black tea, but without milk. There is—the Netherlands. And in those studies, black tea was associated with the same drop in risk as the green tea studies.^{3682,3683} So maybe it has something to do with the milk.

Researchers found the addition of milk “completely prevents the biological activity of tea.”³⁶⁸⁴ Both the artery function benefits and the thermogenic calorie-burning effects were inhibited by casein, a protein in milk that apparently wraps itself about the catechins and blocks their function.³⁶⁸⁵ (Interestingly, this is presumably the same mechanism by which adding milk to tea can reduce teeth staining.³⁶⁸⁶) Milk protein also undercuts the benefits of berries,³⁶⁸⁷ chocolate,³⁶⁸⁸ and coffee.³⁶⁸⁹

What about soy milk? In a test tube, coffee phytonutrients bind not only to dairy proteins but also to egg and soy proteins.³⁶⁹⁰ Eggs haven't been put to the test in people, so we don't know yet if having an omelet with black coffee would impair absorption, but soy has been given the all-clear.³⁶⁹¹ Soy proteins do initially bind up the coffee compounds in the small intestine, but then our good bacteria release them so they can be absorbed down in the lower intestine.³⁶⁹² Almond-, rice-, oat-, and coconut-based milks have so little protein that I'd assume binding would not be a problem, but they have yet to be directly tested.

When the original milk-blocking study on tea was published, the European Society of Cardiology suggested people consider skipping the creamer, noting the protective cardiovascular effects are “totally wiped out by adding milk.”³⁶⁹³ This advice did not go over well. “As doctors,” read one letter to the medical journal editor, “we would not prescribe a new drug to patients if it was studied only in one small study. In analogy, milk abstinence should not be recommended to tea drinkers on the basis of evidence of similar strength.”³⁶⁹⁴ The researchers replied that the effect was so great—milk didn't just reduce the benefit but “completely blunted the effects of tea”—that they didn't need to do a large study.³⁶⁹⁵ As far as I'm concerned, the reason we don't prescribe drugs without overwhelming evidence is that drugs can kill. In fact, prescription drugs kill an estimated 106,000 Americans every year,³⁶⁹⁶ so the benefits better outweigh the risks. But what's the downside of a little milk abstinence?

Coffee

In the Black

What About Green Coffee Extract

Green coffee extract is a supplement made from green (unroasted) coffee beans.³⁶⁹⁷ Advertised as a miracle weight-loss cure, it was hyped by Starbucks and TV doctors citing a study that found remarkable results³⁶⁹⁸—a randomized, double-blind, placebo-controlled, crossover trial that reported an average of eighteen pounds of weight loss over placebo within six weeks.³⁶⁹⁹ Sadly, the too-good-to-be-true study turned out to be too good to be true. It was a disgraceful fraud. Though the lead “researchers” claimed no conflicts of interest, it seems they were glorified ghostwriters handed falsified data, bought and paid for by the supplement manufacturer.³⁷⁰⁰

The company was fined millions by the Federal Trade Commission for making false claims,³⁷⁰¹ and the study has since been retracted.³⁷⁰² There have been a few other studies on different green coffee extracts that suggest modest weight-loss benefits,^{3703,3704,3705} but the field has been so tarnished by the scandal that green coffee may forever remain branded a cautionary tale on the corrupting power of commercial influence in medicine.

We’ve known for more than a century that caffeine can boost our metabolisms.³⁷⁰⁶ But what about that tea study where a cup with every meal raised the metabolic rate, yet the same amount of caffeine alone did not? That’s probably because even black tea usually has less than 50 mg of caffeine per cup, and it typically takes at least 100 mg of caffeine, about the amount found in a typical cup of coffee,³⁷⁰⁷ to have a thermogenic effect.³⁷⁰⁸ In fact, that’s where caffeine got its name—from the German word for coffee, *kaffee*.³⁷⁰⁹

Give people about four cups of coffee’s worth of caffeine and they burn about two extra spoonfuls of fat from an hour of cycling.³⁷¹⁰ Is that just because they pedaled harder, though? Caffeine can make exercise seem less difficult and more enjoyable.³⁷¹¹ Runners randomized to drink coffee shaved about six seconds off their mile,³⁷¹² for example, and weightlifters randomized to coffee were able to squat more weight, worth about six hundred more pounds of reps.³⁷¹³ The cycling workout was standardized, however, so the extra fat loss wasn’t just because the caffeine group pedaled faster.³⁷¹⁴

The metabolic boost also occurs at rest. Drink two cups of coffee, and over the next few hours, your resting metabolic rate goes up about 10 percent.³⁷¹⁵ In fact, you can tell whether someone had just consumed coffee by measuring the heat coming off their skin. Two hours after drinking two cups of coffee, our skin temperatures rise by about half a degree.³⁷¹⁶

On average, every cup of coffee may cause you to end up burning seventeen extra calories.³⁷¹⁷ Since a cup of black coffee only has about two calories,³⁷¹⁸ that leaves a net deficit of fifteen calories per cup. But only a third of U.S. coffee consumers drink their coffee without cream or sugar.³⁷¹⁹ While drinking coffee black could push your calorie ledger into the red, added creamer or caloric sweeteners could easily wipe out any benefit.³⁷²⁰ There are some Dunkin’ Donuts coffee drinks with more than a thousand calories.³⁷²¹

Drinking coffee throughout the day has been shown to burn in excess of one hundred calories,³⁷²² but might we compensate by eating more? One study found that when overweight individuals were given coffee with about 500 mg of caffeine for breakfast, they didn’t eat more throughout the day. In fact, they ate less—550 calories less.³⁷²³ A more typical appetite suppression from coffee seems to be on the order of 55 calories over the course of a day,³⁷²⁴ but with fewer calories going in and more calories going out, one might expect significant weight loss over time.

Sixteen weeks of five cups of coffee a day did lead to statistically significant decreases in body weight, but it was hardly clinically significant with less than an inch off the waist.³⁷²⁵ What about combining coffee and capsaicin? Canadian researchers tried giving people cups of coffee with meals sprinkled with about a tablespoon of red pepper powder. Appetites were suppressed and metabolisms were boosted, leaving people nearly a whopping one thousand calories down by the end of the day.³⁷²⁶ Now if they just would have eaten their meals while sitting on an ice block out in the snow ...

No trial has ever put the cayenne-and-caffeine combination to the test for weight loss, however, so we're just left with the underwhelming coffee data. So again, it comes down to whether it's healthy for you anyway. Nine out of ten North Americans consume caffeine on a daily basis,³⁷²⁷ with three billion pounds of coffee consumed annually in the United States alone.³⁷²⁸ Are there any grounds for concern?

In my chapters on liver disease, depression, and Parkinson's disease in *How Not to Die*, I discussed the benefits of coffee for the liver, mind, and brain. Coffee drinkers do seem to live longer and have lower cancer rates overall,³⁷²⁹ but coffee may worsen acid reflux disease,³⁷³⁰ bone loss,³⁷³¹ glaucoma,³⁷³² urinary issues,³⁷³³ and sleep.³⁷³⁴

We used to think as long as you didn't drink caffeine in the evening, it wouldn't affect sleep, but having the equivalent of four cups of coffee up to even six hours before bedtime can reduce total sleep time by more than an hour.³⁷³⁵ Even just two cups at 7:00 a.m. can change what our brain waves look like on EEG later that night,³⁷³⁶ indicative of shallower sleep.³⁷³⁷ It's not clear, however, if this has any clinical relevance beyond delaying the onset of sleep by an average of ten minutes.³⁷³⁸ On balance and on average, coffee consumption is more often associated with benefits than harms.³⁷³⁹

What About Energy Drinks?

If caffeine can help burn fat, what about energy drinks? The first energy drink—Dr. Enuf—dates back more than a half century, launched in 1949. Today, there are more than one hundred different brands³⁷⁴⁰ fueling a \$50 billion industry.³⁷⁴¹ Some military leaders have questioned their safety,³⁷⁴² based in part on the skyrocketing number of energy drink-related visits to the ER over recent years.³⁷⁴³ To be fair, though, if you look at some of the reports, you'll see cases like this: A 24-year-old male didn't feel well after drinking a can of energy drink ... and "3 bottles of vodka."³⁷⁴⁴ Because energy drinks are often co-consumed with other substances like alcohol, it's hard to specify the culprit.³⁷⁴⁵ That's why you have to put them to the test.

One concern that has been raised by public health advocates is increased blood pressure.³⁷⁴⁶ If you have people chug a can of Red Bull, there's no significant change in blood pressure thirty minutes later.³⁷⁴⁷ Okay, but that was just the little eight-ounce can. What about the big sixteen-ounce cans of Red Bull? Forty minutes after drinking one of those, there was still no significant change, so concerns about energy drinks raising blood pressure were dismissed as overblown³⁷⁴⁸ ... until the bomb dropped in 2014.

Red Bull did indeed significantly raise blood pressure after all. The reason the earlier studies missed it is because the spike doesn't start peaking until about an hour after consumption. And the big shocker was that blood flow in the brain took a dive. These energy drinks are promoted as having beneficial effects, but this instead suggests they're potentially harmful because of the extra workload they force on the heart and the decreased cerebral blood flow.³⁷⁴⁹

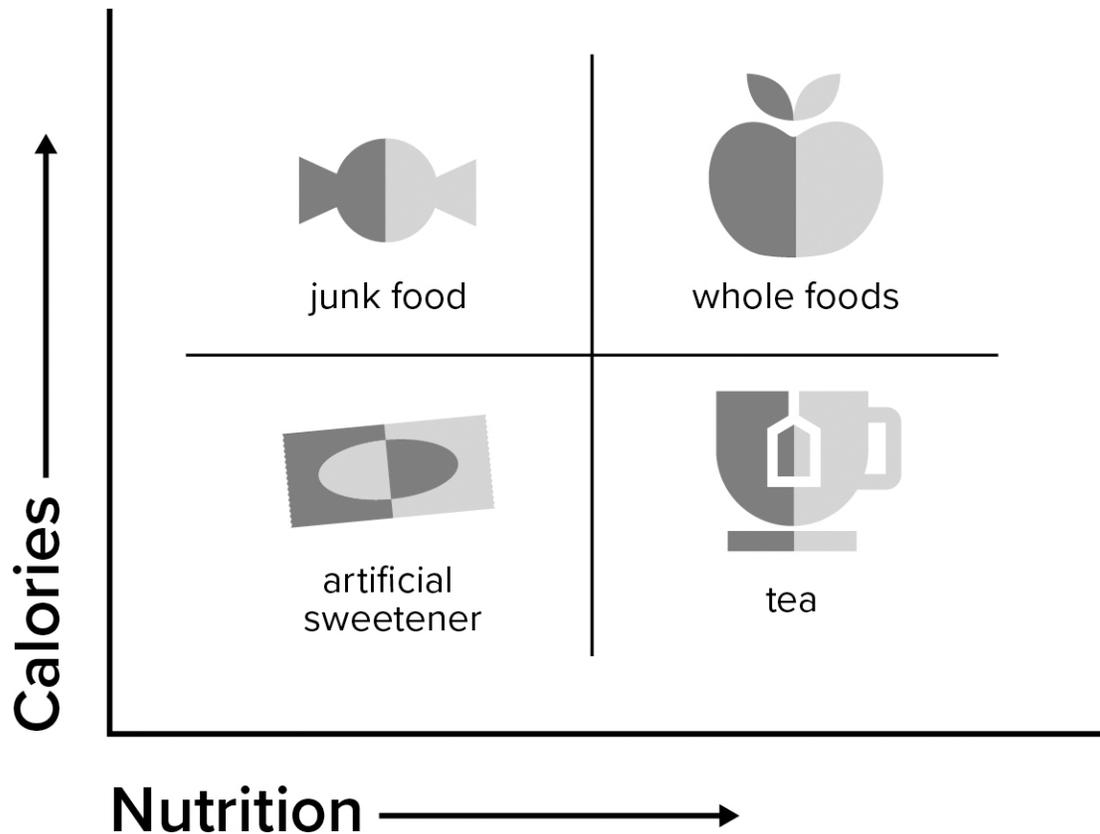
Other adverse effects of Red Bull have been found, such as an increased inflammation,³⁷⁵⁰ and that goes for other brands like Rockstar³⁷⁵¹ and Monster energy drinks too.³⁷⁵² Is it possible it's just the caffeine? Is downing an energy drink any different from having a cup of coffee? To figure that out, a study was conducted in 2017 that compared the effects of an energy drink with a plain drink with the exact same amount of caffeine.

Young, healthy volunteers were randomized to drink two large cans of either an energy drink or a control drink that had the same amount of sugar and caffeine but none of the other proprietary blend ingredients common in energy drinks, such as taurine, carnitine, ginseng, and guarana. It turns out it was *not* just the caffeine. Significantly higher blood pressures were noted on the energy drink, along with a longer "QT interval," which is an EKG finding corresponding to the time it takes for the heart to contract and then refill with blood before beginning its next beat. QT prolongation—which is what the energy drink did, but not the caffeine alone—is a recognized marker of increased risk for developing a sudden fatal heart rhythm.³⁷⁵³

Prolongation of the QT interval by more than sixty milliseconds is a marker for life-threatening arrhythmias. Though the energy drink only prolonged it by about ten milliseconds, there have been drugs pulled from the market—profitable drugs bringing in billions of dollars—because of a five- to ten-millisecond prolongation. The researchers suggested we need to start investigating some of these other ingredients in energy drinks.³⁷⁵⁴ Case in point: Authorities once found cocaine in Red Bull, though the manufacturers insisted that they were just adding the coca leaf for "flavor."³⁷⁵⁵

FOOD FOR THOUGHT

Everything we eat and drink can be grouped into one of four categories:



Most of what we consume fits into the upper-right corner, foods that provide both nutrition and calories, but some offer calories without any nutrition, like candy. Others, like artificial sweeteners, offer neither nutrition nor calories. Then there's a fourth category: nutrition without calories. That's where tea comes in, along with many spices. So imagine making a spicy chai with green tea, ginger, and cinnamon. You'd be nailing three fat burners in just one cup.

Note that premenopausal women or anyone at risk for iron-deficiency anemia ideally should not drink tea within an hour of meals to minimize tea's impact on reducing iron absorption.³⁷⁵⁶

Another option is to try feeling *hot! hot! hot!* by spicing up your meals with chili peppers or hot sauces. (You can even add red pepper flakes to your favorite chai tea.) Then you can cool yourself down by lowering your thermostat in the winter for a money-saving, carbon-friendly way to try to burn off some extra fat. A peppermint lotion foot rub may or may not help, too, but it'll feel good either way.

HABIT FORMATION

Force of Habit

When people were asked to estimate how many food-related decisions they make every day—what to eat, when to eat, where, and how much—most pick a number under twenty. When they were asked to carry around a counter and click each such food choice made over the course of a day, the actual number was more than two hundred.³⁷⁵⁷ We may make hundreds of decisions about food every day, yet the vast majority appear to pass under our conscious radars. They happen almost automatically, without cognizant reflection, deliberation, or even awareness.³⁷⁵⁸ We may be able to take advantage of this mindless eating, though, by harnessing the power of habit formation.

It's been said that "most of the time what we do is what we do most of the time."³⁷⁵⁹ Many of our eating habits are indeed just that—habitual. And the busier we are and the more distracted we are, the more likely we are to fall back on habits.³⁷⁶⁰ That's what they're there for. Habits are like reflexive subroutines our brains use as mechanisms to free up our

mental resources. That can work against us, in the case of bad habits, or for us, in the case of good ones. Imagine if you had to add “buckle seat belt” to your to-do list every day. Maybe put a sticky-note reminder on your dashboard or tie a string around your car keys? If you’re in the habit of buckling up, though, your hand will start reaching for the seat belt without you even knowing.

Once you do something long enough, your brain commits the actions to memory and can whip them out at will to automate away some of your cognitive workload—and the automation happens automatically. The mere repetition of a simple action in a consistent context ultimately leads to the action being activated upon exposure to that same situation.³⁷⁶¹ Do it enough times, and getting into a car (contextual cue) can automatically lead to reaching for the seat belt (action).³⁷⁶²

Habits are defined as “learned behavioral responses to situational cues,”³⁷⁶³ so there are two parts—the cue and the action. The cue can be in any context—for example, an event (such as arriving at work), a time (after breakfast), a location (in the car), or even a mood (anxious).³⁷⁶⁴ It just has to be something salient that is frequently and consistently encountered in daily life.³⁷⁶⁵ Do something over and over again in the same context—whether intentionally or unintentionally—and a habit can form.³⁷⁶⁶

How long does it take? You may have heard that habits take twenty-one days to form. That’s a myth that evidently originated from anecdotal evidence of how long it takes plastic surgery patients to psychologically adjust to their new appearance.³⁷⁶⁷ When it was actually put to the test, the average time to reach automaticity was sixty-six days. Study volunteers were asked to choose an eating, drinking, or activity behavior to carry out each day in the same context. Examples chosen included “eating a piece of fruit with lunch,” “drinking a bottle of water with lunch,” and “running for 15 minutes before dinner.” There was considerable variation in the time it took for these actions to become automatic, from 18 days to 284 days, but the average was 66.³⁷⁶⁸ That might seem like a long time, but be reassured that it does get progressively easier with time, and you only have to maintain your motivation until the habit forms. After that, you’re golden. It’s like uploading a new piece of software into your brain for a built-in, lifelong body hack.

The magic of habits lies in their persistence even after losing conscious motivation or interest. They just become second nature. You don’t have to worry about them anymore. Health can happen effortlessly.

Breaking Bad ... Habits

Of course, bad habits can also form. The first time you snacked in front of the TV at night, you may have been genuinely hungry, but over time, the two activities can become indelibly linked such that your prime-time shows trigger snack cravings even if you’re not really in the mood to eat. It can become something you can’t help—in other words, a bad habit.³⁷⁶⁹ In one oft-cited study, people in the habit of eating popcorn in the movie theater were asked why.³⁷⁷⁰ Most gave some variation of the answer “it tastes good.” Seems reasonable, but then why did they end up eating the same amount when they were given stale, week-old popcorn they “decidedly disliked”? Put people who aren’t habituated in the same scenario, and they eat more of the fresh popcorn and less of the stale,³⁷⁷¹ but strong habits can perpetuate independently of the intentions or consequences of your behavior.³⁷⁷²

There are two ways to break a bad habit: change the cue, or change the action. The most straightforward approach is to try to avoid the situational triggers.³⁷⁷³ Recovering alcoholics and drug addicts know all too well the power of social or environmental cues to prompt cravings and relapses. That may be the reason some people find it easier to quit smoking when they’re traveling or otherwise removed from their typical everyday circumstances.³⁷⁷⁴ So anytime we can remove ourselves from triggering situations—by

walking a different route to work to avoid the donut shop, for instance—we can capitalize on contextual changes to avoid the habitual call-and-response.³⁷⁷⁵

In the popcorn study, when the habituated eaters were moved out of the cinema to instead watch videos in a conference room, the spell was broken. Without the same contextual cues, their actions were released from habitual control, and they, too, pushed away the stale popcorn. That's the first way to break a habit: Block its activation. The other way is to block its execution. In the popcorn study, this was accomplished by surreptitiously forcing the habituated eaters to eat with their nondominant hand.³⁷⁷⁶

There they were, seated in the theater with a bucket of popcorn, so their reflexive response to mindlessly eat even stale popcorn was triggered. Just by having to eat it with their other hand, however, was enough to disrupt the subroutine and regain intentional control.³⁷⁷⁷ Change the cue, or change the action. We can block either a habit's initiation or its fluid implementation.

The researchers went as far as to suggest that dieters “actively disrupt the execution of the activated eating sequence by simple manipulations such as eating with the nondominant hand and, in so doing, bring their eating under their personal control.”³⁷⁷⁸ But do that manipulation long enough and it, too, will become a habit. Junk from the left is just as fattening as junk from the right. A better strategy would be to form new habits of healthy eating.

Change the Cue

Health-wise, it matters little what we eat on birthdays, holidays, or special occasions (unless for you every day is National Hot Dog Day). It's the day-to-day that adds up, which is why our eating habits are so important, for good or for ill.³⁷⁷⁹ Our food choices may start out planned and purposeful but can morph into well-worn tracks over time, and we can become stuck in the rut. There is a tendency for habits to continue regardless of our intentions.³⁷⁸⁰ This may be why just knowing the right thing to do often isn't enough.

Knowledge is power, but it may not be powerful enough on its own to break a habit. Historically, anti-smoking campaigns have been successful in making people aware of the dangers of cigarettes, but they were not very effective in and of themselves in getting people to quit. Media interventions to reduce youth substance abuse may have even backfired. A meta-analysis of more than one hundred papers showed knowledge and attitudes improved, but the information campaigns appeared to actually increase youth drug use.³⁷⁸¹

Habits are propensities to repeat behaviors given the recurring circumstances.³⁷⁸² As habits form, deliberate decision-making recedes by design and is replaced by these reflexive circuits within our brains. The strength of habits, however, is also its weakness. The dependence of habits on contextual triggers renders them vulnerable to modification.³⁷⁸³

Just like smokers trying to quit can remove from sight all their ashtrays, we can try to get rid of all the junk from our pantries.³⁷⁸⁴ If you're used to having a cookie every time you see the cookie jar, it might be better to replace it with a fruit bowl. Strategies like packing healthy snacks to go can help shift our immediate surroundings to become more conducive to healthy choices. To change all our habits at once, though, we can try exploiting major life events, such as a change in living arrangements.

Public health campaigners try to take advantage of this by targeting those experiencing natural shifts in their lives, like when they start a new job.³⁷⁸⁵ A study of personal accounts of successful versus failed attempts at major life changes found that altering one's immediate environment or moving to an entirely different location appeared to help.³⁷⁸⁶ When our existing habits are disrupted, this offers an opportunity to start anew, but you don't have to relocate to start fresh. You can change your existing bad habits to good ones,

or establish new good habits from scratch, using a technique known as *implementation intentions*.

How to Get Teenagers to Change

Millions of taxpayer dollars were spent on the D.A.R.E. (Drug Abuse Resistance Education) program to get teens to *just say no* to drugs³⁷⁸⁷ until the U.S. General Accounting Office publicized the fact that all the studies that had been done to evaluate its impact showed it had “no statistically significant long-term effect on preventing youth illicit drug use.”³⁷⁸⁸

It’s hard enough to get adults already beset with chronic disease to live healthier. How can we possibly motivate teenagers, who feel invincible and for whom concepts like lung cancer and heart disease are nebulous notions better fit for a grandparental purview?

The classic challenge facing public health efforts is to figure out how to counter the temptation of the immediate reward with the hope of distant future health benefits. This is particularly difficult in the adolescent age group, so much so that leading experts in teen development have said things such as, “Classroom-based health education is an uphill battle against evolution and endocrinology, and it is not a fight we are likely to win.”³⁷⁸⁹ A landmark study published in the *Proceedings of the National Academy of Sciences* entitled “Harnessing Adolescent Values to Motivate Healthier Eating” broke through the defeatist pessimism by first starting with a question: *What motivates teens?*³⁷⁹⁰

If you were going to design educational materials to get teens to freely choose baby carrots over Cheetos, what would you do? One of the reasons it’s so difficult to convince teenagers to take better care of themselves is that they are extremely sensitive to perceived encroachments on their autonomy. They seek independence from parents and other authority figures telling them what to do—so the researchers sought to turn this obstacle into an asset. They developed a healthy eating message framed as an exposé of manipulative food industry marketing practices designed to deceive. They talked about how Big Food scientists use sophisticated, industrial techniques to maximize product craveability using salt, sugar, fat, and other flavor additives. The goal was to portray healthy eating as a way to rebel and “stick it to the man.”³⁷⁹¹

The other commonly shared value they tapped into was a concern about injustice. Teens are often stereotyped as self-centered, but anyone who’s worked with them can attest to their sensitivity to unfairness and inequity. So the researchers talked about how the food industry disproportionately targets poor communities and young children with ads for some of their unhealthiest products. Avoiding junk food was presented as a way to take a stand for social justice.

In theory, these two avenues eliminate the need to think about long-term consequences, instead offering immediate symbolic benefit in terms of stoking their rebellious spirits and acting in accordance with their deeply held beliefs. Or at least that’s the theory. To test it, researchers set up a double-blind, randomized, placebo-controlled experiment with more than five hundred eighth graders. They were allocated randomly to one of three groups: the new approach, traditional nutrition education, or a nonfood-related control group. Then hidden observers spied on them surreptitiously at a later date in an unrelated context. The students had access to unhealthy choices, such as Coke, Sprite, Oreos, Doritos, and Cheetos, as well as healthy options, such as sparkling water, fruit cups, trail mix, and baby carrots. What happened? It worked! Compared to the other groups, those given the healthy eating message framed to teen values independently chose to forgo some of the fattening snacks and drinks in favor of the healthier options.³⁷⁹²

Change the Action

Fancied as asphalt for the highway to hell, good intentions have a bad reputation. Oscar Wilde wrote, “Their origin is pure vanity. Their result is absolutely *nil*.”³⁷⁹³ Many who have failed to stick to their New Year’s resolutions can relate.

To help secure our goals, we can call on our built-in cognitive capacity to create habits to automate our actions.³⁷⁹⁴ This starts with implementation intentions.³⁷⁹⁵ Instead of vague self-promises to “do our best,” implementation intentions are specific if-then plans to perform a particular behavior in a specific context. They take the form of *When situation X arises, I will perform response Y*.³⁷⁹⁶ For example, *If I get hungry after dinner, I will eat an apple*. If the triggering circumstance is a regular, daily occurrence, implementation intentions can be the beginning of a beautiful habit.³⁷⁹⁷

Note that to break a bad habit or create a new one, we have to select a new action (eat an apple) rather than just give up an existing behavior (don’t eat potato chips).³⁷⁹⁸ To activate the habit-forming mechanism, you likely need a new alternative response, rather than a nonresponse.³⁷⁹⁹ Evidently, you can’t form a habit of not doing something.³⁸⁰⁰ Then, to lock it in, you have to purposefully repeat it day after day, week after week, and maybe even month after month before it takes on a mind of its own. It may be a lot of work up

front, but once it's ingrained in our brains, then the need for willpower is replaced by an eerie compulsion to just do the right thing.

During the process of habit formation, it gets easier as we go along. This is particularly the case with dietary interventions because our palates change along the way. For example, ever since I stopped regularly drinking coffee,³⁸⁰¹ I've been having a really strong chai tea in the morning. At first, I was using one of the less harmful, low-calorie sweeteners to cut the bitterness. Preliminary data suggest sweeteners like monk fruit,³⁸⁰² erythritol,³⁸⁰³ and allulose³⁸⁰⁴ are relatively benign in small doses, but low-calorie sweeteners tend to have a bad track record when it comes to safety. Given that I'm always trying to expand the percentage of Green Light foods in my diet, I could have tried a more nutritive sweetener like date syrup, but I decided to try to cut down altogether. Every day, I vowed to use less sweetener than the day before. Now, not only do I take my morning tea unsweetened, I *prefer* it that way. As a "treat" to myself one day, I decided to add a little sweetener, and it just tasted gross. So now I'm in the best of both worlds where taste and health preferences unite.

Implementation Intentions Put to the Test

Given their simplicity, implementation intentions appear to be surprisingly effective.³⁸⁰⁵ Imagine you're a dentist who wants your patients to floss their teeth daily. You give them a complimentary pack of dental floss with a handout telling them how important flossing is and encourage them to floss every day. Having read this book, though, you recall the supposed power of implementation intentions. You're skeptical, so you randomize half your patients to get the same free floss and identical handout except their version contains one additional message:

You are more likely to carry out your intention to perform dental flossing every day if you make a decision about when and where. Most people perform dental flossing in the bathroom immediately after they brush their teeth at night. Others prefer to do it in the morning after breakfast. Write down where and when you intend to floss your teeth every day for the next 4 weeks.

Just such an experiment was carried out, and that one additional tweak, that one additional message, *doubled* flossing frequency, from eight days of flossing out of the following month to nineteen days.³⁸⁰⁶ That's the power of implementation intentions. (Note that all randomized, controlled, crossover trials to date show that flossing *before* brushing gets rid of significantly more plaque.^{3807,3808})

Does what works for flossing work with eating? When researchers interviewed maintainers of significant weight loss, action planning to develop healthy habits arose as a consistent theme. The successful losers often decided in advance what they were going to eat, when, and where. Many consciously planned their meals for the day or week, often getting into the habit of eating similar meals for breakfast and lunch every day. They meal-prepped and kept healthy snacks like carrots and fruits in plain sight. Some made double portions of wholesome meals to refrigerate or freeze in case they got busy.³⁸⁰⁹ Several brought home only healthy foods from the store. (As one put it, "You cannot eat what you don't buy.")

Those all sound like good ideas, but just because those successful at weight loss tended to use lots of implementation intentions doesn't necessarily mean the intentions had anything to do with it. You can only prove cause and effect with interventional trials where you randomize people to an intervention—or not—and put it to the test. So that's just what researchers did.

Hundreds of middle-aged women were randomized into one of two groups. Both groups were told about the health benefits of fruits and vegetables, and both groups were encouraged to boost their intakes, but one group got additional instructions to form implementation intentions. They were told to think of all the barriers to healthy eating they encounter on a daily basis and come up with three implementation intentions to overcome them. Typical examples included *If I have no fruits at work, then I will buy an apple in the canteen at lunch* or *If I am eating out for lunch, then I order a salad*.³⁸¹⁰

In the first couple of months, both groups succeeded in eating more fruits and veggies, but by month four, the implementation-intention group pulled ahead. Two years later, the fruit and vegetable consumption in the information-only group had, unsurprisingly, fallen back toward baseline, but the implementation-intention group was still going strong. After just that single meeting with the experimenters years before, they were still eating significantly more fruits and vegetables, presumably because it had become so routine as to become habit.³⁸¹¹ All because of that simple psychological trick.

Other studies have found intention formation to be a useful tool for solidifying healthy eating and exercise interventions,³⁸¹² but what about weight loss? Randomized controlled studies show forming new habits or breaking old ones can not only produce significant weight loss but, more importantly, help keep it off.³⁸¹³ For example, in one twelve-week study, participants randomized to try to turn the “Top Ten Tips” for weight loss into daily habits lost about seven pounds (compared to no significant weight loss in the control group). The tips were just your run-of-the-mill good advice, such as “Make water your first choice,” “Try reaching ten thousand steps each day,” “Pack healthy snacks,” and “Eat more fruits, vegetables, and pulses (beans, split peas, chickpeas, and lentils) and less fast food and high-fat dairy and meats.”³⁸¹⁴ Losing seven pounds is nothing to sneeze at, but the excitement came from what happened after the study ended.

A year later, not only did the participants randomized to try to habituate the weight-loss tips not gain back the weight, they continued to lose another five pounds on average.³⁸¹⁵ Participants described that healthy eating and activity just became “pretty much second nature.”³⁸¹⁶ They “just worm their way into your brain,” one person remarked. “Now I actually feel quite strange if I haven’t [eaten a salad].” Overall, 65 percent achieved clinically significant, sustained weight loss by automating healthy behaviors into habits.³⁸¹⁷

Avoiding a Snowball’s Chance

In the study that determined it took an average of sixty-six days of repetition to form a habit, the researchers found that sporadically missing a day resulted in a tiny dip in automaticity the next day but had no longer-term consequences.³⁸¹⁸ So if you stumble or forget one day, just pick it back up the next. A series of experiments dating back to the 1970s did uncover a curious quirk of human psychology you should be aware of, though, so you don’t fall into the trap.

Imagine enrolling dieters in a study ostensibly to “investigate the effects of prior taste on subsequent taste perception” by having them “taste test” different flavors of ice cream after drinking a milkshake. Half were told the preload milkshake was “very high calorie,” and the other half were told it was “very low calorie”—though, in truth, all shakes were identical. All the subjects were then instructed to taste and rate three bowls of ice cream, eating as much or as little as they wanted and feeling free to finish them all off if they so wished. What do you think happened?

The rational thing to do if you’re trying to watch your weight is to eat less ice cream after you’ve just had a high-calorie milkshake, right? Well, the exact opposite happened. Those told they were drinking the high-calorie shake went on to eat 43 percent more ice cream than those who had drunk what they thought was the low-calorie shake.³⁸¹⁹ How does that

make any sense? Instead of telling themselves they'd overeaten and shouldn't make it worse, their attitude appeared to be, "It's too late now, so I might as well enjoy myself."

As I mentioned [here](#), this irrational reaction to overindulge after overeating because now the "day is lost" has a name in the scientific psychology literature. It's been coined the "what-the-hell effect."^{3820,3821}

Though proximal subgoals, like promising yourself no more than one treat a day, can help keep you on track, they can be counterproductive if they cause you to lose sight of the end goal—that is, losing weight. Slipups can feel like you've let yourself down and demotivate you into all-or-nothing thinking.³⁸²² Two cookies can lead you to binge-eat the whole bag.

There are a few ways to counter the what-the-hell effect. You can try extending the time period of the subgoal. So instead of committing to no more than one treat a day, if you swore to yourself that you wouldn't have more than seven treats in a week, having two cookies in one day might no longer feel like such a face-stuffing failure. You can just make it up tomorrow.³⁸²³

Another way identified by researchers to fight the what-the-hell effect is to choose acquisitional, rather than inhibitional, goals. People seem to be better able to deal with coming up short on positive goals than negative ones. So framing your subgoals as things you want to accomplish, rather than avoid, can help you escape the fatalistic, black-and-white thinking that can subvert your longer-term goals. For example, if you aim to drink a large glass of water before every meal but miss one time, there isn't the same defeatist feeling. *Well, I messed up and didn't drink water before lunch, so forget it. I might as well not drink water before dinner either* doesn't tend to race through your mind. When we have positive subgoals, we're more likely to think positively—*Thankfully, I remembered at breakfast and now dinner, so at least I'm making progress*—whereas violating a negative, don't-do-something goal, like vowing not to touch soda, appears more likely to make what-the-hell break loose.³⁸²⁴

Finally, you can recognize the feeling when what-the-hell arises, realize how ridiculous it is, and try to laugh it off. I had to chuckle at myself the other day when my writing was interrupted by an urgent media call that forced me to delve into a few hours of research unrelated to this book. Afterward, I remember thinking, *Well, my day's shot, so I might as well just stop now and watch a movie or something and start fresh tomorrow*. I had just what-the-hell'd myself! I missed a few hours of writing time, so therefore I should miss more time? Realizing how silly that was, I got back to work.

Avoiding the Self-Licensing Trap

The flip side of subgoal setbacks blowing your end goal is when subgoal successes do the same thing. Remember self-licensing, the other irrational phenomenon where dietary supplements led smokers to light up more and dieters to eat more junk? It's when movement toward our goals can justify indulgences that set us further back. Excuses like *I worked hard this week so I deserve it* fall into this category.³⁸²⁵ There's a reason it's the catchphrase for marketers the world over. (Who can forget, *You deserve a break today at McDonald's?*)

Would you guess that smokers of "light" cigarettes would be more or less likely to quit compared to those who smoke regular cigarettes? You might reason that those choosing to find lower-tar varieties are already acknowledging and trying to cut down on the risks, so they would probably be more ripe to quit, right? But no. They are more than 50 percent less likely to kick the habit. This failure is presumed to be a licensing effect, where their imagined progress toward their goal of not dying from lung cancer is subconscious justification to indulge their addictions that may end up killing them. (The cruel irony of

light cigarettes is that smokers tend to use more of them or instinctively hold the smoke in longer such that the same amount of tar ends up being deposited in their lungs.³⁸²⁶

Check out how this manifests in the world of weight loss. The best predictor of future performance is past performance, right? Haven't we all heard past-as-prelude aphorisms? Well, if you follow dieters over time, it turns out the opposite can be true. Weight loss in one week appears to have a strong negative impact on weight loss in the subsequent week.³⁸²⁷ Naïvely, you might think that progress begets progress, with good news on the bathroom scale inspiring further motivation to stick with it. But instead of taking a victory lap (burning even more calories!), people tend to use the occasion of their progress as a pretext to indulge. After all, they figure, they deserve it.

This counterintuitive consequence draws from a larger literature on "moral licensing." Researchers have found a prior good deed can lead people to act questionably later on. Virtue can lead to veritable villainy. You'd think people would take pride in the integrity of moral consistency, but instead, being good appears to liberate us to be bad.³⁸²⁸

Consider this disturbing study out of the University of Toronto: People were randomly assigned to purchase items from one of two online shopping sites, identical except the products were described as environmentally friendly on one of the sites. Then, in a supposedly unrelated task, they played a computer game and were told to pay themselves out of a provided envelope of money for each correct answer. They were told no one was watching and it was all on the honor system. Who do you think acted more honorably? In actuality, the experimenters really *were* watching them, tallying up the actual number of correct answers, how many the subjects claimed they had gotten correct, and how much money they subsequently took. Shockingly, those randomized to purchase the green products were significantly more likely to then lie, cheat, and steal.³⁸²⁹ Ethical acts may license unethical behaviors, and it may only take a molehill of virtue to create a mountain of immorality.³⁸³⁰

Self-licensing can also involve self-delusion. The effect is so powerful that when people are presented with a temptation, they tend to exaggerate in their minds how well they've been eating in order to justify the indulgence. So not only may progress toward a goal rationalize lapses, but even misremembered distortions of progress can cause us to slide.³⁸³¹ This is why it's so important to be aware of the psychological tricks our minds can play on us so we can counter them.

Even visions of *future* progress can trigger licensing and undercut our goals. How many times have you been tempted to slip "just this once," resolving to make up for it tomorrow? But "tomorrow" may never come. If you offer people watching their weight the choice of a "large Mrs. Field's cookie" or a snack they perceive as healthy (plain fat-free yogurt) around 50–60 percent choose the cookie. If, however, as you offer them the choice, you tell them they'll be given the same choice the following week, the number choosing the cookie jumps up to 70 or 80 percent. Do you see what happened? People told themselves they'll choose the healthier option the next week, thereby justifying their choice to jump at the cookie this week.

What happens if you tell people they can choose between the cookie or the yogurt this week, but only the healthier option will be offered the following week? Those choosing the cookie shoots up to 90 percent! Sadly, our brains don't work the other way around. Telling people they're just going to get the cookie next time doesn't increase their odds of making healthier choices in the present.³⁸³² Our minds are always reaching for the rationalization.

Ironically, those with the greatest self-control are the most vulnerable to this kind of behavior.³⁸³³ They're so sure they're going to be able to resist the temptation—*next* time—they feel licensed to indulge now. To neutralize this effect, try to make each decision on its own merits in the here and now. In that present moment, regardless of what you did before or plan on doing later, consider the best choice to fulfill your long-term goals.

Does that mean you should never splurge, never veer off the path? Self-licensing is dysfunctional if it's your mind tricking you into stumbling too easily or too often, but it can be useful if it supports long-term dietary adherence. If cheating every once in a while helps you sustain a healthier lifestyle, then it could be beneficial in the long run.³⁸³⁴ The difference is in the design. Cheating isn't cheating if it's baked into the plan. Those who prearrange to give themselves a certain number of passes every month to skip the gym or eat whatever they want can do so without deceiving themselves or inviting the wrath of the what-the-hell effect. Because it's all just part of the plan.

FOOD FOR THOUGHT

The business world knows all about how to make things easy. It's the reason Amazon has a 1-Click Buy button.³⁸³⁵ This is why the term *habit-forming* can be a good thing when you consciously turn it to your advantage. It can turn healthy decisions into an impulse buy.

Using implementation intentions, we can begin the process of automating healthy urges away from conscious control. Then we can relax and let the habitual subroutines do all the work. There's no need for willpower when you have chill power.

Those who've seen my "blender burpees" cooking video know a bit about how I style implementation intentions in my own life. A typical if-X-then-Y for me is *As I fill up my water bottle, I'm going to try to fit in ten squats*. Better than just standing there getting nothing else done as I get my water, right? That's actually where my Daily Dozen checklist sprang from, a set of acquisitional goals to remind me to fit in more of the healthiest of healthy foods.

For example, burdened with the knowledge that dark green leafy vegetables are the healthiest foods on the planet, I'm always trying to intentionally implement ways to fit more into my diet. Every time I shop for groceries, for instance, I make myself buy at least two bunches of greens for every day of the week. (But if I run out, I know I always have an emergency stash of bags of frozen greens in my freezer.) I also changed a snacking habit to *If I get hungry, I'll snack on roasted nori*. For me, it was less about the calories (though nori does only have about five to ten calories a sheet), and more about the marvel of enjoying dark green leafy vegetables as a snack. I even sip on matcha tea, so I can drink my dark green leafies too.

To maintain healthy habits, I described the pitfalls—the two psychological glitches that can threaten your goals from both directions. Say you're trying to get into the habit of drinking water instead of soda. On the one hand, if you slip, your morning Mountain Dew can turn into a what-the-hell chugfest. If, on the other hand, you succeed, the licensed self-indulgence side could rationalize one or two "live a little" liters. I know it can be seductive to rationalize. Sometimes when I'm on the road for a weeks-long stretch, jet-lagged after some hectic four-hour book-signing, the junky snacks in the late-night hotel minibar start looking pretty enticing. I've found for me it helps to turn those feelings of entitlement around. *No*, I tell myself. *You know what you really deserve? To be healthy.*

HYDRATION

Just Add Water?

According to a national survey, "Drink plenty of water" was one of the weight-control practices most associated with successful weight loss. The strategy was also associated with *unsuccessful* attempts at losing weight, however.³⁸³⁶ In other words, it's one of the most popular weight-loss tips across the board, heralded in the mainstream media and commonly recommended by physicians to their patients.³⁸³⁷ But does it work?

About a dozen studies have been published on the matter, and overall, there does appear to be a weight-reducing benefit to increased water consumption.³⁸³⁸ What's the obvious confounder, though? Confounding factors, sometimes called *lurking variables*,³⁸³⁹ are those third elements that may end up being the true explanation for a supposed link between two things. For example, there may be a tight correlation between ice cream sales and drowning deaths, but that doesn't mean ice cream causes drowning. A more likely explanation is that there is a lurking third variable—like hot weather or summertime—that explains why drowning deaths are highest when ice cream consumption is at its peak. So what might be a confounding factor that can offer an alternate explanation as to why those who drink more water tend to lose more weight? The most obvious might be that those who drink more water tend to drink less soda.³⁸⁴⁰

The primary reason that the Centers for Disease Control and Prevention, U.S. Department of Agriculture, American Medical Association, American Diabetes Association, American Heart Association, and American Academy of Pediatrics all recommend drinking water for weight management is as a replacement for sugary beverages.³⁸⁴¹ Swapping just one sweetened beverage or beer a day with water is associated with a lower incidence of obesity over time.³⁸⁴² American children and adolescents drink so much soda that replacing all sugary beverages with water could result in an average reduction of 235 calories a day.³⁸⁴³ So does that explain it? Not quite. Even if you take the consumption of calorie-containing beverages into account, water consumption is *still* associated with better weight control, so there has to be something else going on.³⁸⁴⁴

What about exercise? That's another obvious confounder candidate. After all, who drinks a lot of water? Those who spend hours working out. No wonder heavy water drinkers might be slimmer. However, a study of dieting overweight women that took both soda intake and exercise habit into account still found a benefit associated with increased water consumption. Over a year, those who drank at least a liter of water a day lost about five more pounds on average than those who didn't.³⁸⁴⁵ Okay, the researchers were able to account for other beverages and physical activity, but what about other foods? It turns out those who drink more water also tend to eat more fruits and vegetables, greens and beans, and whole grains,³⁸⁴⁶ as well as less fast food³⁸⁴⁷ and total sugars.³⁸⁴⁸ No wonder they're a healthier weight.

To control for dietary factors, the scientific world brought out the big guns: Harvard's massive cohort studies that followed the diets and health of more than one hundred thousand doctors and nurses for decades. The researchers were able to control not only for other beverages and lifestyle factors like exercise, smoking, sleeping, and TV watching but also a wide range of healthy and unhealthy food intakes, from fruits and vegetables to meat and candy. They were the first to show that "increasing water intake per se was independently and significantly associated with less weight gain" over the long term.³⁸⁴⁹

Consumption patterns in these studies were by self-report, though. Participants were asked to fill out detailed questionnaires about their diets. For more objective measure, researchers directly assessed people's hydration status by measuring their blood and urine concentrations. In both children³⁸⁵⁰ and adults,³⁸⁵¹ the more hydrated they were, the less likely they were to be obese. Spot-checking urine from nearly ten thousand men and women, researchers found that nearly half the obese individuals were walking around underhydrated compared to fewer than one in three individuals who were normal weight or lighter.³⁸⁵²

The problem with snapshot-in-time studies is you don't know which came first: Did underhydration lead to obesity, or did obesity lead to underhydration? At a heavier weight, you actually need more water. The daily water requirement of a man of average height weighing 210 pounds may be four cups more than if he weighed 160 pounds.³⁸⁵³ And who's more hydrated? Those who eat more water-rich foods like fruits and vegetables.³⁸⁵⁴ There's that specter of confounding again. The only way to prove cause and effect is to put it to the test.

Milked Dry

Overweight adolescents were randomized into one of two groups, either advised to drink eight cups of water a day or not. What happened after six months? Before you look at the results of any interventional study, the first question you always have to ask is: *Did the participants actually comply with the intervention?* In this case, both groups started out drinking around two cups of water a day, so the study was designed to see if there was a weight-loss benefit to consuming six extra cups of water. Unfortunately, in the end, the difference in water intake between the groups came out to be less than a cup and a half,

which evidently wasn't enough to show any benefit. Only a tiny percentage of teens in the water group reported reaching the target intake.³⁸⁵⁵

To improve compliance, another set of researchers asked kids to keep an eye on their pee. The group of overweight nine- to twelve-year-olds randomized to the water intervention was told to increase their water intakes to the point their urine became straw-colored (pale yellow). Once again, not every kid complied, but those who did lost significantly more weight.³⁸⁵⁶

Inspired by these small pilot studies and early successes with school-based interventions in Europe,³⁸⁵⁷ researchers launched the most ambitious study yet, involving more than a million students in New York City public schools. They compared obesity rates and weight gain in schools that installed cooled, filtered water dispensers compared to control schools that hadn't, and the increased water access appeared to translate into less weight gain and lower likelihood of overweight kids.³⁸⁵⁸

The accompanying editorial in the American Medical Association's pediatrics journal was entitled "The Power of a Simple Intervention to Improve Student Health: Just Add Water."³⁸⁵⁹ But was it the addition of water per se that caused this, or could it have been the subtraction of something like soft drinks? Isn't it possible the students with greater water access just grabbed fewer sodas and that's why they had less weight gain?

The study had been performed a decade *after* NYC schools removed soda from all their vending machines, but they still sold low-fat milk. The corresponding drop in milk purchases is in fact what the researchers suspect may have accounted for the weight-loss benefit in the water group.³⁸⁶⁰ Intake of milk, like soda, can result in weight gain.³⁸⁶¹ This is true for skim milk or even just straight dairy protein, pure whey or casein added to beverages even without the naturally occurring milk sugars.³⁸⁶² The increased fat mass from drinking milk³⁸⁶³ may be in part from the elevation in insulin levels caused by milk protein.³⁸⁶⁴ Even dairy industry-funded studies have found that drinking less than a cup of milk with a low-glycemic-index meal can exaggerate the insulin spike as much as if you just had eaten high-glycemic white bread.³⁸⁶⁵

Burn Fat, Preserve Muscle

While milk can impair fat burning,³⁸⁶⁶ water may have the opposite effect. To get to the bottom of the water-and-weight-loss question, tightly controlled metabolic experiments were performed in which whole-body protein and fat breakdown were measured under different degrees of hydration. Well-hydrated individuals experienced the best of both worlds: increased fat burning and decreased protein breakdown.³⁸⁶⁷ The way the body responds to high water intake is similar to how it responds to acute fasting—by switching toward fat as a fuel source while trying to spare the muscle.

These were proof-of-principle experiments with limited real-world relevance, though. The high fluid states were induced not only by having the participants drink ten cups of water over a twelve-hour period but also by dripping extra free water straight into their veins and even giving them an antidiuretic hormone to cause them to retain even more water. However, there are mechanisms by which our day-to-day hydration status can affect our metabolisms.

When we get dehydrated, our blood volume actually shrinks. This drop is detected by our kidneys, which then release an enzyme into our bloodstreams that triggers the cascade that results in the formation of a hormone called *angiotensin*, which, in turn, causes us to become thirsty and constricts our blood vessels to raise our blood pressures to compensate for the diminished blood volume. (This is how a popular class of blood pressure-lowering medications works. The *ACE* in *ACE inhibitors*—like captopril—stands for angiotensin-converting enzyme.)

That isn't all that angiotensin does, though. Drip the hormone onto human fat cells in a petri dish, and they start piling on more fat.³⁸⁶⁸ This may help explain why those with higher angiotensin levels in their bloodstreams tend to be heavier.³⁸⁶⁹ The thought is that those who don't drink enough end up with chronically elevated angiotensin levels, which can lead to weight gain.³⁸⁷⁰ The most convincing evidence comes from genetic studies showing that those born predisposed to higher angiotensin levels are significantly more likely to become obese.³⁸⁷¹ We can keep our levels down in the normal range, though, by staying adequately hydrated.

What Kind of Water Should You Drink?

Though many distrust the safety of tap water,³⁸⁷² bottled water may be no safer, no cleaner, or of no higher quality than water straight out of the faucet.³⁸⁷³ How much is that saying, though? Two studies published back in the 1970s forever changed our perception that drinking water safety was just about waterborne diseases.³⁸⁷⁴ In fact, it was our fight against microbial contaminants that led to a new kind of contamination in the form of disinfection by-products.

The two landmark papers from 1974 solved the mystery of the source of chloroform in drinking water: We have met the enemy, and he is us. The chlorination of drinking water—crucial for maintaining microbiological safety—was interacting with natural organic matter from the water's source and creating chlorinated compounds that can not only result in off flavors and smells but may also pose a potential public health risk.³⁸⁷⁵ More than six hundred disinfection by-products have been identified so far.³⁸⁷⁶

After decades of research into the matter, it appears that the lifelong ingestion of chlorinated drinking water results in "clear excess risk" for bladder cancer.³⁸⁷⁷ There is also some evidence of increased risk of birth defect rates,³⁸⁷⁸ but most of the concern has focused on the bladder cancer link.³⁸⁷⁹ Forty years of exposure may increase your odds of bladder cancer by approximately 25 percent.³⁸⁸⁰ Environmental Protection Agency scientists estimated that between 2 and 17 percent of bladder cancer cases in the United States are due to these disinfection by-products in drinking water.³⁸⁸¹ However, this is assuming the link is cause and effect, which has yet to be firmly established.³⁸⁸²

The best way to reduce risk is to treat the cause. Countries could prevent the formation of disinfection by-products in the first place through better initial removal of the source water's natural organic matter³⁸⁸³ (or *schmutz*, as my grandmother would say). Some countries in Europe such as Switzerland have newer, well-maintained drinking-water systems that can distribute tap water free from residual disinfectants, but the cost to upgrade the infrastructure of even a small city in the United States could run in the tens of millions.³⁸⁸⁴ As the tragedy in Flint, Michigan, has revealed, we seem to have trouble keeping even undeniable toxins out of the tap.

Nearly 40 percent of Americans use some sort of water purification device.³⁸⁸⁵ Two of the most common approaches—pour-through pitchers and refrigerator filters—were tested head-to-head against Tucson tap water. Both of the fridge filters (GE and Whirlpool) did similarly well, removing more than 96 percent of trace organic contaminants, edging out the three pitcher filters, which ended up catching 93 percent (ZeroWater), 84 percent (PUR), and only 50 percent (Brita).³⁸⁸⁶ A similar discrepancy was found between PUR and Brita brand filters tested specifically against disinfection by-products.³⁸⁸⁷ Reverse osmosis systems can work even better, but their cost, water waste, and loss of trace minerals³⁸⁸⁸ make them seem unworkable.

The annual cost for purifying your water with a pour-through pitcher or fridge filter was calculated to be about the same, at only around a penny per cup (with the exception of the ZeroWater brand, which is up to four times more expensive).³⁸⁸⁹ I figured the "change by" dates on the filters were just company scams to get you to buy more, but I was wrong. Since I drink filtered water mostly just for taste, I used to wait until the water started tasting funky before I changed the filter. Bad idea. Not only do the filters eventually lose much of their removal capacity, but bacterial growth can build up inside them, resulting in your filtered water having higher bacterial counts than the water straight out of the tap.³⁸⁹⁰

FOOD FOR THOUGHT

You can check your hydration situation by monitoring the color of your urine. Originally validated as a way to detect acute dehydration in athletes,³⁸⁹¹ it's now used more broadly in studies of the general population to track hydration status³⁸⁹² (including pregnant and lactating women).³⁸⁹³ The gold standard (or rather, the *pale* gold standard) is the color of straw. For those of you who didn't grow up playing on bales in barns like I did, that means a light yellow. Note that if you take B vitamins or eat riboflavin-rich foods, that can throw off the results.³⁸⁹⁴ Riboflavin (also known as vitamin B2) gets its name from the Latin word *flavus*, for *yellow*.³⁸⁹⁵ So if you dust your air-popped popcorn with nutritional yeast, a vitamin-packed cheesy topping (spritzing the popcorn first with apple cider vinegar to get it to stick, of course), your urine stream can light up neon yellow like a light saber. This can give the false impression that your urine is more concentrated than it is and, hence, that you're more dehydrated than you actually are.

Is there any danger in drinking too much water? Absolutely, yes. Even healthy kidneys can only handle about three cups of water an hour.³⁸⁹⁶ Beyond that, we risk washing the electrolytes out of our brains with potentially lethal consequences. Can you just replenish with a sports drink? No. In fact, there is a high-profile case of a high school athlete who died after drinking two gallons of Gatorade.³⁸⁹⁷ Drinking too much of anything can be dangerous.

So how much water should you drink every day? Unless you have a condition like heart or kidney failure or your physician otherwise advises you to restrict your fluid intake, here is how much water I recommend you drink every day to help your weight (based on the Institute of Medicine's adequate intakes and assuming moderate physical activity at moderate ambient temperatures):³⁸⁹⁸

Recommended Daily Cups of Water

Ages	Female	Male
9–13	7	8
14–18	8	11
19+	9	13

Note that for adults, that comes out to nearly one cup every waking hour, so you could set your watch or phone to ping you if you find yourself forgetting. I always travel with a water bottle wherever I go. There are shatter-resistant glass bottles with silicone sleeves, but I find I drink more when my water's cold, so I use a vacuum-insulated stainless steel bottle. It's really remarkable. I can still hear the tinkle of ice cubes when I land after a transoceanic flight.

INFLAMMATION QUENCHERS

Down in Flames

In the Dietary Inflammatory Index scoring system I discussed in the Anti-Inflammatory section, the single most pro-inflammatory food component is saturated fat. The single most *anti*-inflammatory food component? Fiber.³⁸⁹⁹ Since saturated fat is found mostly in meat, dairy, and junk food, whereas fiber is abundant in whole grains, beans, vegetables, and fruit, that information alone is enough to get a general sense of what an anti-inflammatory diet might look like: one centered around whole plant foods.³⁹⁰⁰ Indeed, in dozens of interventional trials where different diets were put to the test in thousands of individuals, the more plant-based diets won the day in terms of bringing down markers of systemic inflammation, such as C-reactive protein.³⁹⁰¹

What about fish? The purported benefits of the omega-3 fats in seafood are often ascribed to their anti-inflammatory nature, but that's not actually what the medical literature shows. When healthy people were given fish oil supplements equivalent to eating about a serving of salmon, a can of tuna, or ten fillets of tilapia every day³⁹⁰² for weeks or months, overall there was no benefit in terms of reducing key inflammatory markers.³⁹⁰³ No surprise, then, that a compilation of more than twenty randomized placebo-controlled trials of fish oil supplements found no demonstrable effect on weight loss.³⁹⁰⁴

A completely plant-based diet, however, can help drop C-reactive protein levels by 30–40 percent within just a few weeks in both adults³⁹⁰⁵ and children, but it need not be all or nothing.³⁹⁰⁶ Yes, those randomized to a no-meat diet dropped the inflammatory potential of their diets more than those placed on a low-meat diet,³⁹⁰⁷ but even swapping out just a few servings of meat for beans, split peas, chickpeas, or lentils a few days a week can lower

measures of inflammation in the body by about a third within only two months.³⁹⁰⁸ Adding plant foods alone can help too. Five servings of fruits and veggies a day don't appear to be sufficient, but eight daily servings significantly drop C-reactive protein levels compared to those randomized to eat close to the American average.³⁹⁰⁹ a paltry two servings a day.³⁹¹⁰ That's one of the reasons my Daily Dozen recommendation includes a minimum of nine daily servings.

In 2018, researchers at the University of Nebraska published a paper pitting whole grains against fruits and vegetables head-to-head for their anti-inflammatory properties. Which won? Both! Both groups experienced anti-inflammatory benefits, but in distinct ways, affecting different markers of inflammation. This implies that whole grains, fruits, and vegetables lower inflammation through different mechanisms, suggesting consuming them all together could have a synergistic effect.³⁹¹¹ So our best bet may be to eat a variety of foods as grown. Have any plants been shown to be particularly potent?

Crying Wolf(berry)

Obesity is associated with elevated levels of oxidative stress,³⁹¹² which can result in free radical damage to proteins within the body that can trigger inflammation.³⁹¹³ Might an antioxidant-rich fruit be able to help break this vicious cycle? Goji berries, also known as wolfberries, have at least four times the antioxidant activity compared to other dried fruits like raisins or dried cranberries that you might sprinkle on your oatmeal or add to your trail mix.³⁹¹⁴ Beyond its rich antioxidant content, a number of anti-inflammatory compounds have also been specifically identified in the fruit.³⁹¹⁵ In the lab, goji berries do have anti-inflammatory effects on cells from umbilical cords, one of the most convenient sources of human tissue, but what about in whole humans outside the lab?³⁹¹⁶

Petri dish studies on goji berries have concluded they "could be developed as a new anti-inflammatory therapeutic herbal medicine,"³⁹¹⁷ but you don't know until you put it to the test. Randomized, double-blind, placebo-controlled trials have shown anti-inflammatory effects³⁹¹⁸ while otherwise potentially improving immune function (boosting vaccination response among elderly individuals),³⁹¹⁹ but does that translate into weight loss?

Goji berry juice doesn't seem to work for weight loss, or at least the GoChi beverage sold by a multilevel marketing company³⁹²⁰ accused of making such false and misleading claims didn't.³⁹²¹ What about just giving people actual berries? (What a concept!) Brazilian researchers split people into two groups.³⁹²² Both were given identical instructions to follow a healthier diet, but one group was also given fourteen grams of dried goji berries a day, which is about two tablespoons.³⁹²³ Forty-five days later, the goji group appeared to cut two and a half inches off their waistlines compared to no change in the control group. This presumed drop in abdominal fat was accompanied by significant drops of about 20 percent in both LDL cholesterol and triglycerides.³⁹²⁴ Of course, it would have been better if the researchers had given the control group something like raisins (which haven't shown a slimming effect)³⁹²⁵ to help discount the placebo effect, but what's the downside of giving gojis a go?

Anti-Inflammatory from My Head To-ma-toes

How about a weight-reducing, anti-inflammatory vegetable? There's no need to look for an exotic goji equivalent. If you don't count french fries and other potato products, tomatoes are America's most popular vegetable³⁹²⁶ and have been shown to have anti-inflammatory effects in both petri dishes³⁹²⁷ and people.³⁹²⁸ Randomize overweight individuals to a little less than a can of tomato juice a day (330 ml), and see a drop in inflammation within three weeks.³⁹²⁹ Low-sodium V8 juice may also help.³⁹³⁰

Give people about a quarter cup a day of tomato paste, and get an improvement in artery function within fifteen days, an effect attributed to both anti-inflammatory and

antioxidant effects.³⁹³¹ Anti-inflammatory benefits can even be realized at a single meal. Men and women were randomized to a pro-inflammatory meal (containing saturated fat in the form of cream cheese and coconut milk) with or without about a third of a cup of tomato paste. The tomato paste significantly blunted the rise of an inflammatory mediator that occurred within hours of consumption.³⁹³²

Tomatoes are so anti-inflammatory that tomato extracts have been investigated as a potential replacement for aspirin as a blood thinner.³⁹³³ The effects have been attributed to lycopene, the red pigment³⁹³⁴ in tomatoes, watermelon, and other such hued fruits and vegetables, but we now know that tomatoes contain a large number of diverse anti-inflammatory compounds.³⁹³⁵ That may be why giving people Lyc-O-Mato lycopene supplements alone appears to have no effect.³⁹³⁶ The question is: *Can tomatoes help you lose weight?*

Perimenopausal women asked to drink nearly a cup of tomato juice twice a day had an improvement in menopausal symptoms, but no weight loss—though they did appear to get about a 150-calorie-per-day boost in their resting metabolic rates.³⁹³⁷ That may help explain why a study of younger normal-weight women drinking about a cup of tomato juice a day experienced a reduction in weight, body fat, and waist circumference. The changes were minuscule, though, with only about a pound of weight and a half inch off the waist, and more importantly, there was no control group.³⁹³⁸ As we know, just being in a study under observation can get people to lose weight. There was a controlled study, however, that did suggest there may be something special about tomatoes.

UK researchers fed people sandwiches made out of white bread, tomato-enriched white bread that was 40 percent tomatoes by weight, or carrot-enriched white bread that was 40 percent carrots by weight. The tomato bread was significantly more filling, but apparently not only because it was replacing some of the white flour, since the 40 percent carrot-enriched bread failed to cause the same dip in hunger.³⁹³⁹ Where can you find tomato bread, though? Can't you just eat a tomato? Good idea!

Women who were asked to eat a ripe tomato before lunch every day for one month dropped two pounds with improvements in blood sugars, cholesterol, and triglycerides.³⁹⁴⁰ Again, this study had no control group, but you can imagine how such a result could be possible. A tomato is 95 percent water, so you'd effectively be filling up a fist-sized portion of your stomach with only about fifteen calories right before a meal.³⁹⁴¹ This reminds me of the pears-and-apples study that found a similar effect interspersing meals with fruit.³⁹⁴²

Turmeric and Nutritional Yeast—Good as Gold?

If you recall, the spice turmeric is scored as the most anti-inflammatory food in the Dietary Inflammatory Index.³⁹⁴³ In vitro, curcumin—the pigment in turmeric responsible for its bright yellow color—has a stronger and broader anti-inflammatory profile than the powerful anti-inflammatory corticosteroid drug prednisolone.³⁹⁴⁴ Various turmeric preparations have been shown to offer benefit for inflammatory diseases of the joints,³⁹⁴⁵ lungs,³⁹⁴⁶ skin,³⁹⁴⁷ and gut.³⁹⁴⁸ This includes turmeric extracts, purified curcumin, and just about a half teaspoon a day of the plain spice you can find at the store.³⁹⁴⁹ Though curcumin from turmeric doesn't appear to blunt the acute, pro-inflammatory effects of a milkshake,³⁹⁵⁰ randomized controlled trials clearly show a drop in a variety of inflammatory markers when it is taken over time.^{3951,3952}

Turmeric is one of the few foods that have actually been put to the test in people. A turmeric-based spice mix was found to suppress hunger after a meal,³⁹⁵³ but what about weight loss?

Turmeric curcumin “blocks obesity” in mice fed a high-fat diet,³⁹⁵⁴ but the human data are disappointing. Out of eight randomized controlled trials, only three showed any kind of

significant weight-loss benefit.³⁹⁵⁵ A different golden-colored seasoning—nutritional yeast—shows more promise.

A special type of fiber called *beta-glucan* in brewer's, baker's, and nutritional yeasts displays anti-inflammatory effects³⁹⁵⁶ sufficient to improve wound healing³⁹⁵⁷ and alleviate symptoms in ragweed sufferers.³⁹⁵⁸ Randomized, double-blind, placebo-controlled clinical trials of about two teaspoons of nutritional yeast's worth of beta-glucans have resulted in about an inch off the waist within six weeks³⁹⁵⁹ or up to a five-pound weight benefit compared to controls in twelve weeks, along with an improvement in blood pressure.³⁹⁶⁰ Both of these studies were funded by companies trying to sell supplements, but I figure what are the side effects—tastier popcorn? I would, however, caution against the use of nutritional yeast for those with Crohn's disease³⁹⁶¹ or a skin condition known as *hidradenitis suppurativa*³⁹⁶² due to immune reactivity. (Further details can be found on NutritionFacts.org.)

FOOD FOR THOUGHT

The evidence base for weight loss from specific anti-inflammatory foods is pretty weak, but one would only expect benefits from swapping in goji berries for raisins, nailing my Daily Dozen recommendation for at least a quarter teaspoon of turmeric every day, seasoning with nutritional yeast instead of parmesan, for example, or trying my nutritional yeast-based Savory Spice Blend instead of salt (from my *How Not to Die Cookbook*, recipe online at www.nutritionfacts.org/recipe/savory-spice-blend/). Brewer's yeast has the same inflammation-modifying beta-glucan fiber as nutritional yeast, but it also has a bitter flavor that I remember all too well from my childhood. My mom used to mix a spoonful into orange juice to make what she used to call Yeast Juice (and yes, it tastes as bad as it sounds).

You can also try eating a tomato salad as an appetizer. What I like to do is quarter a ripe tomato, grind on some freshly cracked pepper, and add a drizzle of balsamic vinegar and some shreds of fresh basil. Delish!

INTERMITTENT FASTING

Caloric Restriction

The 3,500-Calorie Rule Is Wrong

Fasting is the practice of abstaining from all food for a period of time, while caloric restriction is a dietary regimen that simply reduces caloric intake. Anyone who's seen *The Biggest Loser* television shows knows that hundreds of pounds can be lost with enough exercise and caloric restriction.³⁹⁶³

Similarly, there are cases in the medical literature of what some doctors refer to as *super obesity*, defined as a BMI of 50 or more,³⁹⁶⁴ in which individuals lost up to 374 pounds largely on their own without professional help and kept it off for years.³⁹⁶⁵ In the case of the 374-pound loss, the guy lost about 20 pounds a month cycling two hours a day and reducing intake to eight hundred calories a day, which is down around what some were getting in World War II prisoner camps.³⁹⁶⁶

Perhaps America's most celebrated TV weight loss was when Oprah pulled out a wagonful of fat, representing the sixty-seven pounds she had lost on a very-low-calorie diet, onto the set of her talk show.³⁹⁶⁷ How many calories did she have to cut to achieve that weight loss in four months? If you consult leading nutrition textbooks,³⁹⁶⁸ read prestigious medical journals,³⁹⁶⁹ refer to trusted authorities like the Mayo Clinic,³⁹⁷⁰ or listen to the U.S. Surgeon General,³⁹⁷¹ you'll learn the simple weight-loss rule: One pound of fat is equal to 3,500 calories. Quoting from *The Journal of the American Medical Association*, "This means if you decrease (or increase) your intake by 500 calories daily, you will lose (or gain) 1 pound per week. (500 calories per day × 7 days = 3,500 calories.)"³⁹⁷²

Simple, but not true.

The 3,500-calorie rule can be traced back to a paper published in 1958 that simply noted that since fatty tissue in the human body is 87 percent fat, a pound of body fat would have about 395 grams of pure fat. Multiplying that by 9 calories per gram of fat gives us that 3,500-calories-per-pound approximation.³⁹⁷³ The fatal flaw that leads to “dramatically exaggerated” weight-loss predictions is that the 3,500 rule fails to take into account the fact that changes in the calories-in side of the energy-balance equation automatically lead to changes in the calories-out side—the slowing of metabolic rate that accompanies weight loss known as *metabolic adaptation*, for example.³⁹⁷⁴ That’s one of the reasons weight-loss plateaus.

Imagine a thirty-year-old sedentary woman of average height who weighs 150 pounds. According to the 3,500-calorie rule, by cutting 500 calories from her daily diet, she’d lose a pound a week or 52 pounds a year. In three years, then, she would apparently vanish. She’d go from 150 pounds to -6. Obviously, that doesn’t happen. What *would* happen is that, in the first year, instead of losing 52 pounds, she’d likely only lose 32 pounds and then, after a total of three years, stabilize at about 100 pounds.³⁹⁷⁵ This is because it takes fewer calories to exist as a thin person.

Part of it is simple physics in the same way a Hummer requires more fuel than a compact car.³⁹⁷⁶ Think how much more effort it would take just to get out of a chair, walk across the room, or climb a few stairs while carrying a fifty-pound backpack. That’s no lighter than carrying fifty pounds in the front in your belly. Even when lying at rest, sound asleep, there’s simply less of our bodies to maintain as we lose weight. Every pound of fat tissue lost may mean one less mile of blood vessels our bodies have to pump blood through every minute.³⁹⁷⁷ Since the basic upkeep and movement of thinner bodies take fewer calories, as you lose weight by eating less, you end up needing less. That’s what the 3,500-calorie rule doesn’t take into account.

Imagine it another way. A 200-pound man starts eating 500 more calories a day. That’s like two donuts. According to the 3,500-calorie rule, in ten years, he’d weigh more than 700 pounds. That doesn’t happen because the heavier he is, the more calories he burns simply existing.

If you’re one hundred pounds overweight, that’s like the skinny person inside you trying to walk around balancing thirteen gallons of oil at all times or lugging around a sack containing four hundred sticks of butter wherever you go. It takes about two donuts’ worth of extra energy just to live at 250 pounds compared to 200, so that’s where he’d plateau if he kept eating those extra 500 daily calories.³⁹⁷⁸ So weight gain or weight loss, given a certain calorie excess or deficit, is a curve that flattens out over time rather than a straight line going up or down.

Nevertheless, the 3,500-calorie rule continues to crop up—even in obesity journals.³⁹⁷⁹ That may be a consequence of the well-described innumeracy—mathematical illiteracy—that pervades the medical profession.³⁹⁸⁰ Public health researchers used it to calculate how many excess pounds children might avoid gaining each year if, for example, fast-food kids’ meals included apple slices instead of french fries.³⁹⁸¹ They figured two meals a week could add up to four pounds a year.³⁹⁸² The actual difference, National Restaurant Association-funded researchers were no doubt delighted to point out, would probably add under half a pound—ten times less than the 3,500-calorie rule would predict.³⁹⁸³

The original article was subsequently retracted.³⁹⁸⁴

A Slow Burn

Other players in the weight-loss game are all the compensatory survival mechanisms our bodies use to defend against weight loss. Because of our millions of years of evolution hardwiring us to survive scarcity,³⁹⁸⁵ when we start losing weight, we may unconsciously start moving less as a behavioral adaptation to conserve energy.³⁹⁸⁶ There are metabolic

adaptations as well. Our metabolisms slow down.³⁹⁸⁷ Every pound of weight loss may reduce our resting metabolic rates by seven calories a day.³⁹⁸⁸ This may only translate to a difference of a few percentage points for most,³⁹⁸⁹ but it can rapidly snowball for those who achieve massive weight loss.

During one season, some of *The Biggest Loser* contestants famously had their metabolic rates tracked. Above and beyond the hundreds of fewer calories it takes just to exist more than one hundred pounds lighter, by the end of filming for that season, their metabolic rates had slowed by an extra five hundred calories a day.³⁹⁹⁰ The mindblower was that when they were retested six years later, they still had the five-hundred-calorie-a-day handicap.³⁹⁹¹ So the contestants had to cut five hundred calories *more* than anyone else their size to maintain the same weight loss. No wonder the bulk of their weight was regained. Most did remain at least 10 percent lower than their starting weight, and even a 7 percent drop may cut diabetes rates by more than half,³⁹⁹² but still—the metabolic slowing means they have to work that much harder than everyone else just to stay in place.

Analyzing four seasons of *The Biggest Loser* minute by minute, researchers noted that 85 percent of the focus was on exercise rather than diet,³⁹⁹³ though the exercise component accounted for less than half of the weight loss.³⁹⁹⁴ Even six years after their season ended, the contestants had been maintaining the hour of daily, vigorous exercise, yet still regained most of the weight. Why? They started eating more. They could have cut their exercise from sixty to just twenty minutes a day and still maintained 100 percent of their initial weight loss if they would have just kept their intakes under three thousand calories a day.³⁹⁹⁵ That may not sound like much of a challenge, but weight loss doesn't just slow our metabolisms—it boosts our appetites.

Appetite for Destruction

If it were merely a matter of our weight settling at the point at which our reduced caloric intakes match our reduced caloric outputs, it would take years for our weight loss to plateau. Instead, the plateau often occurs within six to eight months.³⁹⁹⁶ You probably know the drill: Start the diet, stick to the diet, and then weight loss stalls six months later. What happened? Don't blame your metabolism—that only plays a small part. What likely happened is you actually stopped sticking to your diet because your appetite went on a rampage.

If you cut eight hundred calories out of your daily diet and your weight loss stalls after six months, what happened is that despite thinking you're still down eight hundred calories a day, you may actually only be down six hundred daily calories at the end of the first month. By month two, you're only down about five hundred calories, down three hundred by month three, and by month six, you're only eating two hundred fewer calories than before you had started the diet. In other words, you inadvertently suffered an exponential increase in caloric intake over those six months without even realizing it, because, by that time, your body may have ramped up your appetite by six hundred calories. So it still *feels* as if you are eating eight hundred fewer calories, but you're actually only down two hundred. By then, your metabolism and physical activity also may have slowed by two hundred calories a day, so with no difference between calories in and calories out, that's how your weight loss grinds to a complete halt.³⁹⁹⁷

The slow, upward drift in caloric intake on a new diet is not because you got lazy. Once your appetite is boosted by six hundred calories after you've been dieting for a while, eating two hundred fewer calories is as hard as eating eight hundred fewer calories had been at the beginning. So you can maintain the same disciplined level of willpower and self-control, yet still end up stagnating.³⁹⁹⁸ To prevent this from happening, we need to maintain the calorie deficit. How is that possible in the face of a ravenous appetite?

Hunger is a biological drive. Asking someone to eat smaller portions is like asking them to take fewer breaths. You can white-knuckle it for a bit, but eventually nature wins out. That's what this book is for. Remember how I discussed in the Eating Rate section that you can cut more than a thousand calories out of people's daily diets without them even noticing? Sustainable weight loss is not about eating *less* food—it's about eating *better* food.

The Ten-Calorie Rule

If you are able to take advantage of some of the techniques in this book and dutifully maintain a calorie deficit, what weight loss could you expect? If the 3,500-calorie rule is bunk, what's the alternative? There are validated mathematical models that take into account the dynamic changes that occur when you cut calories, such as the metabolic slowdown. They've been turned into free online calculators you can use to make personalized estimates. There's the Body Weight Planner from the National Institutes of Health (NIH) and the Pennington Biomedical Research Center's Weight Loss Predictor out of Louisiana State University (LSU).

- NIH Body Weight Planner: www.bit.ly/NIHcalculator
- LSU Weight Loss Predictor: www.bit.ly/LSUcalculator

The NIH Body Weight Planner has been found to be more accurate, as the LSU model appears to overestimate the drop in physical activity,³⁹⁹⁹ but they each have their pluses and minuses. The Body Weight Planner tells you how many calories you need to restrict and/or how much more exercise you need to do to achieve a specific weight-loss goal by a specific date. Clicking on the Switch to Expert Mode button gives you a graph and exportable chart showing your day-by-day weight-loss trajectory. The LSU Weight Loss Predictor, on the other hand, doesn't allow you to adjust physical activity, but its advantage is that you don't have to choose a goal or time frame. Just put in different calorie changes, and it graphs out your expected course.

Is there any easy rule of thumb you can use? Yes—the Ten-Calorie Rule. Every permanent, ten-calorie drop in daily intake will eventually lead to about one pound of weight loss.⁴⁰⁰⁰ It takes about a year to achieve half the total weight change and about three years to completely settle into the new weight. So cutting five hundred calories a day can cause the fifty-pound weight loss predicted by the 3,500-calorie rule, but that's the total weight loss at which you plateau, not an annual drop, and it takes about three years to get there. A five-hundred-calorie deficit would be expected to cause about a twenty-five-pound weight loss the first year and then an additional twenty-five pounds over years two and three, but that's only if you can *maintain* the five-hundred-calorie deficit.

If you're eating the same diet that led to the original weight problem but just in smaller servings, you should expect your appetite to rev up about forty-five calories for each pound you lose.⁴⁰⁰¹ So if you were cutting five hundred calories a day through portion control alone, before you were down even a dozen pounds, you'd feel so famished that you'd be driven to eat *more* than five hundred calories a day and your weight loss could vanish. That's why if you're dead set on eating the same diet with the same foods only in smaller quantities, you have to cut down more than forty-five calories per pound of desired weight loss to offset your hunger drive.

So to get that one pound off, instead of eating just ten fewer calories a day using the Ten-Calorie Rule, you'd have to eat ten fewer calories *on top of* the forty-five fewer calories to account for the revving of your appetite, so that's a total of fifty-five fewer daily calories. Indeed, just changing diet *quantity* and not *quality* requires you to take in fifty-five fewer calories per day to lose a single pound. That five-hundred-calorie daily deficit would only

net you about a nine-pound weight loss (500 ÷ 55) three years later instead of fifty pounds.⁴⁰⁰² That's why portion-control methods can be such a frustrating failure for so many people.

The Flame That Burns Twice as Bright Burns Half as Long

Though a bane for dieters, a slower metabolism may actually be a good thing. We've known for more than a century that caloric restriction can increase the life spans of animals,⁴⁰⁰³ and the metabolic slowdown may be the mechanism.⁴⁰⁰⁴ That could be why the tortoise lives ten times longer than the hare.⁴⁰⁰⁵ (Harriet, a tortoise evidently collected from the Galapagos by Charles Darwin in the 1830s, lived until 2006.⁴⁰⁰⁶) Slow and steady may indeed win the race.

One of the ways our bodies lower our resting metabolic rates is by creating cleaner-burning, more efficient mitochondria, the power plants that fuel our cells.⁴⁰⁰⁷ It's like our bodies pass their own fuel-efficiency standards. These new mitochondria appear to create the same energy with less oxygen and produce less free-radical "exhaust." After all, our bodies are afraid famine is afoot, so they try to conserve as much energy as they can.

Indeed, the largest caloric-restriction trial to date found both metabolic slowing and a reduction in free radical-induced oxidative stress, both of which may slow the rate of aging.⁴⁰⁰⁸ Whether this will translate into greater human longevity is an unanswered question. Caloric restriction is said to extend the life span of "every species studied,"⁴⁰⁰⁹ but this isn't even true of all strains within a single species.⁴⁰¹⁰ Some scientists don't think caloric restriction will improve human longevity at all, while others suggest a 20 percent caloric restriction starting at age twenty-five and sustained for fifty-two years could add five years onto our life spans.⁴⁰¹¹ Either way, the reduced oxidative stress would be expected to improve our *health* spans.⁴⁰¹²

Members of the CR Society International, self-styled CRONies (for *calorie restriction with optimal nutrition*), appear to be in excellent health, but they're a rather unique, self-selected bunch of individuals.⁴⁰¹³ As always, you don't really know until you put it to the test. Enter CALERIE, the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy, the first clinical trial to test the effects of caloric restriction.⁴⁰¹⁴

Hundreds of nonobese men and women were randomized to two years of 25 percent caloric restriction. Though they only ended up achieving half of that, they still lost about eighteen pounds and three inches off their waists, wiping out more than half their visceral abdominal fat.⁴⁰¹⁵ That translated into significant improvements in blood pressure, insulin sensitivity, triglycerides, and cholesterol levels.⁴⁰¹⁶ Eighty percent of those who were overweight when they started were normal weight by the end, compared to a 27 percent increase in those who became overweight in the control group.⁴⁰¹⁷

In the famous Minnesota Starvation Experiment that used conscientious objectors as human guinea pigs during World War II, the study subjects suffered both physically and psychologically, experiencing depression, irritability, and loss of libido.⁴⁰¹⁸ The subjects started out lean, though, and had their caloric intakes cut in half. The CALERIE study ended up being four times less restrictive, at only about 12 percent below baseline caloric intake, and enrolled normal-weight individuals, which in the United States these days means overweight on average. As such, the CALERIE subjects experienced nothing but positive quality-of-life benefits with significant improvements in mood, general health, sex drive, and sleep.⁴⁰¹⁹ During the final year, they were eating only about three hundred fewer calories than they had been at baseline,⁴⁰²⁰ so they got all those benefits after cutting only about a snack-sized bag of chips' worth of calories from their daily diets.

What happened at the end of the trial, though? In both the Minnesota Starvation Experiment⁴⁰²¹ and experiments on U.S. Army Rangers,⁴⁰²² as soon as subjects were released from restriction, they tended to rapidly regain the weight—and sometimes more.

The leaner they started out, the more their bodies seemed to drive them to overeat to pack back on extra body fat.⁴⁰²³ In contrast, after the completion of the CALERIE study, even though their metabolisms were slowed, they retained about 50 percent of the weight loss two years later.⁴⁰²⁴ They must have acquired new eating attitudes and behaviors that allowed them to keep their weight down. Indeed, after extended caloric restriction, cravings for sugary and fatty foods do go down.⁴⁰²⁵

Potential Pitfalls of Caloric Restriction

One of the most consistent benefits of caloric restriction is improvement in blood pressure in as short as one or two weeks.⁴⁰²⁶ Unfortunately, this can work a little too well and cause orthostatic intolerance,⁴⁰²⁷ manifesting as light-headedness or dizziness upon standing, which, in severe cases, can cause fainting. Staying hydrated can help, though,⁴⁰²⁸ as I discuss in more detail in the Metabolic Boosters section.

What about loss of muscle mass? In the CALERIE trial, 70 percent of the lost body weight was fat and 30 percent was lean body mass,⁴⁰²⁹ so the subjects ended up with an improved body composition, from 67 percent lean and 33 percent fat to 72 percent lean and 28 percent fat.⁴⁰³⁰ Though leg muscle mass and strength declined in absolute terms, relative to their new body size, they generally got stronger.⁴⁰³¹ Is there any way to preserve more lean mass, particularly among older individuals who naturally tend to lose muscle mass with age?

Increased protein intakes are commonly suggested, but most studies fail to show a beneficial effect on preserving muscle strength or function, whether young or old, active or sedentary.⁴⁰³² For example, researchers randomized overweight older men and women to either a normal-protein diet of four grams for every ten pounds of body weight or a high-protein diet with about eight grams per ten pounds, during a 25 percent caloric restriction. A doubling of protein intake had no discernible effect on lean body mass, muscle strength, or physical performance.⁴⁰³³ Most such studies have found the same lack of benefit,⁴⁰³⁴ but after putting them all together, one can tease out a “very small” advantage.⁴⁰³⁵ Unfortunately, high-protein intake during weight loss has been found to have “profound” negative metabolic effects, undermining the benefits of weight loss on insulin sensitivity.⁴⁰³⁶

Though you can always bulk back up after weight loss, the best way to preserve muscle mass during weight loss is exercise. The CALERIE study had no structured exercise component, and, just like after bariatric surgery, about 30 percent of the weight loss was lean mass. In contrast, that proportion was only about 16 percent in *The Biggest Loser* contestants, chalked up to their vigorous exercise programs.⁴⁰³⁷ Resistance training even just three times a week can prevent more than 90 percent of lean body mass loss during caloric restriction.⁴⁰³⁸

The same may be true of bone loss. Lose weight through caloric restriction alone, and you experience a decline in bone mineral density in fracture-risk sites like the hip and spine. However, in the same study, those randomized to lose weight with exercise didn’t suffer any bone loss. The researchers concluded: “Our results suggest that regular EX [exercise] should be included as part of a comprehensive weight loss program to offset the adverse effects of CR [caloric restriction] on bone.”⁴⁰³⁹

You can never argue with calls for increased physical activity, but even without an exercise regimen, the “very small” drop in bone mineral density in the CALERIE study might only increase ten-year risk of osteoporotic fracture by about 0.2 percent.⁴⁰⁴⁰ The benefits of caloric restriction revealed by the CALERIE trial—improved blood pressure, cholesterol, mood, libido, and sleep—would seem to far outweigh any potential risks. The fact that a reduction in calories seemed to have such wide-ranging positive effects led commentators in the American Medical Association’s internal medicine journal to write: “The findings of

this well-designed study suggest that intake of excess calories is not only a burden to our physical homeostasis but also on our psychological well-being."⁴⁰⁴¹

Fasting

The Fast Track to Weight Loss

The greatest caloric restriction is no calories at all. Fasting has been branded the “next big weight loss fad” but has a long history throughout various spiritual traditions, practiced by Moses, Jesus, Muhammad, and Buddha.⁴⁰⁴² In 1732, a noted physician wrote, “He that eats till he is sick must fast till he is well.”⁴⁰⁴³ Today, about one in seven American adults reports using some sort of fasting as a means to control body weight.⁴⁰⁴⁴

Case reports of the treatment of obesity through fasting date back more than a century in the medical literature. In 1915, Harvard doctors described “two extraordinarily fat women” whose weight-loss success led the physicians to conclude that “moderate periods of starvation constitute a perfectly safe, harmless, and effective method for reducing the weight of those suffering from obesity.”⁴⁰⁴⁵

The longest recorded fast, published in 1973, made it into the *Guinness Book of World Records*. To reach his ideal body weight, a twenty-seven-year-old man fasted for 382 days straight, losing 276 pounds, and managed to keep nearly all of it off.⁴⁰⁴⁶ He was given vitamin and mineral supplements, but no calories for more than a year. In their acknowledgments, the researchers thanked him for “cheerful cooperation and steadfast application to the task of achieving a normal physique.”⁴⁰⁴⁷

In a U.S. Air Force study of twenty-five individuals, the majority of whom were at least one hundred pounds overweight and “unable to lose weight on previous diets,” the subjects were fasted for as long as eighty-four days. Nine people dropped out of the study, but the sixteen who remained were “unequivocally successful” at losing between forty and one hundred pounds. According to the researchers, such subjects lose as much as four pounds a day in the first few days. That is mostly water weight, shed as the body starts to adapt to the fast, but after a few weeks, they can be steadily losing about a pound of mostly straight fat per day. The investigator described their “starvation program” as a “dramatic and exciting treatment for obesity.”⁴⁰⁴⁸

Of course, this single *most* successful diet for weight loss—namely, no diet at all—is also the single *least* sustainable. What other diet can cure morbid obesity in a matter of months but be practically guaranteed to kill you within a year if you stick with it?

The reason diets don’t work almost by definition is that people go on them, and then they go off them. Permanent weight loss is only achieved through permanent lifestyle change. So what’s the point of fasting if you’re just going to go back to your regular diet and gain all the weight right back?

Fasting proponents cite the psychological benefit of realigning people’s perceptions and motivation.⁴⁰⁴⁹ Some individuals have resigned themselves to the belief that weight loss is somehow impossible for them. They may think they’re made differently in some way, and the pounds just won’t come off no matter what they do.⁴⁰⁵⁰ The rapid, unequivocal weight loss during fasting demonstrates to them that, with a large enough change in eating habits, it’s not just possible but also inevitable. This morale boost from reasserting control may then embolden them to make better food choices once they resume eating.⁴⁰⁵¹

The break from food may allow some an opportunity to pause and reflect on the role food is playing in their lives—not only the power it has over them but the power they then have over it.⁴⁰⁵² In a fasting study entitled “Correction and Control of Intractable Obesity,” a subject’s personality was described as changing “from one of desperation, with abandonment of hope, to that of an eager extrovert full of plans for a promising future.” She realized that her weight was within her own power to control.⁴⁰⁵³ The researchers

reported: “This highly intellectual social worker has been returned to a full degree of exceptional usefulness.”

After a fast, newfound commitments to more healthful eating may be facilitated by a reduction in overall appetite reported post-fast compared to pre-fast.⁴⁰⁵⁴ Even during a fast, hunger may start to dissipate within thirty-six hours.⁴⁰⁵⁵ As such, challenging people’s delusions about their exceptionality to the laws of physics with a period of total fasting may “seem barbaric,” wrote a group of researchers in the journal of the American Medical Association, but “in reality, this method of reduction is remarkably well tolerated by obese patients.”⁴⁰⁵⁶ This seems to be a recurring theme in these published series of cases. In an influential paper entitled “Treatment of Obesity by Total Fasting for Up to 249 Days,” the researchers remarked, “The most surprising aspect of this study was the ease with which the prolonged fast was tolerated.” Evidently, all their patients spontaneously commented on their increased sense of well-being throughout the process. The researchers concluded: “We are convinced that it is the treatment of choice, certainly in cases of gross obesity.”⁴⁰⁵⁷

Fasting for a day can make people moody, irritable,⁴⁰⁵⁸ and distracted,⁴⁰⁵⁹ but a few days into a fast, many report feeling clear, elated, and alert—even euphoric.⁴⁰⁶⁰ This may be due in part to the significant rise in endorphins that accompanies fasting.⁴⁰⁶¹ Mood enhancement during fasting is thought perhaps to represent an adaptive survival mechanism to motivate the search for food. This positive outlook toward the future may then facilitate the behavioral change necessary to lock in some of the weight-loss benefits.⁴⁰⁶²

Is Fasting Effective?

How do fasted patients do long term? (As we’ve said, in obesity research, *long term* typically means only one or two years, which itself says much about the field.) Some research groups reported “extremely disappointing” results. At around the one-year follow-up after an average weight loss of twenty-seven pounds in twenty-five days of “inpatient starvation,” one study of twenty-three subjects found they had gained back an average of twenty-nine pounds.⁴⁰⁶³ In another study with follow-ups ranging up to fifty months, only four out of twenty-five “superobese” patients achieved even partial sustained success.⁴⁰⁶⁴ Based on these kinds of data, some investigators concluded that “complete starvation is of no value in the long-term treatment of obese patients.”⁴⁰⁶⁵

Other research teams have reported better outcomes. One series of more than one hundred individuals found that 60 percent either retained at least some weight loss at follow-up (43 percent) or even continued losing weight (17 percent).⁴⁰⁶⁶ The follow-up periods varied from one to thirty-two months with no breakdown as to who lasted how long, though, making the data hard to interpret.⁴⁰⁶⁷ In another study, one year after fasting sixty-two patients down sixteen pounds in ten days, 40 percent retained at least seven pounds of that weight loss.⁴⁰⁶⁸

Putting six such studies together, hundreds of obese subjects who fasted for an average of forty-nine days lost an average of fifty-two pounds, and around one or two years later, 40 percent had retained at least some of the weight loss.⁴⁰⁶⁹ So although most gained back all their weight, 40 percent keeping off at least some weight is extraordinary for a weight-loss study. By comparison, researchers followed one hundred obese individuals on a standard low-calorie diet while getting treatment at a weight-loss clinic and found only one out of one hundred had lost more than forty pounds, and only about one in ten had lost even twenty pounds, with the overall successful weight maintenance at only 2 percent over two years.⁴⁰⁷⁰ That’s why having a control group is so important. What may look like a general failure in the fasting trials may actually be a relative success compared to more traditional weight-loss techniques.

Researchers new to the field may find the results reported in a seventy-five-subject “long-term follow-up of therapeutic starvation” to be “clearly disappointing.”⁴⁰⁷¹ One year later, two-thirds were “failures” with more than one-third regaining all the weight they had initially lost. But 12 percent were labeled successes, maintaining sixty pounds of weight loss two years later.⁴⁰⁷² In a direct comparison of different weight-loss approaches at another clinic, five years after initiating a conventional low-calorie approach, only about one in five was down twenty pounds compared to nearly half in the group who instead had undergone a few weeks of a fasting program years previously. By year seven, most of those instructed on daily caloric restriction were back to, or had exceeded, their original weight, but that was true of only about one in ten of the fasted group.⁴⁰⁷³ In an influential paper published in *The New England Journal of Medicine* on seven myths about obesity, fallacy number three was that “large, rapid weight loss is associated with poorer long-term weight-loss outcomes, as compared with slow, gradual weight loss.”⁴⁰⁷⁴ In reality, the opposite is true. The hare may end up skinnier than the tortoise.

Researchers set up a study comparing the sustainability of weight loss at three different speeds: six days of fasting, three weeks of a very-low-calorie diet of six hundred daily calories, or six weeks of a low-calorie diet of twelve hundred daily calories. A year later, the fasting group was the only one who had sustained a significant loss of weight.⁴⁰⁷⁵ That was just after one year, though. How about nine years later? “Therapeutic Fasting in Morbid Obesity” is the largest, longest follow-up study I could find.⁴⁰⁷⁶ At least some of the fast-induced weight losses sustained a year later were maintained by the “great majority” (90 percent) of the 121 patients. Nine years later, however, that number dropped to fewer than one in ten. Almost everyone had regained the weight they had fasted away. Many patients reported they thought the temporary loss was worth it, though. As a group, they had lost an average of about sixty pounds. They described improved health and quality of life, claiming reemployment was facilitated and earnings increased during that period of time, but the fasting didn’t appear to result in any permanent change in eating habits for the vast majority. The small minority for whom fasting led to sustainable weight loss “all admit to a radical change in previous eating habits.”⁴⁰⁷⁷

Fasting only works long term if it can act as a jump-start to a more healthful diet.

In a retrospective, long-term comparison of weight reduction after an inpatient stay at a naturopathic center, those who were fasted lost more weight at the time but were back to the same weight around seven years later. No surprise, since most returned to the same diet they had eaten before. Those who were placed instead on a more healthful, whole-food, plant-based diet were more likely to make persistent changes in their eating patterns and, seven years later, were on average lighter than when they had started.⁴⁰⁷⁸

Can’t we have it both ways? Why not use fasting to kick-start a big drop in weight and *then* start a healthy diet? The problem is that initial big drop is largely illusory.

Fasting for a week or two can cause more weight loss than caloric restriction, but, paradoxically, it may actually lead to *less* loss of body fat. Eating more calories can lead to more fat loss? Yes. During fasting, the body starts cannibalizing itself and burning more of our protein for fuel.⁴⁰⁷⁹ Emperor penguins, elephant seals, and hibernating bears can survive just burning fat without dipping into their muscles, but our voracious, big brains appear to need at least a trickle of blood sugar, and if we’re not eating any carbohydrates, our bodies are forced to start turning our protein into sugar to burn.⁴⁰⁸⁰ Even just a few grams of carbs, like those consumed by people who add honey to their water when they fast, for example, can cut protein loss up to 50 percent.⁴⁰⁸¹ What about adding exercise to prevent loss of lean tissues during a fast? That may make it even worse!⁴⁰⁸² At rest, most of our heart and muscle energy needs can be met with fat, but if we start exercising, some of the blood sugar meant for our brains is used and our bodies may have to break down even more protein.⁴⁰⁸³

Less than half the weight lost during the first few weeks of fasting comes from our fat stores.⁴⁰⁸⁴ So even if we double our daily weight loss on a fast, we may actually be losing less *fat*. An NIH-funded study placed obese individuals on an eight-hundred-calorie-a-day diet for two weeks, and they steadily lost about a pound of body fat a day. They then switched to about two weeks of zero calories and started losing more protein and water, but, on average, only lost a few ounces of fat a day. When the subjects were subsequently switched back to the initial eight-hundred-calorie-a-day diet for a week, they rapidly replaced the protein and water they had lost, so the scale registered that their weight went up, but their body fat loss accelerated back to the approximate pound lost a day.⁴⁰⁸⁵ The scale made it look as though they were doing better when they were completely fasting, but the reality is they were doing worse. During the five-week experiment, they would have lost more body fat sticking to their calorie-restricted diet than completely stopping eating in the middle of the trial.

Is Fasting Safe?

Eventually, after the third week of fasting, fat loss starts to overtake the loss of lean body mass in obese individuals, but is it safe to go that long without food? Proponents speak of fasting as a cleansing process, but some of what they are purging from their bodies are essential vitamins and minerals.⁴⁰⁸⁶ Heavy-enough people can go up to 382 days without calories, but no one can go even a fraction that long without vitamins. Scurvy, for example, is diagnosable within as few as four weeks without any vitamin C.⁴⁰⁸⁷ Beriberi is the disease caused by thiamine deficiency, the inadequate intake of vitamin B1. It may start even earlier than scurvy in fasting patients⁴⁰⁸⁸ and, once manifest, can result in brain damage within days,⁴⁰⁸⁹ which can eventually become irreversible.⁴⁰⁹⁰ Even though fasting subjects report problems such as nausea and indigestion taking supplements,⁴⁰⁹¹ all the months-long fasting cases I've mentioned were given daily multivitamins and mineral supplementation as necessary. Without supplementation, hunger strikers and those undergoing prolonged fasts for therapeutic or religious purposes, like the Baptist pastor hoping to "enhance his spiritual powers for exorcism," have ended up paralyzed,⁴⁰⁹² comatose,⁴⁰⁹³ or worse.⁴⁰⁹⁴

Nutrient deficiencies aren't the only risk of extended fasting. Reading about all the successful reports of massive weight loss from prolonged fasting in the medical literature, one doctor decided to give it a try. Of the first dozen patients he put on fasts, two died. His report, "Death During Therapeutic Starvation for Obesity," certainly put a damper on the enthusiasm for fasting.⁴⁰⁹⁵ In retrospect, the two patients who died started out with heart failure and had been on diuretics. Fasting itself produces a pronounced diuresis, a loss of water and electrolytes through the urine, so it was the combination of fasting on top of the "water pills" that likely depleted their potassium and triggered their fatal heart rhythms.⁴⁰⁹⁶ The doctor went out of his way to point out that "both the deaths in this series were admitted in severe heart-failure ... but both had improved greatly whilst undergoing starvation therapy."⁴⁰⁹⁷ Small consolation since they were both dead within a matter of weeks.

It would be one thing if all therapeutic fasting fatalities had come from complications of concurrent diuretic use, but that is not the case. "At first he did very well and experienced the usual euphoria," described one doctor about a fasting patient. His electrolytes remained fine, but, in the middle of the third week, he suddenly collapsed and died. "This line of treatment is certainly tempting because it does produce weight-loss and the patient feels so much better," the doctor concluded, "but the report of case-fatalities must make it a very suspect line of management."⁴⁰⁹⁸

Contrary to the popular notion that the heart muscle is specially spared during fasting, the heart appears to experience similar muscle wasting.⁴⁰⁹⁹ This was noted in the victims of

the Warsaw ghetto during World War II in a remarkable series of detailed studies carried out by the ghetto physicians before they themselves succumbed.⁴¹⁰⁰ In a case entitled “Gross Fragmentation of Cardiac Myofibrils After Therapeutic Starvation for Obesity,” a twenty-year-old woman achieved her ideal body weight after losing 128 pounds fasting for thirty weeks. After a breakfast of one egg, she had a heart attack and died. On autopsy, the muscle fibers in her heart showed evidence of widespread disintegration. The pathologists suggested that “this regimen should no longer be recommended as a safe means of weight reduction.”⁴¹⁰¹

Breaking the fast appears to be the most dangerous part.⁴¹⁰² After World War II, as many as one out of five starved Japanese prisoners of war tragically died following liberation.⁴¹⁰³ Now known as *refeeding syndrome*, multi-organ system failure can result from resuming a regular diet too quickly.⁴¹⁰⁴ Some critical nutrients, such as thiamine and phosphorus, are used to metabolize food. In the critical refeeding window, if too much food is taken before these nutrients can be replenished, demand may exceed supply and whatever residual stores are still left can be driven down even further, with potentially fatal consequences.⁴¹⁰⁵ That’s why rescue workers are taught to always give thiamine before food to victims who had been trapped or otherwise unable to eat.⁴¹⁰⁶ Thiamine is responsible for the yellow color of “banana bags,” a term you might have heard used on medical dramas, used to describe an IV fluid concoction often given to malnourished alcoholics to prevent a similar reaction.⁴¹⁰⁷ Anyone with negligible food intake for more than five days may be at risk of developing refeeding problems.⁴¹⁰⁸

Don’t Try This at Home

Medically supervised fasting has gotten much safer now that there are proper refeeding protocols, we know what warning signs to look for, and we know who shouldn’t be fasting in the first place⁴¹⁰⁹ (such as those with advanced liver or kidney failure, porphyria, or uncontrolled hyperthyroidism, and women who are pregnant or breastfeeding).⁴¹¹⁰ The most comprehensive safety analysis of medically supervised, water-only fasting was recently published out of the TrueNorth Health Center in California. From the 768 visits to their facility for fasts up to forty-one days, were there any adverse events? Yes, 5,961 of them. Most were mild, known reactions to fasting, however, such as fatigue, nausea, insomnia, headache, dizziness, upset stomach, and back pain. Only two serious events were reported, with no fatalities.⁴¹¹¹

Fasting longer than twenty-four hours and, particularly, for three or more days should only be done under the supervision of a physician and preferably in a live-in clinic.⁴¹¹² This is not just legalistic mumbo-jumbo. For example, your kidneys normally dive into sodium-conservation mode during fasting, but should that response break down, you could rapidly develop an electrolyte abnormality that may only manifest with nonspecific symptoms like fatigue or dizziness, which could easily be dismissed until it’s too late.⁴¹¹³

The risks of any therapy must be premised on the severity of the disease. The consequences of obesity are considered so serious that effective therapies could have “considerable acceptable toxicity.”⁴¹¹⁴ For example, many consider major surgery for obesity to be a justifiable risk, but the key word is *effective*.

Therapeutic fasting for obesity has been largely abandoned by the medical community not only because of its uncertain safety profile but also because of its questionable short- and long-term efficacy.⁴¹¹⁵ Remember, for a fast that only lasts a week or two, you might be able to lose as much body fat, or even more, on a low-calorie diet than a no-calorie diet. Abstinence may be easier to practice than temperance, though. Paradoxically, studies suggest people experience less hunger on a total fast compared to a low-calorie diet.⁴¹¹⁶ This may be thanks to ketones.

We've discussed how blood sugar (glucose) is a universal go-to fuel for the cells throughout our bodies.⁴¹¹⁷ Our bodies can break down proteins and make glucose from scratch, but most glucose comes from our diets in the form of sugars and starches. If we stop eating carbohydrates, most of our cells switch over to burning fat, but fat has difficulty getting through the blood-brain barrier.⁴¹¹⁸ Our brains burn through about a half cup of sugar a day.⁴¹¹⁹ That's up to a quarter of our resting metabolic rates (and up to 50 percent in children).⁴¹²⁰ To make that much sugar, we'd need to break down about a half pound of protein a day,⁴¹²¹ which means we'd cannibalize ourselves to death within approximately two weeks. But people can fast for months. How is that possible?

The answer to the puzzle was discovered in 1967. Harvard researchers famously stuck catheters into the brains of obese subjects who had been fasting for more than a month and discovered that ketones had replaced glucose as the primary fuel for the brain.⁴¹²² Your liver turns fat into ketones, which can then breach the blood-brain barrier and sustain your brain.

In this state of ketosis, when you have high levels of ketones in your bloodstream, your hunger is dampened. This may be why people's hunger can dissipate after a few days on a fast, as their brain switches over to ketones for fuel.⁴¹²³ When ketones are injected straight into people's veins, even those who are not fasting lose their appetites, sometimes even to the point of getting nauseated and vomiting.⁴¹²⁴ So ketones can explain why you might feel hungrier on a low-calorie diet than on a total fast. Can we then exploit the appetite-suppressing effects of ketosis by eating a ketogenic diet? If you ate too few carbs to sustain brain function, couldn't you trick your body into thinking you're fasting and start pumping out ketones? Yes. But is it safe? Is it effective?

Ketogenic Diets

Seizing Upon the Ketogenic Diet

The prescription of fasting for the treatment of epileptic seizures dates back to Hippocrates,⁴¹²⁵ and according to Mark 9:29, Jesus seems to have concurred.⁴¹²⁶ To this day, it's unclear why switching from blood sugar to ketones as a primary fuel source has such a dampening effect on brain overactivity.⁴¹²⁷ To prolong the therapy, in 1921, a distinguished physician and scientist at the Mayo Clinic suggested trying what he called a *ketogenic diet*, a high-fat diet designed to be so deficient in carbohydrates it could effectively mimic the fasting state.⁴¹²⁸ "Remarkable improvement" in seizures was noted the first time it was put to the test,⁴¹²⁹ efficacy that was later confirmed in randomized controlled trials.⁴¹³⁰ Ketogenic diets started to fall out of favor in 1938 with the discovery of the anti-seizure drug phenytoin (later sold as Dilantin),⁴¹³¹ but they are still in use today as a third-line treatment for drug-refractory epilepsy in children.⁴¹³²

Oddly, the success of ketogenic diets against pediatric epilepsy seems to get conflated by keto diet proponents into suggesting a ketogenic diet is beneficial for everyone.⁴¹³³ You know what else sometimes works for intractable epilepsy? Brain surgery, but I don't hear people clamoring to get their skulls sawed open. Since when do medical therapies translate into healthy lifestyle choices? Ketogenic diets are also being tested to see if they can slow the growth of certain brain tumors.⁴¹³⁴ Even if they are successful, you know what else can help slow cancer growth? Chemotherapy. Why go keto when you can just go chemo?

Promoters of ketogenic diets for cancer, paid by "ketone technology" firms⁴¹³⁵ or companies that market ketogenic meals,⁴¹³⁶ report "extraordinary" anecdotal responses in some cancer patients.⁴¹³⁷ I'm sure they do. But more concrete evidence is lacking.⁴¹³⁸ Even the theoretical underpinnings may be questionable. A common refrain is that "cancer feeds on sugar."⁴¹³⁹ True, but *all* cells feed on sugar. Advocating ketogenic diets for cancer is like saying Stalin breathed air, so we should boycott oxygen.

Cancer can also feed on ketones. Indeed, ketones have been found to fuel human breast cancer growth and drive metastases in an experimental model, more than doubling tumor growth.⁴¹⁴⁰ Some have even speculated that may be why breast cancer often metastasizes to the liver, the main site of ketone production.⁴¹⁴¹ When ketones were dripped on breast cancer cells in a petri dish, the genes that got turned on and off made for a much more aggressive cancer and were associated with a significantly lower five-year survival in breast cancer patients.⁴¹⁴² Researchers are even considering ketone-*blocking* drugs to prevent further cancer growth by halting ketone production.⁴¹⁴³

High-fat diets in general are purported to increase breast cancer risk through “oxidative stress, hormonal dysregulation, or inflammatory signaling.”⁴¹⁴⁴ A strong association has also been found between saturated fat intake and prostate cancer progression. Those in the top third of saturated fat consumption appeared to triple their risk of dying from prostate cancer.⁴¹⁴⁵ A meta-analysis of studies on diet and breast cancer mortality concluded that “saturated fat intake negatively impacts upon breast cancer survival,” finding a 50 percent increase in the hazard of breast cancer-specific death for those with the most saturated fat intake compared to those women with the least.⁴¹⁴⁶ There’s a reason the official American Cancer Society / American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines recommend a dietary pattern for breast cancer patients that’s essentially the opposite of a ketogenic diet: “high in vegetables, fruits, whole grains, and legumes; low in saturated fats.”⁴¹⁴⁷

So far, not a single clinical study has shown a measurable benefit from a ketogenic diet for any human cancer.⁴¹⁴⁸ There are currently at least a dozen trials under way, however, and the hope is that at least some cancer types will respond.⁴¹⁴⁹ Still, that wouldn’t serve as a basis for recommending ketogenic diets for the general population any more than would recommending everyone go out and get radiation, surgery, and chemo just for kicks.

Ketogenic Diet Put to the Test

By eschewing carbohydrates, you force your body to burn fat. And indeed, the amount of fat you burn shoots up when you eat a ketogenic diet.⁴¹⁵⁰ At the same time, however, the fat you *take in* shoots up when you eat a ketogenic diet. The question is *what happens to our overall body-fat balance?* ⁴¹⁵¹ You can’t empty a tub by widening the drain if you’re also cranking open the faucet. Low-carb advocates had a theory, though—the so-called carbohydrate-insulin model of obesity.

Proponents of low-carbohydrate diets, whether a ketogenic diet or some more relaxed form of carbohydrate restriction, suggested that the decreased insulin secretion would lead to less fat storage. So even if you were eating more fat, less of it would stick to your frame. You’d be burning more and storing less—the perfect combination for fat loss—or so the theory went.⁴¹⁵² To their credit, instead of just speculating about it, they decided to put it to the test.

In 2012, Gary Taubes co-formed the Nutrition Science Initiative reportedly to sponsor research to validate the carbohydrate-insulin model.⁴¹⁵³ He’s the journalist who wrote the controversial 2002 *New York Times Magazine* piece “What If It’s All Been a Big Fat Lie?” which attempted to turn nutrition dogma on its head by arguing in favor of the Atkins diet and its bunless bacon cheeseburgers based on the carbohydrate-insulin model.⁴¹⁵⁴ (Much of Nina Teicholz’s more recent *The Big Fat Surprise* is simply recycled from Taubes’s earlier work.⁴¹⁵⁵) Some of the very researchers Taubes cited to support his thesis accused him of twisting their words.⁴¹⁵⁶ “The article was incredibly misleading,” one said. “I was horrified.” “He took this weird little idea and blew it up, and people believed him,” said another. “What a disaster.”⁴¹⁵⁷ It doesn’t matter what people say, though. All that matters is the science.

Taubes attracted \$40 million in committed funding for his Nutrition Science Initiative in part to prove to the world that more body fat could be lost on a ketogenic diet and contracted noted NIH researcher Kevin Hall to perform the study. Seventeen overweight men were effectively locked in what's called a *metabolic ward* for two months to allow researchers total control over their diets. For the first month, they were placed on a typical carbohydrate-rich diet (50 percent carbohydrate, 35 percent fat, and 15 percent protein) and then switched to a low-carb ketogenic diet (5 percent carbohydrate, 80 percent fat, and 15 percent protein) for the second month. Both diets had the same number of daily calories. If a calorie is a calorie when it comes to weight loss, then there should be no difference in body fat loss on the regular diet versus the ketogenic diet. But, if Taubes were right, if fat calories were somehow less fattening, then body fat loss would become accelerated on the keto diet. What happened instead, in the very study funded by his Nutrition Science Initiative, was that body fat loss *slowed* upon switching to the ketogenic diet.⁴¹⁵⁸

Just looking at the readings on their scales, the ketogenic diet would seem like a smashing success. The subjects went from losing less than a pound a week on the regular diet to losing three and a half pounds within seven days after switching to the ketogenic diet. What was happening *inside* their bodies, however, told a totally different story. On the keto diet, their rates of body fat loss were slowed by more than half, so most of what they were losing was water. The reason they started burning less fat on a ketogenic diet is presumably the same reason people who start fasting may start burning less fat: Without carbohydrates, the preferred fuel, their bodies started burning more of their own protein. Switching to a ketogenic diet made them lose less fat mass and more fat-free mass.⁴¹⁵⁹ That may help explain why the leg muscles of CrossFit trainees placed on a ketogenic diet may shrink as much as 8 percent.⁴¹⁶⁰

The study subjects did start burning more fat on the ketogenic diet, but they were also eating so much more fat on that diet that they ended up retaining more fat, despite the lower insulin levels. This is “diametrically opposite”⁴¹⁶¹ to what the keto crowd had predicted. In science-speak, the carbohydrate-insulin model “failed experimental interrogation.”⁴¹⁶²

In a separate experiment, Dr. Hall showed that if you cut about eight hundred calories of carbohydrates a day from your diet for six days, you lose fifty-three daily grams of body fat, but, if you cut eight hundred calories of *fat*, you lose eighty-nine daily grams of body fat. That's nine pats of butter worth of extra fat melting off their bodies every day. Same number of calories, but 68 percent more daily fat loss when they cut down on fat instead of carbs. The title of the study speaks for itself: “Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss Than Carbohydrate Restriction in People with Obesity.”⁴¹⁶³

Once again, the scale would mislead us into thinking otherwise. After six days on the low-carb diet, study subjects lost four pounds, but they lost less than three pounds on the low-fat diet. Less loss of body fat, but, stepping on the scale, it *looks* like the low-carb diet wins hands down, so it's easy to see why low-carb diets are so popular. But yet again, what was happening inside their bodies told the real story. The low-carb group was losing mostly lean mass—water and protein. This loss of water weight helps explain why low-carb diets have been such “cash cows”⁴¹⁶⁴ for publishers over the last 156 years.⁴¹⁶⁵ As one weight-loss expert noted, “Rapid water loss is the \$33-billion diet gimmick.”⁴¹⁶⁶

What we care about is body fat, not water weight. Over those six days, the low-fat diet extracted a total of 89 percent more fat from the body than the low-carb diet.⁴¹⁶⁷ A meta-analysis of thirty-two controlled feeding studies swapping fat and carbs found the same thing: Less fat in the mouth means less fat on the hips, even when taking in the same number of calories.⁴¹⁶⁸

In light of the “experimental falsification”⁴¹⁶⁹ of the low-carb theory, the Nutrition Science Initiative effectively collapsed in 2016,⁴¹⁷⁰ but not before Taubes personally pocketed in excess of a half million dollars.⁴¹⁷¹

Losing Your Appetite

The new data are said to debunk “some, if not all, of the popular claims made for extreme carbohydrate restriction.”⁴¹⁷² But what about the suppression of hunger? In that metabolic ward study where the ketogenic diet flopped, everyone was made to eat the same number of calories. So, yes—you may lose less body fat on a ketogenic diet than on a nonketogenic diet eating the same number of calories, but out in the real world, maybe all those ketones would spoil your appetite enough that you’d end up eating significantly less overall. On the low-carb diet, people ended up storing 340 more calories of fat every day,⁴¹⁷³ but outside the laboratory, being in a state of ketosis could allow you to offset that if you were able to sustainably eat sufficiently that much less.

The secret to long-term weight loss on any diet, of course, is compliance.⁴¹⁷⁴ Diet adherence is difficult, though, because, as you know, anytime you try to cut calories, your body ramps up your appetite to compensate. This is why traditional weight-loss approaches like portion control tend to fail. For long-term success, measured not in weeks or months but in years and decades, this day-to-day hunger problem must be overcome. On a wholesome plant-based diet, this can be accomplished, thanks in part to calorie density—you’re just eating so much more food. On a ketogenic diet, it may be accomplished with ketosis. The answer to a systematic review and meta-analysis entitled “Do Ketogenic Diets Really Suppress Appetite?” was yes.⁴¹⁷⁵ What’s more, ketogenic diets offer the additional advantage of being able to track dietary compliance in real time with ketone test strips you can pee on to see if you’re still in ketosis.⁴¹⁷⁶ There’s no pee stick that will tell you if you’re eating enough fruits and veggies. All you have is the scale.

Keto compliance may be more in theory than practice, however. Even in studies where ketogenic diets are being used to control seizures, after a few months, dietary compliance may drop to less than 50 percent.⁴¹⁷⁷ This can be tragic for those with intractable epilepsy, but for everyone else, the difficulty in sticking to ketogenic diets long term may actually be a lifesaver.

Gut Reaction

Given the decades of use of ketogenic diets to treat certain cases of pediatric epilepsy, a body of safety data has accumulated. Nutrient deficiencies would seem the obvious issue.⁴¹⁷⁸ Inadequate intake of seventeen micronutrients has also been documented in those on ketogenic diets. Children have gotten scurvy,⁴¹⁷⁹ and some have even died from deficiency of the mineral selenium, which can cause sudden cardiac death.⁴¹⁸⁰ The vitamin and mineral deficiencies can be solved with supplements, but what about the paucity of prebiotics, the eight types of fiber and resistant starches found concentrated in whole grains and beans? ⁴¹⁸¹

Not surprisingly, constipation is one of the most frequently cited side effects,⁴¹⁸² but more seriously, starving our microbial selves can have myriad negative consequences, as I reviewed in the Microbiome-Friendly section. Ketogenic diets have been shown to reduce the richness and diversity of our gut flora.⁴¹⁸³ Microbiome changes can be detected within twenty-four hours of switching to a high-fat, low-fiber diet.⁴¹⁸⁴ It’s not just the lack of fiber, though. We used to think dietary fat was nearly all absorbed in the small intestine, but we now know that about 7 percent of the fat in a fat-rich meal can make it down to the colon (based on studies using radioactive tracers).⁴¹⁸⁵ Saturated fat in particular appears to cause obesogenic and pro-inflammatory changes in gut flora, but most of the data are derived from animal models.⁴¹⁸⁶ Human studies have shown a drop in beneficial *Bifidobacteria* and

a decrease in overall short-chain fatty-acid production, both of which would be expected to increase the risk of gastrointestinal disease.⁴¹⁸⁷

Striking at the Heart

What might all that saturated fat be doing to the heart? A meta-analysis of four cohort studies following the diets, diseases, and deaths of more than a quarter million people found that those who eat lower-carb diets suffer a significantly higher risk of all-cause mortality, meaning they live, on average, significantly shorter lives.⁴¹⁸⁸ The risk of cardiovascular disease specifically appears to depend on the source of fat. In a Harvard study of heart attack survivors, those who adhered more to a lower-carb diet based on animal sources of fat and protein had a 50 percent higher risk of dying from a heart attack or stroke, but no such association was found for lower-carb diets based on plant sources.⁴¹⁸⁹ These studies were based on low-carb scoring systems, though, so they speak more to the risks of lower-carb eating rather than a truly low-carb ketogenic diet.

Cholesterol production in the body is directly correlated to body weight.⁴¹⁹⁰ Every pound of weight loss by any means is associated with about a one-point drop in cholesterol levels in the blood.⁴¹⁹¹ But when people are put on ketogenic diets, the beneficial effect on bad LDL cholesterol is blunted or even completely neutralized.⁴¹⁹² Counterbalancing changes in LDL size or HDL cholesterol are not considered sufficient to offset this risk.⁴¹⁹³ You don't have to wait until cholesterol builds up in your arteries to have an effect, though. Within three hours of eating a meal high in saturated fat (even from plant sources such as coconut oil), you can see a significant impairment of artery function.⁴¹⁹⁴ Even with about a dozen pounds of weight loss, artery function worsens on a ketogenic diet instead of getting better,⁴¹⁹⁵ which appears to be the case with low-carb diets in general.⁴¹⁹⁶

How Not to Die-abetes

Ketogenic diets can certainly lower blood sugars,⁴¹⁹⁷ so much so that there is a keto product company that claims ketogenic diets can “reverse” diabetes,⁴¹⁹⁸ but that is confusing the symptom—high blood sugars—with the disease, which is carbohydrate intolerance. People with diabetes can't properly handle carbohydrates, and this manifests as high blood sugars. Sure, if you stick to eating mostly fat, your blood sugars will stay low, but you may actually be making the underlying disease worse.

We've known for nearly a century that if you put people on a ketogenic diet, their carbohydrate intolerance can skyrocket within just two days.⁴¹⁹⁹ One week on an 80 percent fat diet, and you can quintuple your blood sugar spikes in reaction to the same carb load compared to a week on a low-fat diet.⁴²⁰⁰ Even one high-fat day can do it.⁴²⁰¹ If you're going in for a diabetes test, having a fatty dinner the night before can adversely affect your results.⁴²⁰² Just a single meal high in saturated fat can make the cause of diabetes, carbohydrate intolerance, worse within four hours.⁴²⁰³ With enough weight loss by any means—whether cholera or a good meth habit—type 2 diabetes can be reversed, but a ketogenic diet for diabetes may not just be papering over the cracks but actively throwing fuel on the fire. One of the cofounders of MasteringDiabetes.org suggested it's like a CEO who tries to make the bad bottom line look better by borrowing tons of cash. The outward numbers look better, but on the inside, the company's just digging itself into a deeper hole.

The reason keto proponents claim they can “reverse” diabetes is that they can successfully wean type 2 diabetics off their insulin.⁴²⁰⁴ The way they do it, however, is akin to faith healing someone out of the need for their wheelchair by putting them on permanent bed rest for the rest of their life. You won't have any more need for that wheelchair when you can't ever get out of bed! The diabetics' carbohydrate intolerance isn't gone—they're just not eating many carbs. Their diabetes isn't gone—it could be as bad or even worse. Type 2 diabetes is reversed when you have *normal* blood sugars on a

normal diet off all medications. In other words, it is reversed when you're no longer intolerant to carbohydrates. Any diabetic can maintain normal blood sugars eating a stick of butter; only a *cured* diabetic can maintain the same feat eating a banana. As I detailed in *How Not to Die*, diabetes truly can be reversed this way with a healthy enough diet, sometimes in a matter of weeks and even *without* weight loss.⁴²⁰⁵

Spoiler alert: The true diabetes reversal diet, with more than three hundred grams of carbs a day, is practically the opposite of a ketogenic diet.⁴²⁰⁶

The irony doesn't stop there. One of the reasons diabetics suffer such nerve and artery damage is an inflammatory metabolic toxin known as *methylglyoxal*, which forms at high blood sugar levels. Methylglyoxal is the most potent creator of advanced glycation end products (AGEs),⁴²⁰⁷ which are implicated in degenerative diseases from Alzheimer's disease and cataracts to kidney disease and strokes.⁴²⁰⁸ One would expect high exposure to preformed AGEs on a ketogenic diet, since they are found concentrated in animal-derived foods that are high in fat and protein, but less internal, new AGE formation due to presumably low levels of methylglyoxal given the low blood sugars.⁴²⁰⁹ Dartmouth researchers, however, were surprised to find *more* methylglyoxal. Two to three weeks on the Atkins diet led to a significant increase in methylglyoxal levels, and those in active ketosis did even worse, experiencing a doubling of the glycotxin levels in the bloodstream.⁴²¹⁰ It turns out high sugars may not be the only way to create methylglyoxal.

One of the ketones you make on a ketogenic diet is acetone (known for its starring role in nail polish remover). Acetone does more than just make keto dieters fail Breathalyzer tests⁴²¹¹ and develop what's described as "rotten apple breath."⁴²¹² Acetone can oxidize in the blood to acetol, which may be a precursor for methylglyoxal.⁴²¹³ That may be why nondiabetic keto dieters can end up with methylglyoxal levels as high as those with out-of-control diabetes⁴²¹⁴ or end up with a heart attack.⁴²¹⁵ So the irony of "treating diabetes" with a ketogenic diet extends beyond just the potential of making the underlying disease worse, but by mirroring some of diabetes' dire consequences.

Bad to the Bone

An official International Society of Sports Nutrition position paper covering ketogenic diets notes "ergolytic" effects—that is, performance-impairing, the opposite of ergogenic—for both high- and low-intensity workouts.⁴²¹⁶ For nonathletes, ketosis can increase the feelings of perceived effort and fatigue during physical activity, which could potentially undermine exercise efforts.⁴²¹⁷ I already mentioned the shrinkage of measured muscle size among keto-dieting CrossFit trainees.⁴²¹⁸ A ketogenic diet may not only blunt the performance of endurance athletes⁴²¹⁹ but strength trainers, as well.⁴²²⁰ This is why bodybuilding on a ketogenic diet has been referred to as an "oxymoron" in *Exercise and Sports Science Reviews*, a journal of the American College of Sports Medicine.⁴²²¹

What about bone loss? Sadly, bone fractures are one of the side effects that disproportionately plague children placed on ketogenic diets, along with growth stunting and kidney stones.⁴²²² Ketogenic diets may cause a steady rate of bone loss (measured in the spine),⁴²²³ presumably because ketosis can put people in a "chronic acidotic state."⁴²²⁴ Ketones themselves are acidic⁴²²⁵ and can result in a mild metabolic acidosis.⁴²²⁶

As with anything in medicine, it's all about risks versus benefits. Up to 30 percent of patients with epilepsy don't respond to anti-seizure drugs, and the alternatives aren't pretty, including procedures like brain surgery,⁴²²⁷ which can involve implanting electrodes deep through the skull or even removing a lobe of the brain. This can obviously lead to serious side effects,⁴²²⁸ but so can having seizures every day. So if a ketogenic diet helps, the pros can far outweigh the cons. For those just choosing a diet to lose weight, though, the cost-benefit analysis would clearly seem to go the other way.

Intermittent Fasting

In and Out of the Fast Lane

Rather than cutting calories day in and day out, what if, instead, you just ate as much as you wanted every other day? Or for only a few hours a day? Or what if you fasted two days a week or five days a month? These are all examples of intermittent fasting regimens, and they may even be the way we were built to eat. Three meals every day may be a relatively novel behavior for our species. For millennia, our ancestors often may have consumed only one large meal a day or went several days at a time without food.⁴²²⁹

Intermittent fasting is often presented as a means of stressing our bodies—in a good way. There is a concept in biology called *hormesis*, which can be thought of as the “that which doesn’t kill you makes you stronger” principle. Exercise is the classic example: You put stress on your heart and muscles, and as long as there’s sufficient recovery time, you are all the healthier for it.⁴²³⁰ Is that the case with intermittent fasting? Mark Twain thought so: “A little starvation can really do more for the average sick man than can the best medicines and the best doctors. I do not mean a restricted diet; I mean *total abstention from food for one or two days*.”⁴²³¹

Twain also said, “Many a small thing has been made large by the right kind of advertising.”⁴²³² Is the craze over intermittent fasting just hype? Many diet fads have their roots in legitimate science, but over time, facts can get distorted, benefits overstated, and risks downplayed. As one medical journal news editor put it: “Science takes a back seat to marketing.”⁴²³³ At the same time, you don’t want to lose out on any potential benefit by dismissing something out of hand based on the absurdist claims of overzealous promoters. You don’t want to throw the baby out with the baby fat.

Alternate-Day Fasting: Efficacy

The most studied form of intermittent fasting is religious fasting,⁴²³⁴ specifically Ramadan, a monthlong period during which devout Muslims abstain from food and drink from sunrise until sunset.⁴²³⁵ The effects are complicated by a change in sleeping patterns, as well as thirst.⁴²³⁶ The same dehydration issue arises with Yom Kippur, when observant Jews stop eating and drinking for about twenty-five hours.⁴²³⁷ The most studied form of intermittent fasting that deals only with food restriction is alternate-day fasting, which involves eating every other day, alternating with days consuming little or no calories.⁴²³⁸

At rest, we burn about a 50:50 mix of carbs and fat,⁴²³⁹ but we usually run out of our glycogen stores within twelve to thirty-six hours of when we stop eating. At that point, our bodies have to shift to rely more on our fat stores.⁴²⁴⁰ This “metabolic switch” may help explain why the greatest rate of breakdown and burning of fat over a three-day fast happens between the hours of eighteen and twenty-four of the seventy-two-hour period.⁴²⁴¹ So the hope is to reap some of the benefits of taking a break from eating without the risks of prolonged fasting.⁴²⁴²

One of the potential benefits of alternate-day fasting over chronic caloric restriction is that you get regular breaks from feeling constant hunger. Might people become so famished on their fasting day, though, that they turn the next into a *feasting* day and overeat? If you ate more than twice as much as you normally would, then that presumably would defeat the whole point of alternate-day fasting. Mice fed every other day don’t lose weight. They just eat roughly twice as much in one day than nonfasted mice would regularly eat in two.⁴²⁴³ That is not, however, what people do.⁴²⁴⁴

When study subjects were randomized to fast for thirty-six hours, from 8:00 p.m. on day one to 8:00 a.m. on day three, the thirty-six-hour fast only led to people eating an average of 20 percent more the day after they broke the fast, compared to a control group who

didn't fast at all. That would leave the thirty-six-hour fasters with a large calorie deficit, equivalent to a caloric restriction of nearly a thousand calories a day.⁴²⁴⁵ That particular study involved lean men and women, but similar results have been found among overweight or obese subjects, typically only a 10-25 percent compensatory increase in caloric intake over baseline.⁴²⁴⁶ This seems to be the case whether the fasting day was a true zero-calorie fast or a few-hundred-calorie "modified" fast.⁴²⁴⁷

Some studies found subjects appeared to eat no more⁴²⁴⁸ or even eat *less* on days after a daylong mini-fast.^{4249,4250} Even within studies, however, great variability is reported. In a twenty-four-hour fasting study where folks ate dinner and then, the next day, skipped breakfast and lunch, the degree of compensation at the dinner on day two ranged from 7 to 110 percent. This means some got so hungry by the time the dinner rolled around the next day that they ate more than twenty-four-hours' worth of calories in a single meal. The researchers suggested that perhaps people first try "test fasts" to see how much their hunger and subsequent intakes ramp up before considering an intermittent fasting regimen.⁴²⁵¹ Hunger levels can change over time, though, dissipating as our bodies habituate to the new normal.

In an eight-week study in which obese subjects were restricted to about five hundred calories every other day, they reported beginning to feel very little hunger on their slashed calorie days after approximately two weeks. This no doubt helped them lose about a dozen pounds on average over the duration of the study, but there was no control group with whom to compare.⁴²⁵² A similar study that did have a control group found a similar amount of weight loss—about eleven pounds—over twelve weeks in a group of "normal-weight" (that is, overweight on average) individuals.⁴²⁵³ For these modified regimens where people were prescribed five hundred calories on their "fasting" days, researchers found that, from a weight-loss perspective, it did not appear to matter whether those calories were divided up throughout the day or eaten in a single meal, either at lunch or dinner.⁴²⁵⁴

Instead of prescribing a set number of calories on "fasting" days, which many people find difficult to calculate outside of a study setting, a pair of Iranian researchers came upon the idea of unlimited above-ground vegetables. Starchy root vegetables are relatively calorie-dense compared to veggies that grow above the ground, including stem vegetables like celery and rhubarb, flowering vegetables like cauliflower, leafy vegetables like, well, leafy vegetables, and all the fruits we tend to think of as vegetables, such as tomatoes, peppers, okra, eggplants, string beans, summer squash, and zucchini. So instead of just prescribing a certain number of calories for the "fasting" days, subjects alternated between their regular diets and helping themselves every other day to all-you-can-eat above-ground vegetables (along with naturally noncaloric beverages like green tea or black coffee). After six weeks, subjects lost an average of thirteen pounds and two inches off their waists.⁴²⁵⁵

The same variability discovered for calorie compensation was also found for weight loss. In a twelve-month trial in which subjects were instructed to eat only one quarter of their caloric needs every other day, weight changes varied from a gain of about eight pounds to a loss of around thirty-seven pounds. The biggest factor appeared to be not how much they feasted on their regular diet days but how much they were able to comply with the caloric restriction on their fast days.⁴²⁵⁶

Overall, ten out of ten alternate-day fasting studies showed significant reductions in body fat.⁴²⁵⁷ Small, short-term studies show a 4-8 percent drop in body weight after three to twelve weeks.⁴²⁵⁸ How does that compare with continuous caloric restriction? Zero-calorie, alternate-day fasting was compared head-to-head to a daily restriction of four hundred calories a day for eight weeks. Both groups lost the same amount of weight, about seventeen pounds, and, in the follow-up check-in six months after the trial had ended, both groups had maintained a similar degree of weight loss, still down about a dozen pounds.⁴²⁵⁹

The hope that intermittent fasting would somehow improve compliance or avoid the metabolic adaptations that slow weight loss doesn't seem to have materialized. The same compensatory reactions in terms of increased appetite and a slower metabolism plague both methods,⁴²⁶⁰ and the largest, longest trial of alternate-day fasting found that it may be even less sustainable than more traditional approaches.⁴²⁶¹ By the end of a year, the dropout rate of the alternate-day fasting group was 38 percent compared to 29 percent in the continuous calorie-restriction group.⁴²⁶²

Though alternate-day fasting regimens haven't been shown to produce superior weight loss, for the individuals who may prefer this pattern of caloric restriction, are there any downsides?

Alternate-Day Fasting: Safety

Might going all day without eating impair our ability to think clearly? Surprisingly, the results appear to be equivocal. Some studies show no measurable effects, and the ones that do fail to agree on which cognitive domains are affected.⁴²⁶³

Might the fasting-feasting cycles cause eating disorder-type behavior like bingeing? So far, no harmful psychological effects have been found,⁴²⁶⁴ though the studies that have put it to the test specifically excluded people with a documented history of eating disorders, for whom the effects may differ.⁴²⁶⁵

No change in bone mineral density was noted after six months of alternate-day fasting despite about sixteen pounds of weight loss, which would typically result in a dip in bone mass. However, there also were no skeletal changes noted in the control group who had lost a similar amount of weight using continuous caloric restriction. The researchers suggest this is because both groups tended to be more physically active than the average obese individual by one or two thousand steps a day.⁴²⁶⁶

Proponents of intermittent fasting suggest it can better protect lean body mass,⁴²⁶⁷ but most of the intermittent trials have employed a less accurate method of body composition analysis (bioelectrical impedance), whereas the majority of continuous caloric-restriction trials used vastly more accurate technologies (dual-energy x-ray absorptiometry and magnetic resonance imaging).⁴²⁶⁸ To date, it's not clear if there's a difference in lean mass preservation.⁴²⁶⁹

Improvements in blood pressure and triglycerides have been noted on intermittent-fasting regimens, though this is presumed to be due to the reduction in body fat, since the effect appears to be dependent on weight loss.⁴²⁷⁰ Alternate-day fasting can also improve artery function, though that depends on what is eaten on the nonfasting day.⁴²⁷¹ Randomized to an alternate-day diet high in saturated fat, artery function worsened despite a twelve-pound loss in body fat, whereas it improved as expected in the lower-fat group. The decline in artery function was presumed to be because of the pro-inflammatory nature of saturated fat.⁴²⁷²

A concern has been raised about the effects of alternate-day fasting on cholesterol. After twenty-four hours without food, LDL cholesterol may temporarily bump up, but this is presumably just because so much fat is being released into the system by the fast.⁴²⁷³ An immediate negative effect on carbohydrate tolerance may stem from the same phenomenon.⁴²⁷⁴ After a few weeks, LDL levels start to drop as the weight comes off,⁴²⁷⁵ but results from the largest and longest trial of alternate-day fasting have given me pause.

One hundred obese men and women were randomized into one of three groups: alternate-day modified fasting (25 percent of baseline calories on fasting days and 125 percent calories on eating days), continuous daily caloric restriction (75 percent of baseline), or a control group instructed to maintain their regular diets. So if you went into the trial eating 2,000 calories a day, you would continue to eat your 2,000 a day in the control group, you'd be prescribed 1,500 calories each day in the calorie-restriction group,

and you would alternate between 500 calories one day and 2,500 calories the next in the intermittent-restriction group.

With the same overall average calorie-cutting prescribed in both weight-loss groups, each lost about the same amount of weight, but surprisingly, the cholesterol effects were different. In the continuous calorie-restriction group, as the pounds came off, the bad LDL dropped as expected compared to the control group. But in the alternate-day modified fasting group, they didn't. At the end of the year, the LDL cholesterol in the intermittent-restriction group ended up 10 percent *higher* than that of the constant calorie-restriction group, despite the exact same loss in body fat.⁴²⁷⁶ Given that LDL cholesterol is a prime risk factor⁴²⁷⁷—or even *the* prime risk factor⁴²⁷⁸—for our number one killer, heart disease, this strikes a significant blow against alternate-day fasting. If you do want to try it anyway, I would advise you have your cholesterol monitored to make sure it comes down with your weight.

If you're diabetic, it's critical to talk with your physician about medication adjustment for any changes in diet, including fasting of any duration. Even with proactive medication reduction, advice to immediately break the fast should sugars drop too low, and weekly medical supervision, type 2 diabetics fasting even just two days a week were twice as likely to suffer from hypoglycemic episodes compared to an unfasted control group. We still don't know the best way to adjust blood sugar medications to prevent blood sugars from dropping too low on fasting days.⁴²⁷⁹

Consultation with one's medical professional is a good idea before fasting for anyone on medication. Even just fasting for a day can significantly slow the clearance of some drugs like the blood-thinning drug coumadin or increase the clearance of others like caffeine. Indeed, fasting for thirty-six hours can cut your caffeine buzz by 20 percent.⁴²⁸⁰

La Dieta de Hambre

Doctors have anecdotally attributed improvements in a variety of disease states to alternate-day fasting, including asthma, seasonal allergies, autoimmune disease (rheumatoid arthritis), osteoarthritis, infectious diseases (toenail fungus), periodontal disease, viral upper-respiratory-tract infections, neurological conditions (Tourette's syndrome, Ménière's disease), atrial fibrillation, and menopause-related hot flashes.⁴²⁸¹ However, the *actual* effect on chronic disease remains unclear.⁴²⁸²

Alternate-day fasting has been put to the test for asthma in obese adults. Asthma-related symptoms and control significantly improved, as did their quality of life, including objective measurements of lung function and inflammation. However, their weight also improved—about a nineteen-pound drop in eight weeks—so it's hard to tease out effects specific to the fasting beyond the benefits we might expect from weight loss by any means.⁴²⁸³ Surprisingly, for the most remarkable study on alternate-day fasting, you have to go back more than a half century.

While that cholesterol finding was the most concerning data I could find on alternate-day fasting, the most enticing was published in Spain sixty-one years earlier in 1956. The title of the study translates as "The Hunger Diet on Alternate Days in the Nutrition of the Aged." Inspired by the data being published on life extension with caloric restriction on lab rats, researchers split 120 residents of a senior home in Madrid into two groups. Sixty residents continued to eat their regular diets, and the other sixty were put on an alternate-day modified fast. On the odd days of the month, they ate a 2,300-calorie, regular diet and, on the even days, were given only a pound of fresh fruits and a liter of milk,⁴²⁸⁴ an estimated 900 calories.⁴²⁸⁵ This continued for three years. What happened?

Over the duration of the study, thirteen died in the control group, compared to only six in the modified intermittent-fasting group, but those numbers were too small to be statistically significant. What was highly significant, though, was the number of days they

spent hospitalized. Residents in the control group spent a total of 219 days in the infirmary, whereas those in the alternate-day fasting group were hospitalized for only 123 days.⁴²⁸⁶ This is held up as solid evidence that caloric restriction in general, and alternate-day fasting in particular, may improve one's health span and potentially even one's life span. However, a few caveats must be considered. It's not clear how the residents were allocated to their respective groups. If instead of being randomized, healthier individuals were placed inadvertently in the intermittent-fasting group, the results could have been skewed in their favor. Also, it appears the director of the study was also in charge of medical decisions at the home. In that role, he could have unconsciously been biased toward hospitalizing more people in the control group.⁴²⁸⁷ Given the progress that has been made regulating human experimentation, it's hard to imagine such a trial being run today, so we may never know if such impressive findings can be replicated.

The 5:2 Diet

Instead of eating every other day, what if you ate five days a week and fasted the other two? The available data are actually similar to those of alternate-day fasting. About a dozen pounds of weight loss were reported in overweight men⁴²⁸⁸ and women⁴²⁸⁹ over a six-month period with no difference found between those on the 5:2 intermittent-fasting regimen and those on a continuous five-hundred-calories-a-day restriction. The largest trial to date found an eighteen-pound weight loss within six months in the 5:2 group, not significantly different from the twenty pounds lost in the continuous calorie-restriction group. Weight maintenance over a subsequent six months was also found to be no different.⁴²⁹⁰

Though feelings of hunger may be more pronounced on the 5:2 pattern than an equivalent level of daily calorie cutting,⁴²⁹¹ it does not seem to lead to overeating on the nonfasting days.⁴²⁹² One might expect going two days without food may negatively impact mood, but no adverse effect was noted for those fully fasting (zero calories)⁴²⁹³ or sticking to just two packets of oatmeal on each of the "fasting" days (approximately five hundred calories).⁴²⁹⁴ Like alternate-day fasting, the 5:2 fasting pattern appeared to have inconsistent effects on cognition,⁴²⁹⁵ no clear advantage for lean mass preservation,⁴²⁹⁶ and it failed to live up to the popular notion that intermittent fasting would prove to be easier to adhere to than daily caloric restriction.⁴²⁹⁷

Fewer subjects on the 5:2 pattern expressed interest in continuing the diet after the study was over, compared to a continuous-restriction control group.⁴²⁹⁸ This was attributed to quality of life issues, citing headaches, lack of energy, and the difficulty of fitting the fasting days into their weekly routine.⁴²⁹⁹ However, there has yet to be a single 5:2 diet study showing elevated LDL cholesterol compared to continuous caloric restriction at six months^{4300,4301} or a year,⁴³⁰² which offers a potential advantage over alternate-day regimens.

Alternate-Week Fasting

Some intermittent-fasting patterns employ longer alternating periods. Hundreds of pounds of weight loss have been documented in those who had had previously intractable obesity but were then fasted in blocks of ten days on, ten days off.⁴³⁰³ Ten days of total fasting is too long to do safely on your own without medical supervision, so alternating weeks of caloric restriction were put to the test in the hope that giving your body weeklong breaks may prevent it from going into energy-conservation mode to slow weight loss. However, no significant weight-loss advantage was found in an eight-week study compared to the same degree of continuous calorie-cutting,⁴³⁰⁴ and a fifteen-week study found a negative effect on lean body mass preservation.⁴³⁰⁵

Overweight postmenopausal women were randomized either to fifteen weeks of constant caloric restriction or the same fifteen weeks interspersed with two five-week periods of their baseline diets. Same overall length of the study and same overall number of calories restricted, so similar decreases in weight of about twenty-two pounds, but those on the intermittent regimen lost twice as much lean body mass, about four pounds compared to two.⁴³⁰⁶ The longest such study, however, involving sixteen weeks of caloric restriction in middle-aged obese men, either uninterrupted or alternating two weeks on, two weeks off, found no significant difference in lean mass loss. What they discovered instead was 50 percent greater loss of body fat: twenty-seven pounds of fat loss versus eighteen pounds in the continuous calorie-restriction group despite an equivalent overall “dose” of caloric restriction. This was due at least in part to less metabolic slowing on the back-and-forth pattern.⁴³⁰⁷

Putting all such studies together, it appears to be a wash between intermittent and continuous caloric restriction.⁴³⁰⁸ Until further data allow us to iron out the inconsistencies found in these studies, it may be prudent at least for postmenopausal women to refrain from using intermittent caloric restriction as a weight-loss strategy.⁴³⁰⁹

Fasting-Mimicking Diet

Instead of 5:2, what about 25:5, spending five days a month on a “fasting-mimicking diet”? Longevity researcher Valter Longo designed a five-day meal plan to try to simulate the metabolic effects of fasting by being low in proteins, sugars, and calories with zero animal protein or animal fat. By making it plant-based, he was hoping to lower the level of the cancer-promoting growth hormone IGF-1 related to animal protein consumption, which he accomplished, along with a drop in markers of inflammation, after three cycles of his five-days-a-month program.⁴³¹⁰

One hundred men and women were randomized to consume his fasting-mimicking diet (FMD) for five consecutive days per month or maintain their regular diets for the duration of the study. After three months, the FMD group was down about six pounds compared to control, with significant drops in body fat and waist circumference accompanied by a drop in blood pressures. Three months after completion of the study, some of the benefit appeared to persist, suggesting the effects may last for several months. However, it’s unclear if those randomized to the FMD group used it as an opportunity to make positive lifestyle changes that helped maintain some of the weight loss.⁴³¹¹

Dr. Longo created a company to commercially market his meal plan but says, to his credit, that he donates 100 percent of the profits he receives from it to charity.⁴³¹² The whole diet appears to be mostly a few dehydrated soup mixes of vegetable, mushroom, and tomato, herbal teas like hibiscus and chamomile, kale chips, nut-based energy bars, an algae-based DHA supplement, and a multivitamin dusted with vegetable powder.⁴³¹³ But why spend fifty dollars a day on a few processed snacks when you could instead eat a few hundred calories a day of real vegetables?

Time-Restricted Feeding

Taking a Break

The reason many blood tests are taken after an overnight fast is that meals can tip our systems out of balance, bumping up certain biomarkers for disease, such as blood sugars, insulin, cholesterol, and triglycerides, yet fewer than one in ten Americans may even make it twelve hours a day without eating. As evolutionarily unnatural as eating three meals a day may be, most of us are eating even more than that. One study using a smartphone app to record more than twenty-five thousand eating events found that people tended to eat

about every three hours over an average span of around fifteen hours a day.⁴³¹⁴ Might it be beneficial to give our bodies a bigger break?

Time-restricted feeding is defined as fasting for periods of at least twelve hours but less than twenty-four hours.⁴³¹⁵ This involves trying to confine caloric intake to a set window of time, typically three to four hours, seven to nine hours, or ten to twelve hours a day, resulting in a daily fast lasting twelve to twenty-one hours. When mice were fed high-fat diets of mostly lard,⁴³¹⁶ they gained less weight when restricted to a daily feeding window, even when fed the exact same amount.⁴³¹⁷ Rodents have such high metabolisms, though, that a single day of fasting can starve away as much as 15 percent of their lean body mass,⁴³¹⁸ which makes it difficult to extrapolate from mouse models.⁴³¹⁹ You can't know what happens in humans until you put it to the test.

Different as Night and Day

The dropout rates in time-restricted feeding trials certainly appear lower than in more prolonged forms of intermittent fasting, suggesting they're more easily tolerable,⁴³²⁰ but do they work? When people stopped eating between 7:00 p.m. and 6:00 a.m. for two weeks, they lost about a pound each week compared to no time restriction. Note that no additional instructions or recommendations were given on the amount or type of food consumed. There were no gadgets, calorie counting, or record keeping. They were just told to limit their food intakes to the hours of 6:00 a.m. through 7:00 p.m. and they lost weight. A simple intervention, easy to understand and implement.⁴³²¹

The next logical step was to try putting it to the test for months instead of just a couple of weeks. Obese men and women were asked to restrict eating to the eight-hour window between 10:00 a.m. and 6:00 p.m. Twelve weeks later, they had lost five pounds.⁴³²² This deceptively simple intervention may be operating from a number of different angles. People tend to eat more food⁴³²³ and higher-fat foods later in the day,⁴³²⁴ and the late-evening hours may represent a high-risk time for overeating.⁴³²⁵ By eliminating eating in the late-evening hours, one removes prime-time snacking on the couch.⁴³²⁶ And indeed, during the time-restricted weeks, the subjects in both studies were inadvertently eating about three hundred fewer calories a day.⁴³²⁷

There are also the chronobiological benefits of avoiding late-night eating. Remember how calories in the morning cause less weight gain than the same calories eaten in the evening? ⁴³²⁸ A diet with a bigger breakfast causes more weight loss than the same exact diet with a bigger dinner.⁴³²⁹ Nighttime snacks are more fattening than the same snacks eaten in the daytime.⁴³³⁰ Thanks to our circadian rhythms, metabolic slowing,⁴³³¹ hunger, carbohydrate intolerance, triglycerides, and our propensity for weight gain are all things that go bump in the night.⁴³³²

What about the fasting component? There's already the double benefit of consuming fewer calories and avoiding nighttime eating. Does the fact that the subjects in those two studies were fasting for eleven or sixteen hours a day play any role, considering that the average person may only make it about nine hours a day without eating? ⁴³³³ How would you design an experiment to test that? What if you randomized people into one of two groups and forced both to eat the same number of calories a day and also to eat late into the evening, but one group was designated to fast even longer, for twenty hours? That's exactly what researchers at the USDA and National Institute on Aging did.

Men and women were randomized to eat three meals a day or fit all those same calories into a single four-hour window between 5:00 p.m. and 9:00 p.m. and then fast the rest of the day.⁴³³⁴ If the weight-loss benefits from the other two time-restricted feeding studies were due to the passive caloric restriction or avoidance of late-night eating, then presumably, both groups should end up the same in this study. That's not what happened. After eight weeks, the time-restricted feeding group ended up with nearly five pounds less

body fat. About the same number of calories, but they lost more weight. A similar study with an eight-hour eating window resulted in three pounds of additional fat loss.⁴³³⁵ So there does seem to be something to giving our bodies daily breaks from eating around the clock. Because the four-hour eating window was at night, though, the subjects suffered the chronobiological consequences—significant elevations in blood pressure and cholesterol levels—despite the weight loss.⁴³³⁶

The best of both worlds was demonstrated in 2018 with time-restricted feeding in a narrower window earlier in the day.⁴³³⁷ Individuals randomized to stick to a six-hour eating window ending before 3:00 p.m. experienced a drop in blood pressure, oxidative stress, and insulin resistance even when all the study subjects were maintained at the same weight. The average drop in blood pressure was extraordinary, from 123/82 down to 112/72 in just five weeks, comparable to the effectiveness of potent blood pressure drugs.

The longest study to date on time-restricted feeding only lasted sixteen weeks, a pilot study with no control group that involved only eight people. Nonetheless, the results are worth noting. Overweight individuals who, like most of us, were eating more than fourteen hours a day, were instructed to stick to a consistent ten- to twelve-hour feeding window of their own choosing. On average, they were able to successfully reduce their daily eating duration by about four and a half hours, and within sixteen weeks, they had lost seven pounds. They also reported sleeping better and feeling more energetic. This may help explain why all the participants voluntarily expressed their interest in continuing the time-restricted feeding on their own after the study ended. You don't often see that after weight-loss studies. Even more remarkably, eight months later, they had retained their weight loss and improved energy and sleep—all from one of the simplest of interventions.⁴³³⁸

How did it work? As with the other time-restricted feeding trials, even though they weren't told to change calorie quality or quantity, they appeared to unintentionally eat hundreds of fewer calories a day. With self-selected time frames, you wouldn't necessarily think to expect circadian benefits, but because they were asked to keep the eating window consistent throughout the week, there may have been. Remember social jet lag, the discrepancy between eating and sleeping patterns on weekdays and weekends? Breakfast may get pushed back an hour or two on free days, as if you had just jumped time zones, so some of the metabolic benefits may have been due to maintaining a regular eating schedule.⁴³³⁹

Surviving the Test of Time

Early or midday time-restricted feeding may have other benefits as well. Prolonged nightly fasting with reduced evening food intake has been associated with lower levels of inflammation⁴³⁴⁰ and better blood sugar control, both of which might be expected to lower the risk of diseases such as breast cancer.⁴³⁴¹ Data were collected on thousands of breast cancer survivors to see if nightly fasting duration made a difference. Those who didn't go more than thirteen hours every night without eating had a 36 percent higher hazard of cancer recurrence.⁴³⁴² These findings have led to the suggestion that efforts to “avoid eating after 8 pm and fast for 13 h[ours] or more overnight may be a beneficial consideration for those patients looking to decrease cancer risk and recurrence,”⁴³⁴³ though we'd need a randomized controlled trial to know for sure.

Early time-restricted feeding may even play a role in the health of perhaps the longest living population in the world, the Seventh-day Adventist Blue Zone in California. Slim, vegetarian, nut-eating, exercising, nonsmoking Adventists live about a decade longer than the general population.⁴³⁴⁴ Their greater life expectancy has been ascribed to these healthy lifestyle behaviors, but there's one lesser-known component that may be playing a role. Historically, eating two large meals a day, breakfast and lunch, with a prolonged overnight fast was a part of Adventist teachings. Today, only about one in ten Adventists surveyed

was eating just two daily meals, but most (63 percent) reported breakfast or lunch was their largest meal of the day. Though this has yet to be studied with respect to longevity, frontloading one's calories earlier in the day with a prolonged nightly fast has been associated with significant weight loss over time, leading the researchers to conclude: "Eating breakfast and lunch 5-6 h[ours] apart and making the overnight fast last 18-19 h[ours] may be a useful practical [weight control] strategy."⁴³⁴⁵

FOOD FOR THOUGHT

Because of the metabolic slowing and increased appetite that accompany weight loss, *sustained* weight loss requires a persistent calorie deficit of three hundred to five hundred calories a day,⁴³⁴⁶ which can be accomplished without reducing portion sizes just by lowering the calorie density of meals. Doing so can result in the rare combination of weight loss with an increase in both quality—and even quantity—of food consumed.

Those who are pregnant or breastfeeding, have an active infection, or are already underweight should not consider a dramatic cut in calories by any means, and anyone on medications or with a chronic medical condition, including diabetes, heart, liver, or kidney disease, or a history of fainting, should do so only under guidance from their health-care providers.

Prolonged water-only fasting is no longer recommended as a clinical treatment option for obesity due to the associated risks of complications.⁴³⁴⁷ Fasting more than a day or two should be done only under strict medical supervision.

Ketogenic diets are also not recommended. When you think of the ideal attributes of a diet for weight control—safe, effective, protective, healthful, wholesome, sustainable, nutritionally complete, and life-extending—typical keto diets guarantee none of them.

Some forms of intermittent fasting, on the other hand, may be safe and effective (and it's safe to say cost-effective when it comes to your grocery bills), but apparently no more so for weight loss than continuous caloric restriction.⁴³⁴⁸ However, combining intermittent-fasting regimens, such as early or midday time-restricted feeding with a healthier diet during the feeding windows, may prove to be particularly powerful. The weight may be worth the wait.

MEAL FREQUENCY

Nibbling vs. Gorging

Since the 1970s, the size of our meals has increased about 10 percent, from 1.2 pounds of food to 1.3 pounds, but the number of our meals has gone up closer to 20 percent, from eating around four times a day to five.⁴³⁴⁹ The typical time between meals has shrunk by an hour. On average, American adults are now eating every three waking hours.⁴³⁵⁰ Given this, increased eating frequency may have played double the role of increased portion size in the current obesity epidemic.⁴³⁵¹ But don't the popular press⁴³⁵² and even weight management professionals advise people to eat frequent smaller meals throughout the day? ⁴³⁵³ Frequent eating is purported to reduce hunger, increase metabolic rate, and mobilize body fat, but might all that extra snacking just pile on the pounds? ⁴³⁵⁴ Let's see what the science says.

Population studies since the 1960s have often shown that those who report eating less frequently tend to be more overweight, leading to the suggestion that a "nibbling" pattern of grazing throughout the day may be better than a "gorging" pattern of trying to fit all our calories into a few large meals.⁴³⁵⁵ Alternatively, as with all such epidemiological findings, the results could have been due to confounding factors or reverse causation. Indeed, those who report eating fewer meals also report eating healthier meals⁴³⁵⁶ and engaging in less physical activity,⁴³⁵⁷ so perhaps those habits, rather than the eating frequency, contributed to being overweight. And, as with the breakfast-skipping data, perhaps instead of fewer meals leading to obesity, obesity led to fewer meals, as folks tried to omit meals to lose weight.⁴³⁵⁸ The most likely explanation, though, is massive underreporting bias.⁴³⁵⁹

Self-Deception

Obese individuals not only report eating fewer meals but also eating fewer calories. Most studies of reported caloric intake and body weight suggest that the *more* calories you eat, the *slimmer* you are. Let that sink in for a moment. Based on interviews and questionnaires asking people how much they eat, as well as monitored eating in restaurants or laboratory settings, there is said to be “overwhelming evidence” that those who are obese eat fewer calories, misleading people to proclaim that the presumption that obesity is caused by overeating is simply a myth.⁴³⁶⁰ But if you objectively measure how much people are actually eating, the whole charade collapses.⁴³⁶¹

For centuries, there have been claims of people thriving on little or no food.⁴³⁶² A Catholic “mystic,” for example, reportedly not only survived for thirty-five years but even gained weight consuming nothing but a daily communion wafer.⁴³⁶³ This reminds me of the founder of the Breatharian Institute of America. You could attend one of his workshops on how to live on air alone for the low, low price of \$100,000—“no refunds”⁴³⁶⁴—that is, until he evidently got busted sneaking out of a 7-Eleven with a hot dog, Slurpee, and box of Twinkies.⁴³⁶⁵

When actual caloric intakes are measured, it turns out those who claim they can’t lose weight no matter how little they eat are fooling themselves into thinking they’re eating less than they actually are.⁴³⁶⁶ A group of “diet resistant” obese individuals were found to be underreporting their actual food intakes by a whopping 47 percent and overreporting their physical activity by about the same amount.⁴³⁶⁷ So, in reality, the failure to lose weight on a calorie-restricted diet is due to not actually being on a calorie-restricted diet. Were the subjects straight-up lying about their overeating? They didn’t appear to be intentionally deceiving the researchers as much as they apparently were deceiving themselves. When they were informed of the results of the study, they were reportedly surprised and distressed by the findings. Interventional studies have shown for nearly a century that if you lock people in a room, everyone loses weight as predicted.⁴³⁶⁸

Dietary underreporting by overweight individuals has been called “one of the most robust biopsychological phenomena ever described.”⁴³⁶⁹ Since snacks appear to be “preferentially forgotten” when obese individuals underreport intake on diet surveys,⁴³⁷⁰ it isn’t difficult to see how obesity would be correlated with eating less frequently.⁴³⁷¹ When you control for the underreporting, the relationship gets flipped on its head, going from heavier individuals *appearing* to eat *less* frequently to *actually* eating *more* frequently.⁴³⁷² This would make sense if our bodies aren’t able to fully compensate for snacks by eating that much less at subsequent meals, but you don’t know until you put it to the test.⁴³⁷³

Three Squares or Seventeen?

The purported benefits of eating more frequent meals on appetite,⁴³⁷⁴ metabolic rate,⁴³⁷⁵ fat mobilization,⁴³⁷⁶ and weight loss have failed to materialize. Randomizing people to eat the same number of calories in either a single daily meal or spread out all the way up to nine meals per day has failed consistently to yield differences in weight loss in studies ranging in duration from a week to a year.⁴³⁷⁷ That doesn’t mean there aren’t other health impacts, though. Eating all our calories in a single evening meal is worse for cholesterol⁴³⁷⁸ and blood sugar control,⁴³⁷⁹ but that is presumably due to less of a meal frequency effect than an adverse chronobiology effect of pushing calorie intake to later in the day.

The most extreme meal frequency study switched people from three meals a day to seventeen. Each day, people were given a snack when they woke up and then another snack every hour for the next sixteen hours. This resulted in significantly lower average insulin levels, thought responsible for an 18 percent drop in bad LDL cholesterol. Insulin stimulates the same cholesterol-synthesizing enzyme that statin drugs block,⁴³⁸⁰ so by lowering insulin levels, the same food resulted in a twenty-point drop in bad cholesterol within two weeks.⁴³⁸¹ The researchers went out of their way to say they “do not

advocate⁴³⁸² what has been called a “clearly ... impractical”⁴³⁸³ “extreme model.”⁴³⁸⁴ It was just a proof-of-principle study to show how leveling insulin spikes with a low-glycemic-index diet might end up lowering cholesterol levels,⁴³⁸⁵ as has indeed been shown to be the case (though that may be primarily because lower-glycemic diets tend to have more fiber).⁴³⁸⁶

In an experimental setting, you can increase eating frequency without causing weight gain by doling out carefully measured portions. In the real world, though, the more times people eat, the more they tend to increase their daily caloric intakes.⁴³⁸⁷ When that happens, meal frequency can have significant metabolic consequences. If you’re going to add something to your diet that’s going to spike your insulin, it’s better to add it *to* meals rather than *between* meals. Men, for example, were randomized to add three liters of sugary soda to their daily diets either with meals or between meals as snacks. Looking at the scale, it didn’t seem to make any difference: Both groups gained the same amount of weight. However, what was happening within their bodies told a different story. Increasing meal frequency by adding soda “snacks” between meals, instead of increasing meal size by adding the same amount of soda to meals, led to a 65 percent greater relative increase in liver fat,⁴³⁸⁸ which, over time, could increase the risk of fatty liver disease and diabetes.⁴³⁸⁹

It need not be liters of soda. Drinking about two cups of 100 percent orange juice three times a day between meals is worse than drinking the same amount of juice with meals. Drinking juice between meals led to the accumulation of nearly three more pounds of body fat within two weeks compared to the same amount of juice taken with meals.⁴³⁹⁰

FOOD FOR THOUGHT

Decreasing the number of times you consume calories a day, whether from dining, snacking, or drinking soda, juice, or the like, may help with weight control, especially if you’re eating junk. If you’re going to eat processed foods, tack them onto meals rather than having them as between-meal snacks.

The healthiest snacks are fresh fruits and vegetables, of course, but I also enjoy snacking on nori sheets, lentil sprouts, “air-fried” purple sweet potato fries, edamame, and seasoned air-popped popcorn.

The worst snacks, according to national snacking guidelines from around the world, are snacks that are sugary, fatty, or salty.⁴³⁹¹ One study found body fat benefits to nut-based snack bars. Compared to what, though? You could tell the study was funded by the nut bar company when researchers felt the need to use as a comparator the likes of Oreo Double Stuf cookies.⁴³⁹²

Tempted by unhealthy foods? There are “choice architecture” methods to help cut down on impulsive snacking. For example, placing healthier foods at eye level in the store or at the beginning of a buffet line may nudge people toward better choices. Similarly, when chocolate candies are left on the desks of office workers, more are eaten than if they are placed just out of reach or in an opaque container.⁴³⁹³ In a large field study at Google headquarters, for instance, the separation of the snack station from the beverage station by less than a dozen feet appeared to cut down snacking rates by about 40 percent. The researchers concluded that employers or even families may be able to reduce snack consumption “easily, cheaply, and without backlash” just by adding mild inconvenience. In the Greger household, I am able to instill maximum inconvenience by just not keeping any junk in the house.

Unable to purge your surroundings? The next time cravings hit, try Tetris. A study entitled “Playing ‘Tetris’ Reduces the Strength, Frequency and Vividness of Naturally Occurring Cravings” found that three minutes of distracting oneself with a video game may help tackle cravings⁴³⁹⁴—though I imagine playing Candy Crush might be counterproductive.

METABOLIC BOOSTERS

Fighting a Losing Battle

Thermogenic drugs like DNP can increase resting metabolic rates by 300 percent or more but, as you may remember from the Fat Burners section, also caused people to overheat to death.⁴³⁹⁵ A more normal range would vary about ten times less, from a 30 percent slower metabolism in people with an underactive thyroid to a 30 percent higher metabolism when the part of our nervous systems that controls our fight-or-flight response is activated.⁴³⁹⁶ In

response to a fright or other acute stressor, special nerves release a chemical called *noradrenaline* to ready us for confrontation. You experience that as your skin getting paler, cool, and clammy as blood is diverted to your more vital organs. Your mouth can get dry as your digestive system is put on hold, and your heart starts to beat faster. What you don't feel is the extra fat being burned to liberate energy for the fight. This is why people started taking ephedra for weight loss.

Ephedra is an evergreen shrub that has been used for thousands of years in China to treat asthma.⁴³⁹⁷ It causes that same release of noradrenaline that offers relief to asthmatics by dilating their airways.⁴³⁹⁸ In the United States, it was appropriated for use as a metabolic stimulant, shown to result in about two pounds of weight loss a month in nineteen placebo-controlled trials.⁴³⁹⁹ By the late 1990s, millions of Americans were taking it.⁴⁴⁰⁰ The problem is ephedra had all the other noradrenaline effects, too, like increasing heart rate and blood pressure, so chronic use resulted in strokes, heart attacks, and death.⁴⁴⁰¹ The FDA warned the public of the risks in 1994, but it wasn't banned until a decade later after a Major League pitcher dropped dead.⁴⁴⁰²

As we've discussed, in the current Wild West of lax dietary supplement regulation, a supplement can be marketed without any safety data at all and the manufacturer is under no obligation to disclose adverse effects that may arise.⁴⁴⁰³ Online vendors assured absolute safety: "No negative side effects ... 100% safe for long-term use."⁴⁴⁰⁴ The president of Metabolife International, a leading seller of ephedra, assured the FDA that the company had "never received one notice from a consumer that any serious adverse health event has occurred." Liar. In reality, Metabolife had received thirteen thousand health complaints, including reports of serious injuries, hospitalizations, and deaths.⁴⁴⁰⁵

This is not to say prescription obesity drugs have fared much better. Dozens have been pulled from the market, on average eleven years after the first reports of serious adverse effects.⁴⁴⁰⁶ If only there were a way to speed your metabolism without suffering cardiovascular side effects.

Music to Our Ears

Music can impact our metabolisms. You can imagine how it might get you pumped up, but the original study showed the opposite effect. Published in the journal of the American Academy of Pediatrics, a study on preterm infants found that their resting metabolic rates slowed within ten minutes of researchers piping in Mozart. This was good news for the preemies, since that meant they could potentially put on weight faster and go home earlier.⁴⁴⁰⁷

Gaining weight faster is great for premature babies, but not so much for overweight adults. Could listening to music slow our metabolisms and contribute to weight gain? One study out of Sweden found no effect on adults, but the researchers used Bach, not Mozart.⁴⁴⁰⁸ Bach doesn't cause a drop in energy expenditure in babies either. The researchers concluded it may be "more a 'Mozart effect' than a universal 'music effect.'"⁴⁴⁰⁹

What happens to our metabolisms when we just listen to music of our choice? We didn't know until 2014, when Brigham Young University researchers reported that listening to self-selected music appears to give our metabolic rates a tiny bump, such that you would burn around thirty extra calories if you listened all day.⁴⁴¹⁰ That's only about eight M&M's candies' worth, so it's better to use music to get up and start dancing or exercising. Music may not only improve exercise enjoyment but also power output,⁴⁴¹¹ touted as a "legal method" to improve athletic performance.⁴⁴¹²

What about making music? In terms of calorie expenditure, playing piano or a brass or woodwind instrument isn't much better than taking a casual stroll, though trombone is the exception given all the associated arm movement, making it equal to light calisthenics.⁴⁴¹³ Rock drummers, however, can burn more than six hundred calories an hour.⁴⁴¹⁴ One study

concluded, “The metabolic demands required during heavy metal drumming meet the American College of Sports Medicine guidelines for the development of health related fitness.”⁴⁴¹⁵

The Diving Reflex

Picture walking across a frozen lake and suddenly falling through the ice, plunging into the frigid depths. It’s hard to think of a greater instantaneous fight-or-flight shock than that. Noradrenaline would be released, causing the blood vessels in our arms and legs to constrict to bring blood back to our cores. You can just imagine how fast your heart might start racing. That would be counterproductive, though, because you’d use up more oxygen. Remarkably, what happens instead is that your heart rate actually slows down. That’s called the *diving reflex*, first described in the 1700s.⁴⁴¹⁶ Air-breathing animals are born with this automatic safety feature to help keep us from drowning.

In medicine, we can exploit this physiological quirk with what’s called a *cold face test*. To test whether a comatose patient has intact neural pathways, you can apply cold compresses to their face and see if their heart immediately starts slowing down.⁴⁴¹⁷ Or, more dramatically, it can be used to treat people who flip into an abnormally rapid heartbeat.⁴⁴¹⁸ Remember that episode of *ER* where Carter dunked the patient’s face into a tray of ice water? (*ER* was on the air when I was in medical school, and a group of us would gather around and count how many times the doctors and nurses violated “universal precautions.”)

What does this have to do with weight loss? The problem with noradrenaline-releasing drugs like ephedra is the accompanying rise in heart rate and blood pressure. What the diving reflex shows is that it’s possible to experience *selective* noradrenaline effects, raising the possibility there may be a way to get the metabolic boost without risking stroking out. Unbelievably, this intricate physiological feat may be accomplished by the most simple of acts—instead of nearly drowning in water, simply drink it.

How to Prevent Yourself from Fainting

We know how important it is to stay hydrated, enough so that this book has an entire Hydration section. But did you know that when you drink three or four cups of water, within three minutes, the level of noradrenaline in your bloodstream can shoot up 60 percent?⁴⁴¹⁹ Have people drink two cups of water with needle electrodes stuck in their legs, and within twenty minutes, you can document about a 40 percent increase in bursts of fight-or-flight nerve activity.⁴⁴²⁰ Chug two or three cups of water, and blood flow clamps down in your calves⁴⁴²¹ and arms⁴⁴²² as arteries to your limbs and skin⁴⁴²³ constrict to divert blood to your core. That’s why drinking water can be a safe, simple, effective way to prevent fainting.⁴⁴²⁴

Fainting (known medically as *syncope*) is the sudden, brief loss of consciousness caused by diminished blood flow to the brain. About one in five people experience this at least once, and about one in ten may have repeated episodes, causing millions of emergency room visits and hospitalizations every year.⁴⁴²⁵ Though fainting can be caused by heart problems, it is most often triggered by prolonged standing, as blood pools in our legs, or by strong emotions, which can cause our blood pressures to bottom out.

About one in twenty-five people has what’s called *blood, injury, or injection phobia*, where getting stuck with a needle, for example, can cause you to faint. More than 150,000 people experience fainting or near-fainting spells each year when donating blood.⁴⁴²⁶ All you have to do to help prevent yourself from getting woozy, though, is simply chug two cups of water five minutes before you get stuck with the needle.⁴⁴²⁷ The secret isn’t in bolstering overall blood volume; drinking two cups of water or even a whole quart doesn’t change our blood volume more than 1 or 2 percent.⁴⁴²⁸ Rather, a fainting spell can be dispelled due to the shift in the distribution of blood toward our centers, caused by the

noradrenaline-induced peripheral artery constriction. Might all that noradrenaline help with weight loss in the same way ephedra did, but without the side effects?

Be Still Your Beating Heart

Drinking water stimulates as much of a noradrenaline release as drinking a couple of cups of coffee or smoking a couple of unfiltered cigarettes.⁴⁴²⁹ If the simple act of drinking water causes such a profound fight-or-flight reaction, why doesn't it cause your heart to pound and your blood pressure to shoot through the roof? It's like the diving reflex—when you drink water, your body shoots out noradrenaline while simultaneously sending signals to your heart to slow it down. Try this at home: Measure your heart rate before and after drinking two cups of water. Within ten minutes of drinking the water, your heart rate should slow by about four beats per minute, and by fifteen minutes, you should be down six or seven beats.⁴⁴³⁰

One of the ways scientists figured this out is by studying heart transplant patients. When a heart is moved from one person to another, all the attached nerves first have to be severed. Amazingly, some of the nerves can grow back, but even so, give healed heart transplant patients two glasses of water and their blood pressures go up as much as twenty-nine points.⁴⁴³¹ The body is unable to sufficiently quell the effect of that burst of noradrenaline. Some people have a condition known as *autonomic failure*, in which blood pressure regulation nerves don't work properly, and their pressures can skyrocket dangerously more than one hundred points after drinking two cups of water.⁴⁴³² That's how powerful an effect the simple act of drinking a glass of water can be, and the only reason that doesn't happen to all of us is that we have an even more powerful counterresponse to keep our hearts in check. It reminds me of the poor woman who had a stroke after taking the ice bucket challenge due to an insufficient diving reflex to tamp down all that extra noradrenaline.⁴⁴³³

The remarkable water effect can be useful for people suffering from milder forms of autonomic failure, such as orthostatic hypotension, which causes dizziness when people stand up suddenly. Drinking some water before getting out of bed in the morning can be a big help.⁴⁴³⁴ But what about that metabolic boost? With so much noradrenaline being released, might drinking a few glasses of water cause you to burn more body fat? Could tap water be a safe alternative to ephedra, with all the weight loss but a nice slowing of your heart rate instead? Researchers decided to put it to the test.

A Tall Drink of Water

Published in *The Journal of Clinical Endocrinology & Metabolism*,⁴⁴³⁵ the study's results were described as "uniquely spectacular."⁴⁴³⁶ Drinking two cups of water increased the metabolic rate of men and women by 30 percent. The increase started within ten minutes of water drinking and reached a maximum within an hour. In the ninety minutes after drinking a single tall glass of water, the subjects burned an extra twenty-four calories.⁴⁴³⁷ Simply drinking a tall glass of water four times throughout the day would wipe out nearly one hundred extra calories, more than the calories burned by taking weight-loss doses of the now-banned ephedrine three times a day.⁴⁴³⁸ Plain, cheap, safe, and legal tap water!

Using the Ten-Calorie Rule I explained in the Intermittent Fasting section, unless we somehow compensated by eating more or moving less, drinking that much water would cause us to lose ten pounds over time. "In essence," concluded one research team, "water drinking provides negative calories."⁴⁴³⁹

A similar effect was found in overweight and obese children. Drinking about two cups of water led to a 25 percent increase in metabolic rate within an hour.⁴⁴⁴⁰ So just getting the recommended, daily "adequate intake" of water—about five cups a day for children aged

four through eight and seven cups a day for girls and eight daily cups for boys aged nine through thirteen⁴⁴⁴¹—may offer more than just hydration benefits.

Not all research teams were able to replicate these findings, though. Others found only about a 10–20 percent increase,⁴⁴⁴² a 5 percent increase in metabolic rate,⁴⁴⁴³ or effectively none at all, pouring cold water on the whole concept.⁴⁴⁴⁴ What we care about, though, is weight loss, and the proof is in the pudding.

Testing the Waters

According to some researchers, “The increase in metabolic rate with water drinking could be systematically applied in the prevention of weight gain.”⁴⁴⁴⁵ Talk about a safe, simple, side effect-free solution—in fact, free in every sense. Pharmaceutical companies may spend billions getting a new drug to market.⁴⁴⁴⁶ Surely a little could be spared to test something that, at the very least, couldn’t hurt, right? That’s the problem, though. Water is a “cost-free intervention.”⁴⁴⁴⁷

As I discussed in the Hydration section, there are observational studies suggesting those who drink four or more cups of water a day, for example, appear to lose more weight independent of confounding factors, such as less soda or more exercise.⁴⁴⁴⁸ As always, you can’t really know until you put it to the test.

In 2013, a study entitled “Effect of ‘Water Induced Thermogenesis’ on Body Weight, Body Mass Index and Body Composition of Overweight Subjects” was published.⁴⁴⁴⁹ Fifty overweight women aged eighteen through twenty-three were asked to drink, over and above their regular water intakes, two cups of water three times a day a half hour before meals without otherwise changing their diets or physical activity. They lost an average of three pounds in eight weeks. What happened to those in the control group? There was no control group, which is a fatal flaw for any weight-loss study, due to the Hawthorne effect, where just knowing you’re going to be watched and weighed may subtly affect behavior.⁴⁴⁵⁰ Of course, we’re just talking about water, so, with no downsides, you might as well give it a try. Nevertheless, I’d feel more confident if there were some randomized controlled trials to *really* put it to the test. Thankfully, there are.

Overweight and obese men and women randomized to two cups of water before each meal lost nearly five pounds more body fat in twelve weeks than those in the control group.⁴⁴⁵¹ Both groups were put on a calorie-restricted diet, but the group with the added water lost weight 44 percent faster. A similar randomized controlled trial found that about one in four in the water group lost more than 5 percent of their body weight compared to only one in twenty in the control group.⁴⁴⁵² This is comparable to some commercial weight-loss programs, and all they did was drink a couple of extra cups of water.⁴⁴⁵³ The average weight-loss difference was only about three pounds, but those who adhered to the three-times-a-day instructions lost about eight more pounds compared to those who only drank the extra water once a day or less.⁴⁴⁵⁴

Optimum Dose, Type, and Temperature

A single cup of water may be sufficient to rev up the noradrenaline nerves, but additional benefit is seen at two or more cups.⁴⁴⁵⁵ To get the metabolic boost, do you have to drink straight, plain water? Water is water, whether flavored or sweetened in a diet drink, right? No. When trying to prevent fainting before blood donation, juice doesn’t work as well as plain water,⁴⁴⁵⁶ and when trying to keep people from getting dizzy when they stand up, water works, but the same amount of water with salt added doesn’t.⁴⁴⁵⁷ What’s going on?

We used to think the trigger was stomach distension. When we eat, our bodies shift blood flow to our digestive tracts, in part by releasing noradrenaline to pull in blood from the limbs. This has been called the *gastrovascular reflex*.⁴⁴⁵⁸ So drinking water was thought to be a zero-calorie way of stretching our stomachs. But if you instead drink two cups of

saline (essentially salt water), the metabolic boost vanishes, so stomach expansion can't explain the water effect.⁴⁴⁵⁹

We now realize our bodies appear able to detect osmolarity, the concentration of liquid. You can demonstrate this by monitoring sweat production (used as a proxy for noradrenaline release) after covertly slipping liquids of varying concentrations into people's stomachs via a feeding tube.⁴⁴⁶⁰ This uncanny ability may be a spinal reflex, as it's preserved in quadriplegics,⁴⁴⁶¹ or picked up by the liver, as we see less noradrenaline release in liver transplant patients who've had their liver nerves severed.⁴⁴⁶² Whichever the pathway, our bodies can tell. Thought we only had five senses? The current count is upward of thirty-three.⁴⁴⁶³ (Maybe the Bruce Willis movie should have been called *The Thirty-Fourth Sense!*)

In my Daily Dozen recommendation, I rank certain herbal teas as among the most healthful beverages. After all, they would seem to have all the benefits of water with an antioxidant bonus. But from a weight-loss perspective, plain water may have an edge. One research team even suggested this may help explain the results of a series of diet soda studies I document in the Wall Off Your Calories section.⁴⁴⁶⁴ Basically, overweight and obese individuals randomized to replace diet beverages with water lost significantly more weight.^{4465,4466} This was chalked up to getting rid of all those artificial sweeteners, but could it be that the diet drinks were too concentrated to offer the same water-induced metabolic boost? Diet soda, like herbal tea, has about ten times the concentration of dissolved substances compared to tap water.⁴⁴⁶⁷ So plain water on an empty stomach may be best.

Does the temperature of the water matter? In a journal published by the American Society of Mechanical Engineers, an engineering professor proposed that the "secret" of a raw food diet for weight loss was the temperature at which the food was served. To bring two cups of room-temperature water up to body temperature, he calculated the body would have to dip into its fat stores and use up about six thousand calories. But his math was faulty.⁴⁴⁶⁸ In nutrition, a "calorie" is actually a kilocalorie, a thousand times bigger than the same word used in the rest of the sciences. Confusing, right? Still, I'm shocked the submission was published.

Drinking two cups of water at room temperature actually only takes six calories to warm up to body temperature, not six thousand. If you were a hummingbird drinking four times your body weight in chilly nectar, you could burn up to 2 percent of your energy reserves warming up the nectar,⁴⁴⁶⁹ but it doesn't make as much of a difference for us. What about really cold water, though? A letter called "The Ice Diet" published in the *Annals of Internal Medicine* estimated that eating a quart of ice—like a really, really big snow cone without syrup—could rob our bodies of more than 150 calories, the "same amount of energy as the calorie expenditure in running 1 mile."⁴⁴⁷⁰ You don't directly burn fat to warm up the water, though. What our bodies do is just corral more of the waste heat we normally give off by constricting blood flow to our skin.⁴⁴⁷¹ How do they do that? Noradrenaline!

If you compare drinking body-temperature water to room-temperature water to cold water, a significant constriction in blood flow to the skin occurs only after drinking room-temperature water and cold water, and neither the warm nor tepid water could boost metabolic rate as much as cold (fridge temperature) water.⁴⁴⁷² So it turns out our bodies do end up—at least indirectly—burning off more calories when we drink our water cold.

FOOD FOR THOUGHT

Drink two cups of cold water on an empty stomach a few times a day. Does it matter when? I'll cover that question in the Negative Calorie Preloading section.

Caution: Never drink more than three cups in an hour, since that starts to exceed the amount of fluid our kidneys can handle.⁴⁴⁷³ If you have kidney or heart failure, your physician may not want you drinking extra water at all, but even with healthy kidneys, any more than three cups an hour can critically dilute the electrolytes in your brain with

potentially critical consequences. (The first patient I ever lost in the hospital was a man who tragically drank himself to death—with water. He suffered from a neurological condition that causes pathological thirst. I knew enough to order his liquids be restricted and shut off his sink, but didn't think to turn off his toilet.)

Note if you're on a beta-blocker drug, the entire strategy may fail. If you give people the drug metoprolol (sold as Lopressor) before they chug their two cups of water, the metabolic boost is almost completely prevented.⁴⁴⁷⁴ This makes sense since the “beta” being blocked are the beta receptors triggered by noradrenaline. Beta blockers are often prescribed for heart conditions or high blood pressure, and typically end with the letters *lol*, such as *atenolol*, *nadolol*, or *propranolol*, sold as Tenormin, Corgard, or Inderal, respectively.

MILD TRENDELENBURG

The Way to a Person's Stomach Is Through the Heart

In the Hydration section, I detailed what happens when our kidneys detect a drop in blood volume. What happens when our blood capacity expands? Upswings in blood volume are detected by our hearts, which, in response, release a hormone called *atrial natriuretic factor*, or *ANF*. We used to think the heart was just a pump, but we now know it's a gland too. There are stretch receptors in the first chamber of the heart that can detect when excess blood pours in, triggering the release of ANF directly into the bloodstream. What does the hormone do? As the title of a review in an obesity journal puts it: “Heart Hormones Fueling a Fire in Fat.”⁴⁴⁷⁵

If you drip ANF on human fat and muscle tissue, fat is released rapidly⁴⁴⁷⁶ and muscle cells ramp up their capacity to burn it.⁴⁴⁷⁷ Infuse ANF into people, and the rate at which fat is mobilized and burned can bump up by 15 percent.⁴⁴⁷⁸ You can take muscle biopsies from people and show how much better their muscles burn fat in the presence of elevated ANF levels.⁴⁴⁷⁹ No surprise, then, that obese and overweight individuals tend to have considerably lower levels in their bloodstreams.⁴⁴⁸⁰

Why would this stretch-sensitive heart hormone tap into our fat stores? Well, when does the heart get stretched? During intense physical activity. We used to think adrenaline-type hormones were released when we exercise to mobilize fat from our tissues, but we now know ANF from our hearts also plays a key role.⁴⁴⁸¹ If you inject people with the amount of ANF they'd normally get in their systems by exercising, their whole-body-fat burning goes up even if they're just lounging on the couch.⁴⁴⁸²

How else can we stretch our hearts that extra little bit to release ANF? By expanding our blood volume through drinking extra water.⁴⁴⁸³ If you don't drink any water for twelve hours straight, the ANF levels in your blood may fall by about 25 percent,⁴⁴⁸⁴ but if you chug about four glasses of water, your levels can jump 50 percent within ninety minutes.⁴⁴⁸⁵ That's too much to drink at one time,⁴⁴⁸⁶ but it can offer a sense of how much potential control we have over this fat-burning hormone.

A New Slant on Weight Loss

How else might we trick our bodies into producing this “exercise hormone” without lacing up our gym shoes? If it's all about pooling extra blood into our hearts, what about lying down at an angle with your head lower than your feet? It sounds a little funny, but researchers took the possibility seriously enough to run the experiment. They laid people on a slanted surface with their heads down at a six-degree angle, which is enough of a tilt for gravity to pull extra blood up into their torsos. Within an hour, their ANF levels doubled and stayed elevated for the four hours the experiment lasted. Did they suddenly start burning more fat? Yes, the proportion of fat they were burning as fuel shot up by 40 percent—and they were just lying down the whole time.⁴⁴⁸⁷

Certainly, if you have a heart condition, such as congestive heart failure, you won't want to lie tilted back. As many as eight to twelve cups of blood may be displaced into the torso from the extremities,⁴⁴⁸⁸ so you have to have the cardiovascular fitness to handle that. Acid

reflux could also be a problem. In fact, we typically tell heartburn patients to do the reverse and put a few bricks under the posts at the *head* of their beds to have gravity work in their favor to keep stomach acid down where it belongs. But for those without medical problems, is there a harm in lying tilted back for a few hours? Well, it could give you a “space headache.”

It Is Rocket Science

In movies, astronauts are shown training underwater, but the gold standard for simulating the physiological effects of the weightlessness of outer space is HDTBR, head-down-tilt bed rest.⁴⁴⁸⁹ On Earth, our blood tends to collect in our legs, so our bodies are designed to force blood headward. In outer space, our bodies still try to push our blood “up,” but without Earth’s gravity, blood pushes upward in our heads and chests, just as it does when we lie tilted back. This realization came from cosmonauts returning from the space station feeling as though they were slipping toward the foot of the bed and only feeling “normal” when they were tilted back six degrees.

All the extra blood pooling in the head is thought to contribute to the headaches reported by up to 70 percent of astronauts during spaceflights, and a similar percentage of individuals suffer headaches from prolonged head-down-tilt bed rest. This was after days, though. In preparation for a Mars mission,⁴⁴⁹⁰ space agencies put people through head-down-tilt bed rest for prolonged periods, having subjects eating, bathing, and toileting all while lying in bed tilted back for literally months at a time.⁴⁴⁹¹

Extended stretches for weeks may impair brain,⁴⁴⁹² lung,⁴⁴⁹³ and immune function⁴⁴⁹⁴ and cause a loss of muscle mass.⁴⁴⁹⁵ On the last Apollo mission, the astronauts lost about five pounds of fat over the twelve-day trip, but they also lost about two pounds of lean body mass.⁴⁴⁹⁶ Prolonged weightlessness or bed rest, regardless of tilt, can result in muscle and bone loss,⁴⁴⁹⁷ but simply sleeping on a slant for a few hours could theoretically offer the boost in fat metabolism without the long-term adverse effects.

The Pressure to Succeed

Do *not* try this at home if you have any heart or lung issues or problems with your brain (like head trauma) or eyes⁴⁴⁹⁸ (even a family history of glaucoma disqualifies you). And first ask your physician if they think it’s safe for you to sleep in “mild Trendelenburg.” Friedrich Trendelenburg was a pioneering surgeon who popularized the use of what was formerly referred to as *head-down position* for certain abdominal and pelvic procedures. Angling the operating table back fifteen to thirty degrees pulls some abdominal organs out of the way to help declutter the surgical field, resulting in what is now widely known as the *Trendelenburg position*.⁴⁴⁹⁹

Steep Trendelenburg (twenty-five or thirty degrees) has been associated with transient visual problems, thought due to the increase in pressure within the eyeball.⁴⁵⁰⁰ Cautions have been issued for those at risk for glaucoma, a disease of increased eye pressure, to avoid “inversion” therapy, where people hang upside down,⁴⁵⁰¹ as well as yoga positions like headstands that can have a similar effect.⁴⁵⁰²

Lying back in mild Trendelenburg (less than fifteen degrees) can cause a fleeting bump in eye pressure⁴⁵⁰³ that normalizes within a few hours,⁴⁵⁰⁴ but the pooling of blood in the head may reduce blood flow to the retina⁴⁵⁰⁵ sufficient to impair nerve impulses.⁴⁵⁰⁶ Similar effects have been noted within the brain. Intracranial pressure normalizes after a few hours at a six-degree head-down tilt,⁴⁵⁰⁷ but the uphill outflow of blood through the jugular veins slows.⁴⁵⁰⁸ This is why you should skip this booster if you have eye or brain pathology.

Good to the Bone

Sleeping in mild Trendelenburg was actually put to the test to prevent bone loss in sedentary individuals. Restrict people's activity to under an average of two miles of walking a day, and, within a year, they can lose as much as 15 percent of their bone mineral density. What happened to those randomized to the same exercise restriction but combined with sleeping first at a two-degree head-down tilt, which was increased by two degrees about every two months so they ended up at the end of the year sleeping at a fourteen-degree slant (or at whatever angle they found comfortable)? Not only did it completely block the bone loss, they built *more* bone. Despite the movement restriction, they ended up with about 12 percent greater bone mineral density than when they had started. Note this bone-building effect was only apparent in sedentary individuals. Another group randomized to the same mild Trendelenburg but also assigned to run an average of five or six miles a day just maintained their same skeletal integrity.⁴⁵⁰⁹

The study was repeated, and the same remarkable effects were found. There is something about the "periodic fluid redistribution" that comes with sleeping tilted back at night that actively builds both bone density and volume after the daylong stagnant pooling of blood in the legs in sedentary individuals. The research team claims this is just the beginning to the benefits, citing "unpublished studies" asserting a near panacea of perks to sleeping in Trendelenburg.⁴⁵¹⁰ I can't be too critical of this apparent dodge when I can't point to a single study supporting my supposition that it will help with weight loss. As far as I can tell, tilting the scales with a head-down tilt has never been tried or even proposed. What I can promise is that any researchers who take up the gauntlet of putting it to the test will definitely have their study featured in a video on NutritionFacts.org!

FOOD FOR THOUGHT

If you want to try losing weight like an astronaut, you can try putting three or four bricks under the posts at the foot of your bed to achieve those six degrees of separation from the floor. Expect to experience symptoms such as stuffiness in the nose or ears and puffiness in the face⁴⁵¹¹ (a common occurrence among astronauts⁴⁵¹²).

My biggest concern, however, is the orthostatic intolerance I talked about in the Metabolic Boosters section. You know how sometimes when you stand suddenly after sitting or lying down for a while you can get a head rush and feel dizzy, faint, or light-headed? This is thought to be because the blood drains from your brain down into your legs before your body has a chance to compensate for the change in position. This can be exacerbated by lying with your head tilted back, so you need to be careful and get up gradually. After four hours of a six-degree head-down tilt, most people experience these symptoms if they get up too fast.⁴⁵¹³ Though it may be impractical, drinking two cups of cold water thirty minutes before rising may also help.⁴⁵¹⁴

At a six-degree tilt, the 50 percent rise in fat-burning ANF occurs within the first four hours and then starts to drop back down to baseline once your heart gets used to the new normal, so you may be able to get the full benefits sleeping just half the night at that angle.⁴⁵¹⁵ If this really works for weight loss, maybe someone will design a bed that slowly dips you down for a couple of hours and then brings you back up. Again, just be really careful and take it slowly when standing back up, and don't try this at all if you have any issues with your heart, lungs, brain (such as head trauma), or eyes (or even a family history of glaucoma). And make sure to ask your physician if they think it's safe for you to sleep in mild Trendelenburg.

NEGATIVE CALORIE PRELOADING

Timing of Water Before Meals

When timed properly, drinking water may be able to affect both sides of the calorie-balance equation. In the Metabolic Boosters section, I explored how drinking two cups of water could increase the calories-out side of the equation. If we time it right before a meal, might we fill ourselves up enough to cut down on the calories-in side too?

Older obese men and women were randomized to drink about two cups of water thirty minutes before a buffet-style meal.⁴⁵¹⁶ Compared to no preload, the water group ate 13 percent less, resulting in seventy-four fewer calories consumed, but this may only work for older individuals. A study of young adults found they ate a similar amount whether or not

they preloaded with water thirty minutes before the meal.⁴⁵¹⁷ This discrepancy was presumed to be because stomach emptying slows when we get older. It takes about a third longer for liquids to empty from our stomachs as we age, keeping us fuller for longer.⁴⁵¹⁸ Give some young whippersnappers a few cups of water, and in just ten minutes, half is nearly gone. After thirty minutes, nearly 90 percent of it has already drained out of the stomach.⁴⁵¹⁹ Okay, so what if you don't wait a half hour?

What if you give young adults two cups of water immediately before a meal? Do they then eat less? Indeed, they eat about 20 percent less, taking in more than one hundred fewer calories.⁴⁵²⁰ Is this why overweight men and women randomized to two cups of water before each meal lost weight 44 percent faster? ⁴⁵²¹ Not entirely. They may have been taking in slightly fewer calories, but not enough to explain the five extra pounds of body fat the water group lost.⁴⁵²² So the metabolic boost from water intake may be the main effect, but if you're going to drink two cups of water a few times every day, you might as well do it before meals to take the added advantage of its stomach-filling effect.

Sparkling or Still?

If it's all about filling up your stomach, wouldn't sparkling water work even better than still? One cup of highly carbonated water can release nearly four cups of gas, so it's no surprise sparkling water makes you feel fuller than drinking the same volume of still water.⁴⁵²³ But does that translate into eating less?

The first study to put it to the test found that drinking a high-fizz beverage (carbonated close to the level one might find in tonic water) ten minutes before a meal resulted in 15 percent lower caloric intake than preloading with a low-fizz beverage (carbonated to the level one might find in lightly carbonated fruit drinks). The effects of a medium-fizz beverage (carbonated to the level one might find in colas) was less consistent.⁴⁵²⁴ A subsequent study, however, found no difference between a higher-fizz drink and one that was completely flat.⁴⁵²⁵ That study only used a 300 ml preload (about 1¼ cups), though, whereas the first study used 400 ml (more like 1⅔ cups), which would mean about 1½ cups more gas in the stomach, but it's unclear if this plays a role in explaining the contradictory findings.

Another potential factor favoring fizz is the oral sensory stimulation. Remember in the Eating Rate section how that helped explain the satiating effects of prolonged chewing? What could be more stimulating than the effervescent tingle of all those bubbles? When people "sham drink" club soda, spitting it out rather than swallowing it, they experience a temporary feeling of fullness in their stomachs even though they didn't drink anything.⁴⁵²⁶ The craziest such study involved measuring the temperatures of people's toes.

If you have people drink a glass of regular water, the temperature of their toes drops about 5°F within thirty minutes. Why? Because of that release of noradrenaline constricting peripheral blood flow. Even just swishing carbonated water in our mouths, though, can have nearly the same effect.⁴⁵²⁷ This suggests sparkling water may have a metabolic edge, but it has never been tested directly. What matters in the end is weight loss, and as of yet, there haven't been any studies comparing sparkling water to still.

Aperitif?

Carbonated or not, drinking a beverage that has calories as a preload could defeat the purpose. Even high-protein beverages, such as liquid yogurt or chocolate skim milk, which were presumed to be satiating, didn't reduce subsequent meal intake any more than did, respectively, a chocolate bar⁴⁵²⁸ and Coca-Cola.⁴⁵²⁹ Given that, they would be expected to increase total caloric intake in the end.⁴⁵³⁰ Alcoholic beverages, however, may be even worse.

Not only does alcohol carry its own calories, it may end up increasing intake. I mean, the whole purported point of an aperitif is to stimulate appetite. When people drink a glass of wine or beer before lunch, they may eat more food than if they had drunk the same volume and calories of grape juice and other nonalcoholic beverages.⁴⁵³¹ Those drinking a beer with quadruple the regular alcohol content ate two hundred calories more at a subsequent meal compared to those drinking a regular beer—and that was above and beyond the beer's own calories.⁴⁵³² So it's like a reverse-preload effect that just makes things worse.

At that level of alcohol intake, judgment may be affected as well. Women given about one shot of vodka were covertly observed eating nearly 50 percent more chocolate chip cookies in one study, which was chalked up more to a loss of control than an increase in appetite.⁴⁵³³ Even if alcohol had a neutral effect on consumption, it would still pile on its own calories.⁴⁵³⁴ That's one of the benefits of a zero-calorie preload like water.

What About Fiber Supplements?

Higher-fiber foods are more satiating for all the reasons I laid out in the High in Fiber-Rich Foods section. Preload people with a chicken appetizer, for example, and they eat significantly more at the subsequent meal than after eating the same appetizer made with more fiber-rich options, either tofu or a meat-free chicken (Quorn).⁴⁵³⁵ What if you just gave people straight fiber isolated into pills or powders?

The data on fiber supplements for weight loss have been inconsistent⁴⁵³⁶ and largely disappointing.⁴⁵³⁷ Randomizing people to mix sachets of wheat bran with water before meals didn't seem to help,⁴⁵³⁸ and neither did water mixed with alginate, the main type of fiber in brown seaweed.⁴⁵³⁹ Even in studies showing an advantage, the benefits were relatively modest—for example, less than a pound a month in those randomized to eat a total of fifteen daily grams of yellow split pea fiber thirty minutes before meals.⁴⁵⁴⁰

Have you seen those shirataki noodles? They are translucent, gelatinous strands made from a fiber derived from the konjac plant (also known as *voodoo lily*, *snake palm*, and *devil's tongue*). Their claim to fame is that they can be up to 97 percent water and boast as few as ten calories per serving. With so few calories, they might seem like a good candidate for a negative-calorie preload, which I define as one that contributes fewer calories than it reduces. In actuality, though, they don't seem to result in a reduction of subsequent caloric intake.⁴⁵⁴¹ If you do eat them, please chew thoroughly, as they can gum together and cause a stomach outlet obstruction requiring surgical intervention.⁴⁵⁴² (And while we're on the subject, never let kids slurp down those little fruit-flavored konjac gel cups often sold in Asian markets.⁴⁵⁴³ Though they've been banned for sale in Australia, Europe, and the United States for choking children to death, they can still be found on store shelves.⁴⁵⁴⁴)

What about PGX, a favorite of diet doctors who also, not so coincidentally, sell it? PGX is short for *PolyGlycopleX*, a brand name for α -D-glucurono- α -D-manno- β -D-manno- β -D-glucan, α -L-gulurono- β -D-mannuronan, β -D-gluco- β -D-mannan, α -D-glucurono- α -D-manno- β -D-manno- β -D-gluco, α -L-gulurono- β -D-mannurono, β -D-gluco- β -D-mannan.⁴⁵⁴⁵ PGX is a designer fiber created through a patented process purported to produce some special properties, but even most of the manufacturer-sponsored trials failed to show weight-loss benefits.⁴⁵⁴⁶ One study that did—six pounds lost in twelve months—failed to beat out psyllium,⁴⁵⁴⁷ a fiber supplement that's more than ten times cheaper.

Sold generically and under the brand name Metamucil, psyllium has been shown to decrease body weight up to four pounds in twelve weeks when taken with a cup of water before each meal. Study subjects just advised to eat more healthfully lost as much weight, though, and there was no additional benefit found for psyllium on top of healthier eating advice.⁴⁵⁴⁸ By six months, however, a different study found that twice-a-day psyllium preloading could edge out healthier eating advice by about five pounds.⁴⁵⁴⁹ One of the

reasons all that extra fiber may not have worked better is that psyllium isn't fermented in the human gut like the fiber found in whole foods, so we may miss out on all the auxiliary microbiome benefits of high-fiber diets.⁴⁵⁵⁰

“Negative Calorie” Salads

A bona fide “negative caloric effect”⁴⁵⁵¹ is easy for water because it doesn't provide any calories of its own. If drinking water gets us to eat just one fewer calorie or burn just one more calorie, then we're left with fewer calories to store as fat. And remember: It wasn't just one fewer calorie, but up to one hundred fewer calories consumed after drinking two cups of water. If preloads can have such a dramatic effect on intake, then what about filling up at the beginning of a meal with low-calorie-density foods?

Celery is the classic example of a food with lots of bulk with few calories, due to its high fiber and water content. There's even a myth that celery contains fewer calories than the energy required for our bodies to digest it. A cup of celery, about two stalks, has sixteen calories. Digesting that much celery takes about fourteen calories.⁴⁵⁵² So, no: The consumption of celery does not induce a negative-energy balance, but you are only left with two calories. If eating a cup of celery before a meal led you to eat even three fewer calories, then celery could end up providing “negative calories” after all.

In a famous series of experiments, researchers at Penn State decided to put water-rich vegetables to the test. Study subjects were served a pasta meal for lunch and told to eat as much or as little as they'd like. On average, they consumed about nine hundred calories. What do you think would happen if as a first course you gave them one hundred calories of salad composed largely of lettuce, carrots, cherry tomatoes, celery, and cucumber? Would they go on to eat the same amount of pasta and end up with a thousand-calorie lunch? Or would they eat one hundred fewer calories of pasta, effectively canceling out the added salad calories? It was even better than that. They ate more than two hundred fewer calories of pasta.⁴⁵⁵³ One hundred calories in; two hundred calories out. So, in essence, the salad had *negative one hundred* calories.

Preloading with vegetables can effectively subtract one hundred calories out of our diets. That's how you can lose weight by eating more food.

Of course, the kind of salad matters. The researchers repeated the experiment, adding a fatty dressing and extra shredded cheese, which quadrupled the salad's calorie density. Eating this version of the salad as a first course didn't turn the nine-hundred-calorie meal into one with fewer than eight hundred calories. Instead, it turned it into a meal with calories in the quadruple digits.⁴⁵⁵⁴ It's like preloading pizza with garlic bread. You could end up with more calories overall, whereas a pre-pizza salad may cut calories even more than preloading with water,⁴⁵⁵⁵ presumably in part because of the combination of water and fiber in vegetables.

We've learned from studies on preloading that eating about a cup of food before a meal decreases subsequent intake by about one hundred calories, so to get a “negative calorie” effect, the preload has to contain fewer than one hundred calories per cup.^{4556,4557} As you can see in the Calories per Cup chart in the Low in Calorie Density section, that would include most fresh fruits and vegetables. So is that it? Are we simply diluting the calories of a meal by adding low-calorie-density foods, or does the timing matter? To figure that out, you'd have to randomize people to either preload with a salad before a meal or eat that same salad during a meal, and that's exactly what researchers did.

Those on a diet randomized to eat a preload of a salad comprised mostly of vegetables fifteen minutes before lunch and dinner for three months lost four more pounds than the group given the same extra foods, but with instructions they be eaten alongside their meals and not before.⁴⁵⁵⁸ This showed that the “negative-calorie”-preload strategy can indeed lead to weight loss, and the effect appears to extend beyond merely adding more

low-calorie-density foods. That actually may be one of the secrets of preloading, though. It's thought that preloading works by allowing time for our satiety hormones to start ramping up before we dive into the main meal. By frontloading the most healthful foods first, when you're hungriest, you may also eat more of them.⁴⁵⁵⁹ Those given a salad before a meal ate more salad than when it was competing for their attention during the meal.⁴⁵⁶⁰ So part of the magic of preloading may indeed lie in eating more low-calorie-density foods after all.

Celery Sun Rash

A warning for those who eat a lot of celery, celery juice, or celeriac (celery root): There are compounds called *psoralens* in the celery/parsnip/parsley family that can make you sensitive to sunlight.⁴⁵⁶¹ Without skin protection, farmworkers can suffer from a condition known as *celery blisters* when handling the plants in the sun,⁴⁵⁶² and even grocery store workers who go from the produce aisle to the tanning salon can get into trouble.⁴⁵⁶³ These compounds can make their way into our skin from the inside out as well, and they are not destroyed by cooking. So too much time in the sun after commencing a "celery soup diet"⁴⁵⁶⁴ or spending time in a tanning bed an hour after eating just one large celery root may be enough to result in a serious blistering burn.⁴⁵⁶⁵

Apple-tizer

What about a fruit salad? We've explored preloading with water and vegetables, but what about fruits? Give people a large apple to eat before that same pasta meal instead of the salad, and rather than consuming about two hundred fewer calories, they consumed more than *three hundred* fewer calories.⁴⁵⁶⁶ So how many calories does an apple have? *It depends on when you eat it.* Before a meal, it may effectively have negative two hundred calories!

Baked and puréed, the same amount of apples preloaded in the form of applesauce only knocked out about two hundred calories from the meal, but that still left people with about a one-hundred-calorie deficit.⁴⁵⁶⁷ Preload experiments with other fruits weren't as successful. Kiwifruit didn't beat out white rice,⁴⁵⁶⁸ melon didn't do much better than cheese and crackers,⁴⁵⁶⁹ and about a cup of fruit smoothie or mixed fruit salad did no better than about the same volume of water in decreasing subsequent intake.⁴⁵⁷⁰ The proof is in the pudding, though. What about weight loss over time?

There was that premeal tomato study showing weight loss that I discussed in the Inflammation Quenchers section, but tomatoes are more often viewed as vegetables. There was also the study that showed that adding three apples or three pears to people's daily diets decreased body weights compared to adding the same number of calories and amount of fiber in oat cookie form, but participants were just told to consume the fruits as snacks between meals, so the timing is unclear.⁴⁵⁷¹ Those told to eat half a grapefruit three times a day before meals lost as much weight as those in the apple and pear study—a few pounds in a few months—but no more than preloading instead with half cups of water.⁴⁵⁷² This would seem to confirm that it is but a "long-held myth"⁴⁵⁷³ that grapefruits have any sort of special fat-burning property, but one could argue that the grapefruit might have had a bit of an edge since it produced roughly the same weight loss, even while adding about 125 calories a day.⁴⁵⁷⁴

Soup's On! Weight's Off?

The United States is not a nation of soup eaters. Even during the winter months, most Americans don't eat soup more than a few times a month, whereas in France, for example, about half eat soup at least a few times a week⁴⁵⁷⁵ and in Japan, the average is soup every day.⁴⁵⁷⁶ In the United States, soup eaters tend to be slimmer on average⁴⁵⁷⁷ and significantly less likely to be overweight,⁴⁵⁷⁸ but as I discussed in the Low in Calorie Density

section, soup eaters also tend to consume healthier diets (with the exception of excess sodium).⁴⁵⁷⁹

When put to the test, those randomized to eat more soup lost up to 50 percent more weight,⁴⁵⁸⁰ but those weren't preload studies. It's like the water and apples—soup anytime is good, but it may work even better right before a meal. If you feed someone a radioactive omelet—that is, one with the egg labeled with an isotope to track it with a gamma-ray camera through the body—those randomized to precede it with about a cup and a half of soup slowed stomach emptying by about 25 percent.⁴⁵⁸¹ This may be why those who have soup as a first course eat so much less throughout the rest of the meal.

Let's go back to the preeminent preloaded pasta experiments. With no first course, about 900 calories were eaten. When people were given about two cups of vegetable soup totaling around 150 calories before the meal, they ate about 250 fewer calories of pasta.⁴⁵⁸² So a healthy soup, like the healthy salad, can end up offering negative 100 calories. A similar study that tracked people's intake throughout the day found that overweight subjects randomized to prelunch vegetable soup deducted an additional 100 calories at dinner, too, a whole seven hours later.⁴⁵⁸³ So the next time you sit down to some soup, you can imagine calories being veritably sucked out of your system with every spoonful. Vegetable soup would seem to be the perfect weight-loss food.

Similar results were found for young children. Without any soup, the kids ate about 400 calories of mac 'n cheese. When they first started their meals with about a half cup of tomato soup, though, they ate about 100 fewer calories of mac 'n cheese.⁴⁵⁸⁴ Since the soup only contained about 50 calories, it effectively subtracted, rather than added, calories to their diets when used as a first course.

There's just something special about soup. If you give people about 250 calories of a casserole and a glass of water before eating a buffet meal, they eat about 250 fewer calories at the buffet, effectively just swapping the different foods, calorie for calorie. But take that same casserole and glass of water and blend them into a soup, and once again serve it before the same buffet meal, people went on to eat 350 fewer calories at the buffet. Same calories, same ingredients, same food, but they were just as satiated eating 100 fewer calories when eaten as a soup.⁴⁵⁸⁵ Is it simply because soup takes longer to eat? No, the researchers made people eat the actual casserole and the soupified casserole at the same rate. So it's not that soup is just salty or served hotter or eaten slower. It could be cognitive factors: Soup seems to be perceived as being particularly filling.⁴⁵⁸⁶ It may be the sieving effect I talked about in the High in Water-Rich Foods section.⁴⁵⁸⁷ We aren't quite sure, but we do know there's just something special about soup.

FOOD FOR THOUGHT

Starting a meal with foods containing fewer than one hundred calories per cup can result in fewer overall calories consumed. This includes many fruits, vegetables, soups, salads, or simply a tall glass of water.

SLEEP ENHANCEMENT

Epidemic Proportions or Distortions?

Conventional wisdom has it that over the last fifty years or so, sleep duration has declined in parallel with the increasing prevalence of obesity, suggesting that an epidemic of sleep loss is associated with the epidemic of weight gain.⁴⁵⁸⁸ Today, our triple-digit TV channels, personal computers, smartphones, and tablets keep us entertained well into the night. "The hurry and excitement of modern life is quite correctly held to be responsible for much

of the insomnia,” concluded one medical journal editorial.⁴⁵⁸⁹ But that was an editorial published in 1894. Are we really sleeping that much less?

Over the last century, sleep duration in children and adolescents has declined by an average of nearly two hours.⁴⁵⁹⁰ Child labor wasn’t outlawed until 1938, though, so much of that may be due to the exhaustion of sweating it out in mines, farms, and factories in the early part of the last century.⁴⁵⁹¹ Indeed, sleep duration in youth has declined only about fifteen minutes per night, and it’s not clear it’s changed much at all in adults. Based on 168 studies of objective measurements of sleep duration (instead of just self-report), sleep duration in adults has remained relatively steady since 1960.⁴⁵⁹² If anything, since 2003, average sleep duration in the United States even seems to have gone up.⁴⁵⁹³

Just because we don’t have evidence there has been a growing epidemic of sleep deprivation doesn’t necessarily mean we’re getting enough sleep.⁴⁵⁹⁴ Maybe we weren’t getting enough sleep fifty years ago either, or since the advent of Edison’s light bulbs, or since candles were invented about five thousand years ago. How might we determine the optimal sleep duration? One way would be to study millions of people and see how many hours a night is associated with the longest life span.

Sleeping in the Sweet Spot

Sleep is a great mystery. A trait shared across animal species, sleep must be of vital importance to survive natural selection pressures to eliminate such a vulnerable state.⁴⁵⁹⁵ Indeed, cringeworthy experiments have shown that keeping animals awake long enough can be fatal within eleven to thirty-two days.⁴⁵⁹⁶ One function of sleep that has been elucidated in recent years is the clearance of toxic waste substances⁴⁵⁹⁷ through a newly discovered drainage system in the brain.⁴⁵⁹⁸ This could help explain why those who routinely get fewer than seven hours of sleep a night are at increased risk of developing cognitive disorders such as dementia.⁴⁵⁹⁹ Even a single all-nighter can cause a significant increase in accumulation of beta amyloid, a gummy substance implicated in the development of Alzheimer’s disease, in critical brain areas.⁴⁶⁰⁰

The lowest risk for developing cognitive impairment was found for those getting seven to eight hours of sleep a night, based on nine studies following twenty-two thousand people for up to twenty-two years.⁴⁶⁰¹ The same range was found for diabetes, based on thirty-six studies following more than a million people, with increasing risk found for those sleeping either six hours a night or less, or nine hours a night or more. Remarkably, the increased risk associated with getting six hours of sleep a night versus seven hours is comparable to the increase in diabetes risk linked to physical inactivity.⁴⁶⁰²

For death from all causes combined, there have been more than fifty studies following more than three million people for up to thirty-four years. Sleeping too little and for too long are both associated with cutting one’s life short, with the apparent sweet spot at seven hours a night.⁴⁶⁰³ Seven hours may seem short, but that may actually be what’s natural for our species. Scientists studied three isolated preindustrial societies across two continents and found a surprising uniformity. Despite no electric lighting or electronic gadgets, they stayed up until approximately three hours after sunset and then typically rose before dawn, accumulating about a solid six and a half hours of sleep out of about seven and a half hours in “bed.”⁴⁶⁰⁴

A mechanism by which excess sleep might be harmful remains elusive, so the association between increased risk of death and disease with sleeping nine or more hours a night has largely been dismissed as implausible.⁴⁶⁰⁵ Could it be reverse causation, like sickness leading to more time in bed instead of vice versa, or confounding factors such as employment status? ⁴⁶⁰⁶ After all, who tends to sleep in? Those without a job. There is, however, experimental evidence showing negative health effects from insufficient sleep, including weight gain.

Midnight Munchies

Population studies have found short sleep duration has been associated with obesity in both children⁴⁶⁰⁷ and adults.⁴⁶⁰⁸ Observational studies can never prove cause and effect, though. Maybe the obesity is leading to sleep loss instead of the other way around. Obesity can cause arthritis, acid reflux, and apnea, all of which can interfere with sleep.⁴⁶⁰⁹ The relationship between obesity and sleep apnea, where breathing repeatedly stops and starts throughout the night, may be explained by increased tongue fat—fat deposited inside the base of the tongue. This may contribute to obstructing your airway when sleeping on your back.⁴⁶¹⁰ The reverse causation explanation of the link between obesity and inadequate sleep is bolstered by the findings that weight-loss interventions can improve daytime sleepiness.⁴⁶¹¹

Potential confounding factors also abound. For example, people with lower socioeconomic status often work less desirable hours, such as rotating or overnight shifts,⁴⁶¹² or may live in noisier neighborhoods with lesser air quality.⁴⁶¹³ The link between inadequate sleep and obesity persists after controlling for these factors,⁴⁶¹⁴ but you can't control for everything. You can't know for certain if sleep deprivation leads to weight gain until you put it to the test.

If you have people pull an all-nighter, they get hungrier⁴⁶¹⁵ and choose larger portions.⁴⁶¹⁶ If you randomize people to shave off a couple of hours of sleep every night, they can start eating an average of 677 more calories a day compared to the normal-sleep control group.⁴⁶¹⁷ Although individual responses vary widely—anywhere from eating 813 fewer calories per day to as many as 1,437 more calories—on average,⁴⁶¹⁸ sleep deprivation tends to lead people to overeat by about 180–560 calories a day.⁴⁶¹⁹

Restrict people's sleep, and they also start craving healthier choices: more snacks⁴⁶²⁰ and more sugary and fatty foods.⁴⁶²¹ And if you stick people in a brain scanner after staying awake all night⁴⁶²² or after a few nights of four hours of sleep,⁴⁶²³ their reward pathways light up brighter in response to high-calorie foods. Sleep deprivation bumps up the levels of the chief endocannabinoid in the body, the natural chemical we synthesize that binds to the same receptors as an active ingredient in marijuana.⁴⁶²⁴ This may help explain the nighttime nibbling.

On the calories-out side of the equation, some short sleepers may take the extra time to exercise, while others will be so sleepy they exercise less.⁴⁶²⁵ The extra wakefulness may raise calorie expenditures up to about one hundred calories a day,⁴⁶²⁶ but if sleep-deprived individuals are overeating hundreds of calories, over time, sleep deprivation may end up putting the “wide” in wide awake.⁴⁶²⁷

Sleep Less, Gain More

With insufficient sleep inadvertently leading to such higher caloric intake, it's no surprise that four out of five studies involving as few as two to five nights of sleep restriction found an increase in body weight.⁴⁶²⁸ Even if you control caloric intake, though, you still lose more fat when you get more sleep.

In an NIH-funded study performed at the University of Chicago Sleep Research Laboratory, overweight subjects who normally got between six and a half to eight and a half hours of sleep a night were randomized to either eight and a half hours of sleep a night or five and a half hours on the same calorie-controlled diet. After two weeks, the groups switched and spent another two weeks on the opposite regimen. They spent a month living in the lab so their diets and sleep could be totally controlled and monitored. By just looking at the scale, sleep duration didn't seem to matter. During both two-week periods, the subjects ate the same number of calories and lost the same amount of weight, but most of the weight lost when getting eight and a half hours of sleep a night was fat, whereas most

of the weight lost when only getting five and a half hours was lean body mass. With the same diet but more sleep, they ended up losing more than twice as much body fat.⁴⁶²⁹

To get better insight into what was going on, researchers took fat and muscle biopsies from people after a night of sleep loss. In terms of the genes that were being turned on and off by the sleep deprivation, molecular signatures were discovered suggesting muscle breakdown and fat buildup.⁴⁶³⁰ That was after an all-nighter, though, and in the weight-loss study, the sleep-restricted groups ended up getting little more than five hours a night.⁴⁶³¹ What about a more realistic scenario?

Overweight adults were randomized to eight weeks of either a calorie-restricted diet or the same diet combined with five days a week of one less hour of sleep a night. The sleep-restricted group slept one less hour each night on weekdays and ended up sleeping one more on weekend days. So, overall, they just cut about three hours of sleep out of their week. Was that enough to result in any weight-loss difference? On the scale, no, but in the normal sleep group, 80 percent of the weight loss was fat, whereas in the group missing a few hours of sleep a week, it was the opposite with 80 percent of the loss being lean body mass.⁴⁶³² This shows that a few hours of “catch-up sleep” on the weekends is insufficient. Indeed, it may in fact be contributing to the problem based on the social jet lag effect I described in the Chronobiology section.

A comparable study was designed for kids, but the sleeping periods only lasted a week. Eight- to eleven-year-olds were randomized to either increase or decrease their time in bed by ninety minutes per night for a week and then switch the following week. On the days they slept less, they ate an average of 134 more calories and gained about a half pound compared to the sleep-more week.⁴⁶³³ The exciting question then becomes: Would sleeping more facilitate weight loss?

Sleep It Off

A benefit of interventional studies is that they can demonstrate cause and effect, but observational studies can more easily allow for the tracking of people and their behaviors over a longer time span. In one such study, researchers followed a group of mostly overweight individuals for six years. At the start of the study, the subjects averaged fewer than six hours of sleep a night. During the five years of the study, however, about half maintained that schedule, but the other half increased their sleep duration up to seven or eight hours a night and ended up gaining five fewer pounds of fat.⁴⁶³⁴ A study entitled “Sleeping Habits Predict the Magnitude of Fat Loss in Adults Exposed to Moderate Caloric Restriction” found that every extra hour of sleep at night was associated with an extra one and a half pounds of weight loss over a period of about three to six months.⁴⁶³⁵ That’s not the same as randomizing people to extra sleep, though. Maybe the subjects were sleeping more because they were exercising more, and that was the real reason they lost more weight. That’s why we need randomized controlled trials.

Getting people to bump up their sleep from about five and a half hours to seven can lead to an overall decrease in appetite within two weeks, particularly for sugary and salty foods.⁴⁶³⁶ A four-week study randomizing habitually short sleepers to sleep about an extra hour a night led them to consume about two fewer spoonfuls’ worth of sugar a day compared to the control group, but this didn’t translate into any changes in body composition.⁴⁶³⁷ A twelve-week study that randomized overweight and obese individuals to a weight-loss intervention with or without a sleep component, on the other hand, found that the sleep group lost weight significantly faster.⁴⁶³⁸

A six-month randomized trial to improve household routines for obesity prevention among young children resulted in a lower BMI.⁴⁶³⁹ A national cross-sectional survey had suggested lower obesity rates among kids in households where they regularly ate dinner together as a family, got adequate sleep, and limited screen times,⁴⁶⁴⁰ so Harvard

researchers decided to put those behaviors to the test. Normally, it's hard to tease out the effects of multicomponent interventions, but in this case, exhortations to limit overall TV watching didn't work, and the families were already eating together six days a week. The only component the researchers were able to get the kids to alter significantly was their sleep, so the improved weight outcomes may be attributed at least in part to the three-quarters of an hour average increase in nightly slumber.⁴⁶⁴¹

Overall, most sleep improvement interventions tend to show improved weight loss, giving a positive spin to the phrase *You snooze, you lose*.⁴⁶⁴² I was intrigued, though, to look up the one study in a published systematic review that failed to show a benefit. The nice thing about systematic reviews—unlike so-called narrative reviews—is that they exhaustively include mention of every study that meets some prespecified criteria. While this keeps reviewers from cherry-picking, it can also lead to the inclusion of some strange studies. Case in point: a randomized controlled trial of playing the didgeridoo, the indigenous Australian wind instrument. Those randomized to the didgeridoo to improve their sleep quality weren't reported as losing any weight, but they also failed to improve the quality of their sleep⁴⁶⁴³ (or, likely, their neighbors').

How to Get a Good Night's Sleep

In the Harvard Nurses' Health Study, women who got five or fewer hours of sleep a night gained about six more pounds over the subsequent sixteen years than those getting seven hours of sleep a night.⁴⁶⁴⁴ Even if that were due solely to the difference in sleep, that's still only six pounds for more than ten thousand additional hours of sleep. If even a tiny fraction of that time were spent on diet and exercise, such as biking to the nearest farm stand, more weight could have been lost in sixteen weeks than during those sixteen years. Every little bit helps, though, which is the theme of this entire Weight-Loss Boosters section, and getting at least seven hours of sleep is probably healthier anyway.⁴⁶⁴⁵

The biggest reason to lose sleep over losing sleep is motor vehicle accident risk.⁴⁶⁴⁶ Driving while drowsy increases your risk of killing yourself and others.⁴⁶⁴⁷ People might think twice about getting behind the wheel after staying awake for forty-eight hours straight, but even just two weeks of sleeping only six hours a night impairs our cognitive performance as much as pulling two all-nighters in a row.⁴⁶⁴⁸ So what's the best way to sleep better?

Sleeping pills are a nonstarter. People prescribed fewer than eighteen pills a year of hypnotics, the class of sleeping pills that includes Ambien, appear to have triple the hazard of dying prematurely.⁴⁶⁴⁹ Since up to 10 percent of the adult population is prescribed these drugs,⁴⁶⁵⁰ if those pills really are killing people, that could mean a six-figure death toll every year.⁴⁶⁵¹ Ambien's manufacturer questioned the study,⁴⁶⁵² but it was just one of two dozen studies that found a significant association between sleeping pills and premature death.⁴⁶⁵³ When the principal investigator at the Scripps Clinic Sleep Center was criticized for "reporting alarmingly high death risks from commonly used medications,"⁴⁶⁵⁴ he replied: "We cannot hide risks, even if they might frighten patients out of taking hypnotics. Patients have a right to know."⁴⁶⁵⁵

What's more, nonpharmacological methods have been found to work as well or even better than the drugs.⁴⁶⁵⁶ The recommended first-line treatment for insomnia is "cognitive behavioral therapy," which combines conditioning techniques to reassociate the bed with sleep and education surrounding optimal sleep hygiene.⁴⁶⁵⁷

Four Rules of Sleep Conditioning:⁴⁶⁵⁸

1. Go to bed only when you're sleepy.
2. Only use the bed for sleep (and sex). No reading, eating, or screen time.

3. If you can't fall asleep within fifteen to twenty minutes or so, get up, leave the bedroom, and don't go back until you're sleepy again. Repeat as necessary.
4. Get up at the same time every morning no matter how little sleep you have had.

Although avoiding napping is often added to the list, contrary to expectations, the majority of research does not show that daytime naps interfere with nighttime sleep.⁴⁶⁵⁹

Four Rules of Sleep Hygiene:⁴⁶⁶⁰

1. Exercise regularly.
2. Avoid caffeine, nicotine, and alcohol before bedtime.
3. Make the bedroom dark, cool, comfortable, and quiet.
4. Establish a relaxing bedtime routine.

The best time to exercise to improve sleep appears to be four to eight hours before bedtime,⁴⁶⁶¹ though it appears to be a myth that exercising right before bed is somehow disruptive to sleep.⁴⁶⁶²

Efforts to replicate the nearly quarter-century-old study I mentioned in the Fat Burners section [here](#) showing even morning coffee may impair sleep⁴⁶⁶³ have yet to be attempted.⁴⁶⁶⁴ However, it's clear that hefty caffeine doses up to six hours before bedtime interfere with sleep. Late-afternoon alcohol consumption (six hours before bedtime) may also impair sleep.⁴⁶⁶⁵ Additionally, nicotine, whether from gum, pill, patch, vape, or cigarette, may have negative sleep effects⁴⁶⁶⁶—though active nicotine withdrawal may as well.⁴⁶⁶⁷

Nocturnal noise can adversely impact sleep even if you're not consciously aware of it. Within a few days, you can become habituated to noises such that they no longer wake you up, but EEG studies and subjective sleep surveys show the quality of our sleep can still be affected.⁴⁶⁶⁸ Earplugs and sound masking, such as with a white noise machine, have been shown to help.⁴⁶⁶⁹ I was kicking myself after I ordered a white noise machine to try out only to then realize there are around a gazillion free white noise apps available for my phone.

Relaxation techniques, such as massage,⁴⁶⁷⁰ mindfulness meditation,⁴⁶⁷¹ and soothing music,⁴⁶⁷² may also help. So, too, may taking a relaxing hot bath or shower. One of the reasons late-night eating can delay sleep is that it may interfere with the drop in core body temperature that normally occurs around bedtime,⁴⁶⁷³ which is thought to be one of the cues that it's time for bed. So wouldn't that make a hot shower counterproductive? No. As soon as you step out of the bath, your rapid decline in skin temperature can accentuate the natural nighttime drop and improve sleep.⁴⁶⁷⁴ Even just a warm footbath may help you fall asleep about fifteen minutes faster.⁴⁶⁷⁵

Food-wise, low fiber intake and high saturated fat and sugar intakes are associated with lighter, less restorative sleep.⁴⁶⁷⁶ Meat intake is associated with napping, suggested to be a proxy for inadequate sleep.⁴⁶⁷⁷ This may help explain why insomnia has been reported as a side effect of ketogenic diets.⁴⁶⁷⁸ I talked about melatonin-rich foods and supplements in the Chronobiology section. Megadoses of vitamin D were found to improve sleep duration and quality in men and women aged twenty through fifty with sleeping disorders, though no associated weight loss was reported.⁴⁶⁷⁹

FOOD FOR THOUGHT

Aim for at least seven hours of regular sleep a night. Have trouble sleeping? Try the Four Rules of Sleep Conditioning and the Four Rules of Sleep Hygiene. *Sweet dreams!*

STRESS HORMONE RELIEF

Stressed Out, Calories In

According to national surveys conducted by the American Psychological Association, the majority of Americans report moderate to high levels of stress.⁴⁶⁸⁰ Though the prevalence of full-blown anxiety disorders hasn't changed much over the last few decades, the level of general psychological stress appears to be getting worse.⁴⁶⁸¹ After following thousands of people and their stress levels over time, there does seem to be a connection between stress and modest weight gain.⁴⁶⁸² In fact, the increased risk of diabetes in veterans with post-traumatic stress disorder (PTSD) may be explained by the link between PTSD and weight gain.⁴⁶⁸³ Effects on both sides of the calorie-balance equation have been used to explain the stress-obesity relationship.

For many who are stressed, structured exercise may be viewed as a disruptive inconvenience, just one more demand on their time, and indeed, the majority of observational studies have found that stress is associated with less physical activity.⁴⁶⁸⁴ Stress may also reduce the thermic effect of food and reduce how much fat is burned after a meal. In one study, those reporting a stressful event the day before testing burned about one hundred fewer calories in the six-hour period after eating compared to days not preceded by anything particularly stressful.⁴⁶⁸⁵

People who are stressed may eat more too. Though some people eat less when stressed, the majority not only eat more,⁴⁶⁸⁶ they tend to gravitate toward foods high in sugar, fat, and calories.⁴⁶⁸⁷ If you give people their own private snack buffet, those with high chronic stress levels eat less fruits and veggies and more chocolate cake.⁴⁶⁸⁸ We suspect it's cause and effect because you can demonstrate the acute effects of stress in a lab. Randomize people between solvable and unsolvable word puzzles, for example, and food choice shifts from a healthy snack (grapes) to a less healthy snack (M&M's) in the more stressful condition.⁴⁶⁸⁹ The stress of public-speaking challenges or being made to plunge and keep your hand in ice water has been found to dull your ability to sense sweetness, tempting you to eat more to achieve the same taste.⁴⁶⁹⁰ Even just watching a video with distressing scenes, including traffic problems, financial hardship, and sexual harassment, can evoke the same shift in eating behavior toward chocolate.⁴⁶⁹¹

They don't call it a comfort food for nothing. Overeating may be a sign that something is eating us.

Stress Belly

Under stress, we tend not only to eat more food but worse food, and we seem to deposit more fat in the worst place, in and around our abdominal organs. Cortisol, known as the *stress hormone*, may be the reason stress levels correlate with visceral obesity (deep belly fat).⁴⁶⁹² Cortisol has been alleged to be a potential "kingpin" in the obesity epidemic.⁴⁶⁹³

We are now at a time in human history where most of our stressors may be psychological rather than physical. These days, we're more likely to fight with our spouses than a saber-toothed tiger, but our bodies respond the same way—we produce cortisol.⁴⁶⁹⁴ Within seconds of a stressor, we get that fight-or-flight burst of adrenaline release, followed within minutes or hours with a rise in cortisol, which is secreted by our adrenal glands above our kidneys.⁴⁶⁹⁵ One effect of cortisol is to boost our appetites, which is adaptive if the stress is a physical threat, such as a predator or famine, but maladaptive if that stress is just trouble at work or financial insecurity—and particularly if the stressor is worrying about your weight!

If you covertly inject people with a drug that increases cortisol levels and then give them a basket of snacks, they eat about 140 more calories than if they had been injected with a placebo instead.⁴⁶⁹⁶ That's why cortisol-like drugs are sometimes given to cancer patients who are wasting away: Corticosteroids may stimulate their appetites,⁴⁶⁹⁷ explaining why

weight gain is a common side effect of these drugs.⁴⁶⁹⁸ Four days on the cortisol-like drug methylprednisolone (sold as Medrol, which is used in many autoimmune diseases) can boost daily intake nearly 60 percent, resulting in more than 1,000 extra calories consumed a day.⁴⁶⁹⁹ Cortisol has been implicated as a factor in motivating food intake even when we're not really hungry.⁴⁷⁰⁰

The weight gain caused by cortisol isn't uniform across the body, however. Fat cells deep in our bellies have a greater density of cortisol receptors,⁴⁷⁰¹ which activate the enzyme that stuffs our fat cells with fat.⁴⁷⁰² There's a disease called *Cushing's syndrome* that is characterized by an extreme excess of cortisol (for example, due to an adrenal gland tumor). The distribution of cortisol receptors of different regions of fat explains why abdominal obesity is a hallmark symptom of Cushing's, which can be resolved once cortisol levels are brought under control.⁴⁷⁰³ There's even been the suggestion that the accumulation of visceral fat is the body's way of sopping up excess cortisol to help buffer the effects of stress.⁴⁷⁰⁴

So are people with higher levels of cortisol in their bloodstreams more likely to gain weight and become obese? This has actually been a difficult research question to answer because there are such wide, day-to-day fluctuations in cortisol based on stress levels.⁴⁷⁰⁵ Even just getting stuck in traffic on the day of the blood test could throw things off. But a new, noninvasive method has been developed to measure long-term average cortisol levels, involving a snip of hair rather than a vial of blood. As our hair grows, it traps a snapshot of cortisol in our bloodstreams at the time. Each inch of hair on our heads represents about three months of cortisol levels, growing out like rings in a tree trunk.⁴⁷⁰⁶ With this new research tool, scientists have been able to show that high cortisol levels over time are indeed associated with measures of abdominal fat.⁴⁷⁰⁷ One study of thousands of children found that higher hair cortisol levels were linked to a whopping nine times the odds of obesity by age six.⁴⁷⁰⁸

Might the stress of dieting increase cortisol levels? Although total fasting can dramatically increase cortisol levels—as much as doubling them within five days⁴⁷⁰⁹—less severe caloric restriction does not.⁴⁷¹⁰ There is a way stress and obesity could turn into a vicious cycle, though: weight stigma.⁴⁷¹¹

It Can Weigh on You

Even after controlling for body size, those who report weight discrimination may end up with 33 percent higher chronic cortisol levels, meaning even at the same weight, those who experience stigma appear significantly more stressed.⁴⁷¹² That may account for some of the correlation between stress and obesity.⁴⁷¹³ The researchers suggest, "Chronic exposure to elevated levels of cortisol may play a role in generating a vicious circle of weight gain and discrimination."⁴⁷¹⁴

The weight of the stigma can be demonstrated experimentally. Researchers from Rutgers and UCLA set up an ethically questionable test. Women were invited to participate in a study allegedly designed to examine the "hormonal responses to shopping." The study subject entered a staging area along with a "thin female confederate" who posed as just another study participant but was actually in on the experiment. The slim conspirator was then congratulated on the great news that she qualified to participate in a group shopping activity for designer clothing and was escorted into a celebration. After returning to the staging area, the researcher told the real study subject one of two manipulations. In the control condition, she was told, "Unfortunately, the group shopping activity is full now, and since you were the last to sign up, we can't include you in the activity." However, those randomized to the stigma condition were instead told, "Unfortunately, your size and shape just aren't ideal for this style of clothing and we really do want everyone to have fun and feel good. Plus, we want to return the clothing to the designer in good condition." Ouch.

Irrespective of their actual weight, study subjects who perceived themselves to be heavy experienced a rise in cortisol within thirty minutes in the stigma compared to control condition.⁴⁷¹⁵

Even just observing weight stigma can be stressful. Compared to cortisol levels measured after watching an emotionally neutral video (like a clip about the invention of the radio), women watching a stigmatizing scene, such as an actress in a fat suit dancing seductively for a group of repulsed construction workers, experienced greater cortisol secretion.⁴⁷¹⁶ Does this then translate into increased calorie consumption? Yale researchers found that when normal-weight women are provided with bowls of M&M's, jelly beans, and chips to snack on after watching clips of stigmatizing material like clumsy, loud, lazy stereotypes getting teased about their weight, they eat about the same amount compared to watching neutral material such as insurance commercials. But when overweight women watch the same two sets of videos, they *triple* their caloric intakes after watching the stigmatizing scenes.⁴⁷¹⁷ A similar finding was reported for overweight youth, who were more likely to respond to being socially ostracized with overeating compared to normal-weight kids.⁴⁷¹⁸

You can dress up skinny people in fat suits and get the same result. The UCLA research team who had helped design the shopping study published a paper entitled "Putting on Weight Stigma" in which slim men and women were randomized to appear obese by wearing a fat suit. Just walking around in public for a few minutes while wearing a fat suit led to hurt feelings of rejection, anger, anxiety, and sadness.⁴⁷¹⁹ Immediately afterward, those in fat suits went on to consume nearly two hundred more calories of chips, chocolate, and soda—and that all occurred even without the internalized stigma, self-blame, and shame that too often plague the truly obese.⁴⁷²⁰ Ironically, this experience of "walking a mile in their shoes" appeared to have zero effect on the skinny study subjects' own anti-fat attitudes.

No one should ever be discriminated against unfairly, but given the current reality, the most effective way to lose the weight stigma may be to lose the weight. That's what this entire book is about, but what are some of the best ways to deal with stress, whether from stigma or otherwise?

Sweat It Out?

Exercise can have a powerful stress-buffering effect. People who regularly exercise report significantly lower stress levels, and when put to the test, randomized controlled trials have shown that acute bouts of exercise are effective in reducing self-reported stress levels and improving quality of life. Physically active individuals have lower cortisol levels and a healthier cortisol response to stressors.⁴⁷²¹

One of the most popular experimental methods to induce psychological stress is the Montreal Imaging Stress Task protocol. It involves timed arithmetic challenges with failure built in by manipulating the difficulty and time limits to be just beyond the individual's mental capacity.⁴⁷²² When you put a group of sedentary individuals through the test, their cortisol spikes higher than aerobically fit subjects, but have them walk on a treadmill for thirty minutes before the test, and their cortisol responses drop right down.⁴⁷²³

Is the drop in cortisol from even just a single exercise session enough to blunt stress-induced eating? To find out, researchers put people through a mental challenge stressful enough to increase post-test pizza consumption by an additional hundred calories. If you first have them do fifteen minutes of high-intensity interval training, though, they end up eating less than they would have without doing the mental challenge. Combined with the calories burned by the exercise, they ended up with about one hundred fewer calories than they would have had they just sat down to the pizza alone.⁴⁷²⁴ So exercising to relieve stress can help control weight from both sides of the calorie equation.

Laugh It Off?

Exercising your funny bone doesn't appear to do much on paper. Genuine voiced laughter only causes about a 10–20 percent increase in calorie expenditure above resting metabolic rate, which is not much more than such activities as light clerical work, writing, or playing cards. Ten to fifteen minutes of laughter a day may only burn about an extra ten to forty calories, depending on body weight and laughter intensity,⁴⁷²⁵ but laughter can have an oversized effect on lowering stress.

The very evolution of laughter is thought to have been as an antidote to stress, the release of nervous energy.⁴⁷²⁶ Within sixty minutes of people watching a comedy video (complete with “Gallagher’s classical Sledge-O-Matic finale”), cortisol levels in their bloodstreams were cut by more than half.⁴⁷²⁷ This has been offered as an explanation as to why mirthful laughter has been shown to improve immune function.⁴⁷²⁸ Cortisol acts as an immunosuppressant, which is why cortisol-like steroids such as prednisone are used for inflammatory autoimmune diseases. This may explain why those laughing heartily at a humorous video had improvements in natural killer cell function—critical for anticancer and antiviral immunity—compared to those randomized to a control group watching tourism videos.⁴⁷²⁹ (Replicating the results these days may be difficult given the original researchers’ choice of comedic stimulus: Bill Cosby.)

Under the assumption that our bodies can't tell the difference between real and fake laughter, “laughter yoga” was developed⁴⁷³⁰ in which participants force themselves to laugh as a form of exercise “akin to internal jogging.”⁴⁷³¹ Drops in cortisol levels have been noted when it has been put to the test, but would spontaneous laughter be better? ⁴⁷³² Researchers in Japan decided to find out. They compared the cortisol changes in people randomized either to simulated laughter in a laughter yoga session, genuine laughter watching a funny video, or no laughter in a control group given some dry reading instead. Both laughter groups actively reduced cortisol levels within half an hour compared to the reading group, but the comedy group beat out the laughter yoga.⁴⁷³³ Maybe our bodies can tell if we're faking it after all.

Strike a Pose?

What about regular yoga? Practiced by as many as twenty million Americans every year,⁴⁷³⁴ yoga in the United States is comprised mainly of body postures, breathing exercises, and meditation.⁴⁷³⁵ A meta-analysis of randomized controlled trials found that yoga interventions can lower cortisol levels, but does this translate into weight loss? ⁴⁷³⁶ A cross-sectional study found that practicing yoga for four or more years was associated with less weight gain over time, but yoga practitioners also tended to exercise twice as much in general and eat more healthful diets (for example, 45 percent higher consumption of fruits and vegetables).⁴⁷³⁷ This may all be related, though. Yoga practitioners often claim they feel “more connected” to their bodies, which may translate into healthier choices.⁴⁷³⁸ However, you can't tell what role yoga itself plays until it's put to the test.

There are randomized controlled yoga trials showing weight loss, but they're often in comparison to control groups who did nothing. Indeed, compared to no changes in physical activity, doing about thirty hours of yoga has been shown to lead to about five pounds of weight loss and an inch off the waist.^{4739,4740} But are there some supplemental benefits to yoga beyond just the three or so calories burned per minute⁴⁷⁴¹ due to the physical exertion alone? Researchers decided to find out.

Yoga was compared head-to-head to resistance exercise and walking for weight loss. Doing thirty-six hours of resistance training with rubber exercise bands, weights, and balance balls led to a 1 percent drop in body fat compared to the sedentary control group. Doing the same amount of yoga led to the same 1 percent drop.⁴⁷⁴² In the walking study,

fulfilling my Daily Dozen recommendation to walk at least a total of ninety minutes a day on a plant-based diet also led to similar amounts of weight loss compared to swapping in the same amount of yoga—about five pounds and an inch off the waist in fifteen days.⁴⁷⁴³ The walking group were told to walk at their own pace, which ended up being more of a leisurely stroll, but that matched the metabolic cost of most yoga, which is classified by American College of Sports Medicine criteria as a light-intensity physical activity.⁴⁷⁴⁴

What about Bikram—or hot—yoga, practiced at a humid 100°F and purported to burn a thousand calories a session? That’s a bit of a stretch. (*Ahem.*) When put to the test, calorie expenditure during hot yoga was no more fat-burning than room-temperature yoga.⁴⁷⁴⁵ Overall, yoga doesn’t appear to have any special weight-reducing benefits,⁴⁷⁴⁶ but the best form of exercise is the one you’ll actually do, so if you enjoy it, go for it. *Namaste.*

Rub It In?

Yoga can be thought of as self-massaging our internal organs, but what about getting a regular massage as a stress-management technique for weight loss? In both term and preterm infants, massage leads to weight *gain*,⁴⁷⁴⁷ which is great for babies, but not necessarily for adults. Repeated massage-like stroking “on the ventral side” of rats (that is, giving them belly rubs) also increases weight gain,⁴⁷⁴⁸ but what about human adults? No effect. Getting weeks⁴⁷⁴⁹ or months⁴⁷⁵⁰ of massages appears to have no effect on body weight or waist circumference.

Turn It Up?

What about music to soothe the savage beast of stress? We’ve been playing music since at least the Paleolithic era forty thousand years ago,⁴⁷⁵¹ and music as therapy has been documented at least since biblical times (1 Samuel 16:23). The first music therapy experiment I could find was published in *The Journal of the American Medical Association* in 1914. Explaining why a phonograph was placed in the operating room as his patients lay fully conscious and awake during surgery, the surgeon said it was “a means of calming and distracting my patients from the horror of the situation.”⁴⁷⁵²

Now that we have good general anesthesia, music is used to calm nerves *before* surgery. Normally, we use Valium-type drugs like midazolam (sold as Versed), but they can have a variety of side effects, including, ironically, sometimes making people even more agitated.⁴⁷⁵³ A study from Sweden sought to determine if relaxing music has a greater anxiety-reducing effect than a standard dose of midazolam. Researchers whipped out some Kenny G, and the music indeed worked significantly better than the drug. Those listening to soft jazz, relaxing pop, classical, new age, and nature sounds all had lower anxiety scores, heart rates, and blood pressures. This was heralded as the first time any antianxiety therapy worked not only as well as but even better than Valium-type drugs, and it didn’t leave patients with the typical “post-operative hangover.” The researchers noted that the “difference in side effects of relaxing music and midazolam is obvious.”⁴⁷⁵⁴

Listening to music while eating does not seem to affect intake,⁴⁷⁵⁵ and though I couldn’t find any studies putting music to the test for weight loss, more than a dozen studies have found that listening to recorded music can reduce cortisol levels.⁴⁷⁵⁶ Not all music, though. Subjectively, Mozart has been found to lead to a greater self-reported reduction in tension than grunge rock (Pearl Jam).⁴⁷⁵⁷ When cortisol lowering was measured, Beethoven beat out techno (Techno Magnetiko’s *Cyber Trip Techno Shock*), but that may just be a function of the tempo.⁴⁷⁵⁸ People get the same bump in breathing and blood pressure listening to fast classical music, such as Vivaldi’s “Summer Presto,” which was as stimulating or even more so, researchers found, than the Red Hot Chili Peppers (the band, not the plants).⁴⁷⁵⁹

What about heavy metal? Kennelled dogs were provided with various Spotify options for audio enrichment.⁴⁷⁶⁰ Soft rock and reggae appeared to reduce stress, but the “loud and

sudden nature of heavy metal may be unsuitable for dogs” as well as the “general experience of shelter employees and potential adopters.”⁴⁷⁶¹ (Maybe they should have played Ozzy’s “Bark at the Moon.”) When people were randomly assigned to self-selected music, classical, heavy metal, or silence, the self-selected and classical music produced increased feelings of relaxation, as did sitting in silence, but heavy metal had the opposite effect.⁴⁷⁶²

Compared to relaxing and pleasant Renaissance music, exposure to “arousing and unpleasant” heavy metal caused a heightened amylase response in men.⁴⁷⁶³ Amylase is an enzyme in our saliva that digests starch into simple sugars. When we go into fight-or-flight mode, we immediately start churning out the enzyme to provide blood sugar for quick energy, so you get a spike when you go skydiving,⁴⁷⁶⁴ if someone dunks you in near-freezing water,⁴⁷⁶⁵ or, apparently, if you just listen to heavy metal for ten minutes.⁴⁷⁶⁶ With all that extra enzyme, if you’re eating bread while banging your head, you may end up digesting it faster.

Change Your Mind?

Mindfulness-based stress reduction involves cultivating a nonjudgmental, accepting, moment-by-moment awareness.⁴⁷⁶⁷ In the context of food, mindful eating is the practice of being fully present for a meal. This may involve slowing down the pace, savoring every bite, and getting in tune with your body’s fullness cues.⁴⁷⁶⁸ When we’re distracted, we tend to eat faster and for longer. For example, men and women randomized to eat while watching TV averaged an extra slice of pizza or 71 percent more mac ‘n cheese, totaling nearly three hundred additional calories.⁴⁷⁶⁹ This may help explain why one survey found overweight individuals reported they ate almost half their meals while watching television.⁴⁷⁷⁰ Researchers at the Stanford Prevention Research Center found that on the weekends, about a quarter of a child’s calories may be consumed in front of the TV.⁴⁷⁷¹

Even just being distracted listening to something can have an impact. Study subjects told to eat while giving their full attention to a radio conversation⁴⁷⁷² or a detective story recorded on cassette tapes (old-school podcast!) ended up eating significantly more, for instance up to 77 percent more ice cream compared to undistracted eating.⁴⁷⁷³ Even just engaging in conversation while eating with friends can inadvertently boost intake.⁴⁷⁷⁴

Distracted eating may also affect subsequent consumption. Have people play computer solitaire while eating a fixed-calorie meal, and they eat nearly twice as many cookies a half hour later, as if they hadn’t fully consciously registered how much they ate while they were distracted by the game.⁴⁷⁷⁵ Conversely, if you have people listen to an audio clip encouraging them to eat mindfully and focus on the look, smell, taste, and texture of the food, they eat fewer cookies hours later than those who had either eaten in silence⁴⁷⁷⁶ or while listening to neutral audiobook content.⁴⁷⁷⁷ Another way mindful eating may help prevent overeating is by sharpening the memory of each meal. Those who could more reliably recall an experimental lunch have been shown to average lower afternoon snack intake.⁴⁷⁷⁸ Most but not all such studies found focused attention during a meal decreased later food intake, at least in a research lab setting.⁴⁷⁷⁹

How to Deal with Cravings

Attending to the sensory qualities of food and our bodies’ reactions is just one aspect of mindful eating. Mindfulness has been described as a “moment-to-moment awareness, cultivated by paying attention in a specific way, in the present moment, as non-reactively, nonjudgmentally, and openheartedly as possible.”⁴⁷⁸⁰ Just being aware may not be enough, though. Practicing mindfulness is said to involve three steps: awareness, acceptance, and then something called *cognitive defusion*.

When we are struck with a craving, a typical reaction is *cognitive restructuring*, a psychological term for challenging our thoughts and replacing them with alternative ones.⁴⁷⁸¹ For example, if we’re hit with a pang for chocolate, instead of reaching for a candy bar, a restructuring response might be: *No, I don’t need chocolate. I can*

have something healthier instead. Unfortunately, this rarely works. More than one hundred self-identified chocolate cravers were randomized to an hour of cognitive restructuring instruction and then given a bag of chocolates to carry around with them for a week to see how well they could resist the temptation. Despite the hour-long instruction at the start of the week, they didn't do much better than the control group who tried the same exercise but without any instruction at all.

The mindful eating approach, on the other hand, involved cognitive defusion. People are taught to defuse their thoughts as "merely thoughts" and place mental distance between themselves and their thoughts. A defusion response to the thought of needing chocolate would involve simply observing the thought (*I notice I'm having the thought that I need to eat some chocolate*) and thanking one's mind for the thought (*Thanks, mind*).⁴⁷⁸² A "mindbus" metaphor is used, in which people are taught to imagine themselves as the driver of a bus and their thoughts as mere passengers.⁴⁷⁸³ You visualize yourself taking control as you stop the bus and let off the negative passengers. *Thanks for the feedback, folks, but this is my bus.*

Cognitive defusion was tested head-to-head against cognitive restructuring in the same chocolate experiment, and those who had gotten an hour of defusion instruction had three times greater odds of remaining "chocolate abstinent" in the face of a week of constant temptation.⁴⁷⁸⁴ Defusion was then pitted against acceptance: Instructing people to observe a thought or feeling, accept its presence, and build up a degree of tolerance for uncomfortable feelings. Study subjects were randomized to less than a half hour of coaching on either defusion or acceptance, or to a control group who spent the time learning a muscle-relaxation technique. They were then asked to carry a bag of chocolate candy with them for five days—untouched. The acceptance group failed to beat out the control group, but the defusion group did.⁴⁷⁸⁵ Of all the mindfulness skills, cognitive defusion, also known as *disidentification*, appears to be the most effective.

Putting Your Mind at Rest

Mindfulness is a major part of the billion-dollar meditation industry,⁴⁷⁸⁶ with as many as one in five Fortune 500 companies implementing some kind of workplace mindfulness program.⁴⁷⁸⁷ It has been rebranded from "hippy dippy nonsense" to portrayals such as "brain training" said to "sell it better."⁴⁷⁸⁸ These reductionist, commodified forms have been derided as "McMindfulness,"⁴⁷⁸⁹ but who cares what they call it if it works? But does it?

Research into mindfulness has been complicated by the fact that the term can mean anything from informal practices, such as conscious awareness while eating, to structured meditation programs involving designating set times to sit in a specific posture attending to your breathing, for instance.⁴⁷⁹⁰ This has made an understanding of the efficacy hard to capture. It can't hurt, though, right? Well ...

There have been more than twenty observational studies or case reports documenting instances of adverse effects, such as meditation-induced psychosis, mania, anxiety, and panic.⁴⁷⁹¹ One study at an intensive meditation retreat assessed participants' negative experiences since they had begun meditation. They found that seventeen of twenty-seven participants—more than 60 percent—reported at least one adverse effect, including an individual who was hospitalized for a psychotic break.⁴⁷⁹² Even outside of an immersive retreat environment, as many as 12 percent of meditators recall negative side effects within ten days of initiating the practice.⁴⁷⁹³

It's considered plausible that adverse effects occur at rates approximating that of psychotherapy,⁴⁷⁹⁴ with about one in twenty patients reporting lasting negative effects of psychological treatment.⁴⁷⁹⁵ With about twenty-five million Americans practicing meditation⁴⁷⁹⁶ and as many as a million new meditators a year,⁴⁷⁹⁷ even a 5 percent adverse-event rate could mean hundreds of thousands of negative side effects a year. As with any medical intervention, though, it's all about risks versus benefits. Unfortunately, many of the benefits have been overstated.⁴⁷⁹⁸

A commentary in a psychiatry journal entitled "Has the Science of Mindfulness Lost Its Mind?" notes that even the books on mindfulness written by scientists are "bursting with magical promises of peace, happiness and well-being."⁴⁷⁹⁹ Contrary to the popular perception, however, the evidence for even the most well-founded benefits is not entirely conclusive.⁴⁸⁰⁰ This is not an issue unique to meditation. There is a "replication crisis" across the entire field of experimental psychology,⁴⁸⁰¹ where many of the landmark findings in the social sciences published in even the most prestigious journals don't appear to be reproducible.⁴⁸⁰²

Drug companies aren't the only ones to suppress the publication of studies that don't come out the way they wanted. The majority of mindfulness-based trials apparently never see the light of day, raising the specter of a similar publication bias.⁴⁸⁰³ Presumably, if the studies showed promising results, they would have been released rather than shelved. What's more, many of the ones that do make it into the scientific record are underwhelming. The federal Agency for Healthcare Research and Quality published a systematic review of the available data and concluded that mindfulness meditation worked best for improving anxiety, depression, and pain, but even then, the quality of evidence was only "moderate."⁴⁸⁰⁴ What about weight loss?

Mindfulness-based modalities can help with stress management⁴⁸⁰⁵ and self-control,⁴⁸⁰⁶ and can decrease impulsive,⁴⁸⁰⁷ binge, and emotional eating, all of which might facilitate weight management.⁴⁸⁰⁸ However, the first review of the available evidence published five years ago failed to find evidence of significant or consistent weight loss.⁴⁸⁰⁹ Part of the problem is compliance.

Like any other diet or lifestyle intervention, mindfulness only works if you do it.

For instance, women were randomized to attend four two-hour workshops that taught mindfulness techniques such as cognitive defusion. After six months, they lost no more weight on average than the control group. However, if those who reported "never" applying the workshop principles at all were excluded and only those who used the techniques at least some of the time were considered, their weight loss *did* beat out the control group by about five pounds.⁴⁸¹⁰

Other studies showed a lack of weight gain rather than loss. For example, one study found that obese subjects in the control group continued to gain weight at about a pound a month, whereas the weight of those in the mindfulness intervention group remained stable.⁴⁸¹¹

Putting all the studies together, the latest and largest review published in 2018 did find that mindfulness-based interventions can lead to weight loss compared to doing nothing, an average of about seven pounds over four months or so.⁴⁸¹² Pitted head-to-head, however, they didn't beat out other lifestyle-change interventions, but the nice thing about stress management and mindfulness is they can be practiced on top of whatever else you're doing.

Get Planted

A single high-fat meal can exacerbate the effects of stress. People randomized to eat a sausage-and-egg McMuffin with hash browns experienced a heightened cardiovascular reactivity to both psychological stress (public speaking) and bodily stress (submerging their hand in ice water for minutes) two hours later. How do we know it wasn't just the carbs in the english muffin and hash browns? Because the control meal was a sugary mess of Frosted Flakes and Froot Loops, and those randomized to the breakfast candy reacted significantly better to the stressors than those in the high-fat group. The McMuffin meal also had more than ten times the cholesterol, thanks to the egg, and the researchers suggest this may also have contributed to the effect.⁴⁸¹³ Population studies show that higher dietary cholesterol is associated significantly with increased risk of impaired cognitive function and memory, effectively mimicking accelerated brain aging. The effect of eating an additional 80 mg of cholesterol a day—which is less than half an egg⁴⁸¹⁴—was similar to the effect of being approximately three years older, appearing to effectively accelerate brain aging.⁴⁸¹⁵

Though effectively all dietary cholesterol comes from animal foods, saturated fat is not exclusive to the animal kingdom. Remember the packs-a-punch study from the Anti-Inflammatory section showing just a few days of a breakfast high in saturated fat can cause learning and memory problems? The researchers used palm oil, so it's not just animal fats.

Tropical oils, including palm and coconut oils, are highly saturated, too, though the vast majority of saturated fat in the American diet continues to come from meat and dairy. Every single one of the top fifteen sources of saturated fat is meat, dairy, or junk.⁴⁸¹⁶ What would happen if we instead centered our diets around whole, healthy, plant foods?

In a study published in *Nutritional Neuroscience* entitled “Vegans Report Less Stress and Anxiety Than Omnivores,” those eating completely plant-based do seem to be significantly less stressed, but it may not necessarily be their diets. The researchers suggest it’s because they’re eating less pro-inflammatory animal fats, but those eating more plant-based also tended to exercise more, spend more time outdoors, and practice more yoga. The omnivores also reported dieting more often, which alone can be stressful.⁴⁸¹⁷

Even if it is the diet, it could be the anti-inflammatory compounds in fruits and vegetables rather than the “cascade of neuroinflammation” (brain inflammation) potentially caused by the arachidonic acid⁴⁸¹⁸ (an inflammatory omega-6 fat) concentrated in chicken and eggs⁴⁸¹⁹ or the saturated fat in red meat and dairy.⁴⁸²⁰ It could also be because of all the beneficial prebiotics in whole grains and beans. Researchers performed a fecal transplant between stress-prone mice and normal mice by feeding them each other’s stool, and the normal mice started exhibiting anxiety and the stressed mice relaxed.⁴⁸²¹ You don’t know for sure until you put it to the test—in people. No studies as of yet trading poop with the Dalai Lama, but there have been interventional trials using plant-based diets.

Five hundred men and women suffering from anxiety and depression were placed on a whole food, plant-based diet and lifestyle program. Most dropped out within the first two weeks because they felt the program was “too rigorous” for them. However, the majority of those who stuck with the program experienced substantial improvements in mood and a “large improvement or full remission” of anxiety symptoms. Most who had been suffering from fatigue and pain got better and, over the twelve-week study period, lost an average of six pounds. What was most remarkable is that three months after the study ended, they were down a total of fifteen pounds, suggesting they stuck with it on their own. Exercise and twenty minutes of relaxation a day were also prescribed with the whole food, plant-based diet, though, so it’s impossible to isolate out the effects of what they ate.⁴⁸²²

There are randomized controlled trials of plant-based diets that have resulted in significant improvements in anxiety, fatigue, depression, and emotional well-being utilizing dietary changes alone,⁴⁸²³ but is that directly because of the diet or indirectly due to the augmented weight loss? Even placed on similar caloric intakes, plant-based diets can result in superior weight loss, with significant reductions in all compartments of body fat.⁴⁸²⁴ Maybe that’s why the subjects reported a greater improvement in quality of life compared to the control group.⁴⁸²⁵ The reason we suspect the causal link may be direct is that if you randomize people to remove all meat and eggs from their diets, you can get a significant drop in stress levels within just two weeks, compared to those who kept eating fish or a third group who continued to include all animal foods. So even before significant weight loss could occur, the researchers suggest “individuals who eliminate meat, fish, and poultry may cope better with mental stress.”⁴⁸²⁶

The Meat of the Matter

A single meal high in animal protein can nearly double the level of the stress hormone cortisol in the blood within a half hour of consumption, more than twice that of a meal closer to the recommended level of protein.⁴⁸²⁷ Give someone a meal of crabmeat, tuna, and cottage cheese, and the level of cortisol in their saliva shoots up within the hour. Instead, give someone some barley soup and a vegetable stir-fry, and cortisol levels drop *down* after the meal.⁴⁸²⁸ Imagine eating meat or dairy meal after meal, day after day. The concern is you might “chronically stimulate” your adrenal glands.⁴⁸²⁹ We don’t always have

control over the stress in our lives, but at least we can make some dietary tweaks to help keep cortisol under control.

Chronic high cortisol levels don't just increase obesity risk. Blood cortisol strongly predicts cardiovascular death in men and women—even among those without any known preexisting cardiovascular disease.⁴⁸³⁰ This may help explain “death from a broken heart,” the heightened heart attack and stroke risk in the weeks immediately following the loss of a spouse.⁴⁸³¹ The higher cortisol levels days, months, or even years after losing someone you love may increase cardiac risk and reduce immune function. Remarkably, the rise in stress hormone levels after losing a spouse⁴⁸³² is less than the bump you may get eating a high-meat diet.⁴⁸³³

If you feed men a high-protein diet packed with fish, poultry, other meat, and egg whites, and then switch them to a lower-protein diet centered around bread, fruits, and vegetables, their cortisol levels drop about a quarter within ten days.⁴⁸³⁴ Interestingly, at the same time, their testosterone levels shoot up by about the same amount. Contrary to the “flagrant misuse of scientific information” in *Men's Health* magazine,⁴⁸³⁵ high-protein diets suppress testosterone.⁴⁸³⁶ That's why if men eating plant-based diets begin eating meat every day, their testosterone levels go down,⁴⁸³⁷ which, over time, might itself contribute to the accumulation of belly fat.⁴⁸³⁸

Controlling Cortisol from Birth

The spikes in cortisol levels that occur each time we eat a meaty meal⁴⁸³⁹ may not just affect our health but that of our children. Substantial evidence now suggests that high-protein diets during pregnancy have adverse effects on the fetus.⁴⁸⁴⁰ Take, for example, the infamous Harlem Trial of 1976. Poor black pregnant women were randomized into one of three groups, either getting forty grams of added animal protein a day, an additional six grams, or none. The added-protein groups suffered an excess of very early premature births, with infant death rates doubling in the six-gram group and quadrupling in the forty-gram group. The babies who survived suffered “significant growth retardation.”⁴⁸⁴¹

In a similar experiment in Scotland, pregnant women were told to eat a high-meat diet in hopes of preventing a disease of pregnancy known as *preeclampsia*.⁴⁸⁴² It didn't work. In fact, the lowest preeclampsia rates I've ever come across were among women eating completely plant-based diets: only 1 case out of 775 pregnancies.⁴⁸⁴³ Preeclampsia normally strikes about 1 in 20,⁴⁸⁴⁴ so a plant-based diet might “alleviate most, if not all, of the signs and symptoms of this potentially serious condition.”⁴⁸⁴⁵

What happened when the Scottish women went from eating about one daily portion of meat to around two a day? The mothers who ate more meat during pregnancy gave birth to children who grew up to have higher blood pressures.⁴⁸⁴⁶ One explanation for the adverse effects of high meat consumption, including fish, is that this may have increased maternal cortisol concentrations, which in turn affected the developing fetus, resetting their stress hormone “thermostat” to a higher level. Indeed, researchers found higher blood cortisol levels in both the sons and daughters of women who had reported higher consumption of meat, including fish—about a 5 percent increase for every daily serving.⁴⁸⁴⁷ This may help explain why animal protein intake during pregnancy has been associated with children becoming overweight later in life.⁴⁸⁴⁸

You Are What Your Mother Ate

Whereas babies of meat-free mothers have lower cortisol levels,⁴⁸⁴⁹ higher-meat diets are considered to present a “metabolic stress” to the mother, effectively reprogramming the adrenal glands of their children, leading to lifelong elevations of stress hormones in their blood.⁴⁸⁵⁰ Every daily portion of meat consumed during late pregnancy was linked to about a 1 percent greater fat mass in their children by the time they reached adolescence.⁴⁸⁵¹

The adult children of mothers who ate more meat during pregnancy don't just walk around with higher baseline stress hormone levels but also appear to react more negatively to whatever life throws at them. Researchers tracked down the now grown-up kids whose mothers had been part of the double-the-meat experiment and measured their cortisol levels after a stressful public-speaking challenge. If their moms had eaten fewer than two daily servings of meat (fish included) while carrying them, they got relatively small surges of stress hormones from their adrenal glands. The cortisol levels in those whose moms had eaten fourteen to sixteen servings a week rose 30 percent higher, and those whose moms had eaten the most meat—seventeen or more servings a week—had their cortisol levels jump more than 50 percent higher in response to the same imposed stress.⁴⁸⁵²

It's no surprise then that animal-protein intake during pregnancy may lead to greater weight gain for her children later in life,⁴⁸⁵³ but remarkably, it may even impact her grandchildren. Recent evidence suggests that the long-term adverse consequences may not be limited to one generation, potentially affecting the ovaries and future eggs of her unborn daughter. "Ultimately," one review concluded, "these findings will shed light on the transmission of diabetes, obesity, and cardiovascular disease that are rapidly expanding in Western countries."⁴⁸⁵⁴

FOOD FOR THOUGHT

The best way to relieve the effects of stress is to relieve the stress itself. To the extent possible, we should try to reorient our lives to avoid major stressors and use exercise to work off what's unavoidable. This can include yoga, walking, or resistance band stretches. Mindfulness techniques can be used to reduce stress and deal with cravings. To buffer the release of the stress hormone cortisol, we can reduce our intake of saturated fats and animal protein, and pile on the plants.

WALL OFF YOUR CALORIES

Liquid Candy Crush

In the Eating Rate booster section, I discussed the classic jelly bean-versus-soda study that showed our bodies may not register calories in liquid form as well as they do calories from solid foods. If you're given an extra one hundred calories, your body tries to take that into account, adjusting your appetite over the remainder of the day so you stay in relative calorie balance. This response isn't perfect, though; your body isn't able to completely compensate calorie for calorie. In studies where this has been measured, those given an extra one hundred calories of food end up eating an average of only sixty-four fewer calories later on, not the full hundred. But if you *drink* those hundred extra calories, your body hardly seems to notice, only downregulating your subsequent appetite by about nine calories.⁴⁸⁵⁵ So by the end of the day, you may be left with a ninety-one-calorie surplus. Our brains just don't seem wired to recognize liquid calories. After all, for millions of years, the only thing on tap was water.

This may help explain why sugary drinks have been blamed as perhaps the single largest driver of the obesity epidemic,⁴⁸⁵⁶ accounting for at least one-fifth of the weight gained between 1977 and 2007 in the United States.⁴⁸⁵⁷ By the year 2000, Americans were drinking an estimated 190 calories a day of sweetened beverages.⁴⁸⁵⁸

It would be bad enough to eat 190 empty calories' worth of candy a day, but it may be even worse to drink it.

It's been estimated that just removing soda and other sugary drinks from the SNAP program (formerly known as *Food Stamps*) would prevent hundreds of thousands of cases of obesity.⁴⁸⁵⁹ Through the program, the soda industry is snatching up billions of taxpayer

dollars every year.⁴⁸⁶⁰ The USDA has denied state requests for excluding soda from SNAP, arguing, “No clear standards exist for defining foods as good or bad, or healthy or not healthy.”⁴⁸⁶¹ The fact that the federal government can’t even agree that sugar water is unhealthy explains a lot about the sad state of the U.S. Dietary Guidelines.

Industries argue that removing soda subsidies would disproportionately hurt the poor, like tobacco taxes. Of course, the public health community sees ending the subsidies as disproportionately *helping* the poor, but it might be more consistent to restrict the use of federal dollars across the board, such as at cafeterias in federal buildings and military bases, for example.⁴⁸⁶² When those actually affected by the policy were asked (*what a concept!*), the majority of SNAP participants surveyed *supported* removing sugary drinks, especially if it led to additional benefits for healthful foods like fruits and vegetables.⁴⁸⁶³

Obesity, like lung cancer, is not an equal-opportunity killer. Those living in poverty are significantly more likely to become obese.⁴⁸⁶⁴ Predatory industries such as fast food,⁴⁸⁶⁵ alcohol,⁴⁸⁶⁶ and tobacco have long targeted low-income neighborhoods and communities of color.⁴⁸⁶⁷ The soda industry appears to be no exception.⁴⁸⁶⁸ As one tobacco industry executive was recorded saying, “We don’t smoke that s***. We just sell it. We just reserve the right to smoke for the young, the poor, the black and the stupid.”⁴⁸⁶⁹

Wining and Dining

Speaking of liquid calories, what about wine? Alcohol and obesity may be a dangerous mix. Up to nine out of ten obese individuals already have nonalcoholic fatty liver disease,⁴⁸⁷⁰ and by age fifty, two-thirds end up with advanced liver scarring from the resultant chronic inflammation.⁴⁸⁷¹ No wonder medical journal editorials have referred to obesity and alcohol consumption as “the double peril.”⁴⁸⁷² Given the dual threat, those who drink alcohol are cautioned to “take care to not become overweight.”⁴⁸⁷³ Might drinking alcohol undermine that goal on its own?

Population studies suggest the term *beer belly* is apropos, with drinking about a pint or more of beer a day associated with abdominal obesity. In some populations, drinking beer is associated with more sedentary lifestyles and poorer dietary choices,⁴⁸⁷⁴ though, so it’s hard to tease out cause and effect until you put it to the test.

Six interventional studies comparing regular beer head-to-head with nonalcoholic beer found more average weight gain on the alcoholic beer. Since the body has no capacity to store alcohol, it may temporarily switch from burning fat to burning alcohol to help clear it out of the system, leaving a small excess fat balance.⁴⁸⁷⁵ However, no such difference was found in a study comparing consumption of wine to grape juice.⁴⁸⁷⁶

Thinking an aperitif might help patients with advanced cancer slow weight loss, researchers randomized subjects to a glass of wine a day, but it didn’t appear to make a difference. One study on wine and appetite showed a significant bump in caloric intake, but not for the reason the researchers were expecting.⁴⁸⁷⁷ When study participants were randomized to drink wine, beer, or soda with a meal, they ended up consuming more calories with the wine—but not because they ate more food. It was because they drank more wine. A quarter of the subjects drank the entire bottle, the “maximum allowed for ethical reasons.”⁴⁸⁷⁸

What about weight gain over time? When people who don’t normally imbibe were randomized to drink a glass of red wine, white wine, or sparkling water with dinner for two years, they ended up with no significant differences in body fat among the three groups.⁴⁸⁷⁹ What about all the other long-term randomized studies on wine and weight? There aren’t any, so the best available balance of evidence suggests a single daily glass of wine, 150 ml or about two-thirds of a cup, does not appear to affect body weight. Although from a health standpoint “the safest level of drinking is none,”⁴⁸⁸⁰ inordinate weight gain may not be one of wine’s adverse effects.

Particle Physics

Liquefied meats, fruits, and vegetables appear to be less satiating than the same foods in solid form. Part of this is due to eating speed. You can eat applesauce four times faster than you can eat the same amount in whole-apple form.⁴⁸⁸¹ However, even at approximately the same rate of ingestion, a chicken smoothie,⁴⁸⁸² blended carrots,⁴⁸⁸³ and apple purée⁴⁸⁸⁴ were found to be less satisfying than their solid equivalents.

Part of it may be psychological. When researchers have tricked study subjects into falsely believing they had just consumed a liquid that would instantly gel in their stomachs, the subjects felt so much fuller that they ended up eating hundreds of fewer calories over the course of a day compared to those who had been given the same liquid without the

lie.⁴⁸⁸⁵ However, there are also physiological reasons why the form food takes may be important for weight control.

Nuts are the classic example. Comparing the absorption of fat from peanuts to the exact same number of peanuts ground into peanut butter, you flush more than twice the amount of fat down the toilet when you eat the peanuts themselves.⁴⁸⁸⁶ No matter how well you chew, small bits of nuts trapping some of that oil make their way all the way through our systems and are lost out the other end.⁴⁸⁸⁷ Same number of calories going into our mouths, but because of the food structure—whole versus blended—fewer calories stay in our bodies. This introduces the concept of *metabolizable energy*. Remember, it's not what you eat but what you absorb. For some foods, the calorie count on the label may not accurately reflect the calories that make it into your bloodstream.

Based on macronutrient content—4 calories per gram of protein or carbohydrate, and 9 calories per gram of fat—a can of almonds may list 180 calories per ounce. However, if you rummage through people's stools after they had eaten an ounce of almonds, you may find that 55 almond calories had escaped. So the metabolizable energy of almonds is really only 125 calories per ounce, not the listed 180. Given that, whole nuts may have 30 percent fewer calories than you'd expect. In contrast, the calculated calories and metabolizable calories in almond butter are nearly identical.⁴⁸⁸⁸ You absorb the full complement of calories from nut and seed butters because none of the oil is trapped inside unchewed fragments.

Which has more calories? Raw almonds or dry, roasted almonds? They may have the same number listed on their respective labels, but raw almonds are harder nuts to crack. Roasting makes nuts more brittle, so they fracture into tinier pieces in our mouths. If you have people chew almonds and then spit them out without swallowing, the size of the particles of chewed raw almonds is twice the size of chewed roasted almonds. And indeed, you end up getting about 10 percent more metabolizable calories when eating roasted almonds than raw, since the roasted nuts get broken down so much smaller when you eat them.⁴⁸⁸⁹

Does this mean you absorb more calories from nuts if you chew them more? Researchers in Indiana decided to put it to the test. People ate about two ounces of nuts every day for four days while their stools were collected. Those instructed to chew ten times per mouthful lost about 25 percent more fecal fat compared to those told to chew twenty-five times.⁴⁸⁹⁰ Same food, same amount of food, yet nearly two hundred fewer calories absorbed based on how they ate them. One would expect the extended orosensory exposure from the extra chewing to suppress appetite, but the meal amounts were fixed so the study can't show how much this might have compensated for the calorie deficit.

In Bad Form

The physical form of food can alter not only fat absorption but carbohydrate absorption as well. It comes as no surprise that Rice Krispies and Corn Flakes cause a much greater spike in blood sugars than rice or corn on the cob,⁴⁸⁹¹ but it's not just the added sugar in the cereals. Even with identical ingredients, food structure can make a big difference. For example, rolled oats have a significantly lower glycemic index than unsweetened instant oatmeal, which is also just straight oats but in thinner flakes,⁴⁸⁹² and oat *flakes* cause lower blood sugar and insulin spikes than *powdered* oats.⁴⁸⁹³ The same single ingredient, oats, in different forms can have different effects.

Why do we care? As I noted in the Low Glycemic Load section, the overly rapid absorption of carbohydrates after eating a high-glycemic-index meal can trigger a sequence of hormonal and metabolic changes that promote excessive eating. In a study out of Harvard's Children's Hospital, a dozen obese teen boys were fed instant oatmeal versus steel-cut oatmeal. After the instant oatmeal, the teens went on to eat 53 percent more than after eating the exact same number of calories of steel-cut oatmeal. The instant

oatmeal group was snacking within an hour after the meal and went on to accumulate significantly more calories throughout the rest of the day.⁴⁸⁹⁴ Same type of food, but different form, yielding different effects.

Steel-cut oatmeal is considered a low-glycemic-index food, averaging under 55. The glycemic index of instant oatmeal is 79, making it a high-glycemic-index food, but not as bad as some breakfast cereals, which can get into the 80s or 90s. This is even true of zero-sugar cereals like shredded wheat.⁴⁸⁹⁵ The new industrial methods used to create breakfast cereals, such as extrusion cooking and explosion puffing, accelerate starch digestion and absorption, causing an exaggerated blood sugar response.⁴⁸⁹⁶ Shredded wheat has the same ingredients as spaghetti—straight wheat—but twice the glycemic index.⁴⁸⁹⁷

When you eat spaghetti, you get a gentle rise in blood sugars.⁴⁸⁹⁸ If you eat the same amount of wheat baked into bread form, however, you get a big spike in blood sugars. All the little bubbles in bread allow our bodies to break it down so fast that it can cause our bodies to overreact with an insulin spike so large it can drive down our blood sugars below fasting levels. This hypoglycemic dip two hours after breaking bread can then trigger hunger sensations. Experimentally, if you infuse someone with insulin so their blood sugars fall, you can cause their hunger to rise⁴⁸⁹⁹ and, in particular, spike cravings for high-calorie foods.⁴⁹⁰⁰ In short, lower-glycemic-index foods may help us feel fuller longer than equivalent higher-glycemic-index foods.⁴⁹⁰¹

A dramatic illustration of this effect was demonstrated by researchers at Columbia University. Individuals were randomized into one of three breakfast conditions—oatmeal made from quick oats, the same number of calories of Frosted Flakes, or just plain water—and then the researchers measured how much the subjects ate for lunch three hours later. Unsurprisingly, those who had eaten the oatmeal felt significantly fuller and less hungry after a few hours and indeed went on to eat significantly less lunch. Overweight participants in the oatmeal group ate less than half as many calories at lunch, hundreds of fewer calories compared to the other groups. How did the cereal group fare? The breakfast cereal was so unsatiating that the Frosted Flakes group ate as much lunch as the breakfast-skipping water-only group.⁴⁹⁰² It's as if the cereal group hadn't eaten any breakfast at all.

Saving Scraps for Our Friendly Flora

White rice has a lower glycemic index than white potatoes, but only, evidently, because you end up swallowing larger particles. If you blend rice into a slurry, its glycemic index rises to match that of the potato.⁴⁹⁰³ The same is not true, however, of beans. Blended lentils have the same low glycemic index as whole lentils.⁴⁹⁰⁴ Even when cooked into a creamy dal, lentils have the same flattened blood sugar curve.⁴⁹⁰⁵ Whole beans, puréed beans, and powdered beans (like you'd find in bean pastas) all have the same low-glycemic response.⁴⁹⁰⁶ Legumes have thicker, fibrous cell walls that protect the inner starch from disruption during processing,⁴⁹⁰⁷ such that the early metabolic response to blended beans is the same, but it may be a different story hours later.

Researchers in Australia randomized people to eat the same whole foods, but during one week, the seeds, grains, beans, and chickpeas they were given were in more or less intact form, and during a different week, the foods were ground up. So, for example, for breakfast, the intact-grain group got muesli, while the ground-grain group got the same muesli but blended into a porridge. In the intact group, beans were added to salads, whereas in the ground group, they were blended into hummus. Note that during both weeks, the subjects were eating the same, whole, unrefined foods but, in one of the weeks, the whole grains, beans, chickpeas, and seeds were just made into flour or blended up.⁴⁹⁰⁸ So what happened?

The intact-grain diet doubled their stool size. They ate the same food and the same amount of food, yet ended up with twice the fecal bulk compared to the ground-grain

diet.⁴⁹⁰⁹ Remember, most of our stool is pure bacteria. No matter how well we chew, when we eat the way nature intended, the little bits and pieces left behind when we swallow transport a smorgasbord of starch and other prebiotic nutrients straight down to our good bacteria, who get fruitful and multiply. Short-chain fatty-acid production shoots up, and we can bask in all the benefits I detailed in the Microbiome-Friendly section.

Just as our bodies weren't designed to handle liquid calories, powdered grains also represent a novel challenge to our systems. In *How Not to Die*, I encouraged everyone to eat whole grains, but from an optimal weight-loss standpoint, that may be insufficient. Intact whole grains are superior to milled whole grains in the same way that whole grains are superior to refined grains. Whole-wheat bread is better than white bread because it has more fiber to feed our good bacteria. If we just ate refined grains, we would starve our microbial selves. But fiber is pretty much all whole-wheat flour has to offer our colonic colleagues. When whole grains are finely milled into flour, the rest of the nutrients are absorbed rapidly high up in the small intestine, leaving few leftovers. It still has the fiber, at least, so 100 percent whole-grain flour won't leave our good gut bacteria completely starving, but they'll certainly be left malnourished compared to if you had eaten an intact whole grain like brown rice, where you eat the entire kernels of grains instead of powder.

Structural Integrity

There's a big difference between how small we can get food particles when we chew and how small they can be ground in a mill. The chomping of our teeth and the churning of our stomachs reduce the size of anything we eat down to under about two millimeters, about one-sixteenth of an inch, before entering our intestines.⁴⁹¹⁰ That may sound small, but a two-millimeter particle of wheat would contain about 10,000 plant cells filled with starch, of which only approximately 3,800 would be ruptured open on their surface.⁴⁹¹¹ That would still leave 62 percent of the starch in that grain particle locked inside indigestible plant walls. Our starch-eating enzymes can diffuse through those walls and get at some of the starch inside, but a bounty will still be left over for our microbiomes.⁴⁹¹² In contrast, flour particles can be one hundred times smaller, even smaller than the size of the cells themselves, so nearly all may be ruptured open to spill their contents early, leaving our gut flora relatively high and dry.⁴⁹¹³

The same goes for nuts and nut butters. Even a tiny two-millimeter nut particle has more than three hundred thousand oil-rich cells, less than 10 percent of which are exposed on the surface for early digestion.⁴⁹¹⁴ This leaves a residual horn of plenty, shown experimentally to boost the growth of our gut flora.⁴⁹¹⁵ In contrast, the specks found in ground nut butters average a thousand times smaller than the chewed particles of whole or chopped nuts, obliterating the cell walls and opening them for easy access.⁴⁹¹⁶ This explains why feeding people almonds can alter their microbiomes for the better, boosting the growth of bugs that produce short-chain fatty acids, but feeding people the same amount of almond butter appears to have no prebiotic influence.⁴⁹¹⁷

Remember the amazing second-meal effect where people fed beans at dinner aren't as hungry at breakfast the next morning? ⁴⁹¹⁸ When you eat nuts whole, not only do you feel fuller at the time compared to nut butter⁴⁹¹⁹ (presumably because of all that extra chewing and orosensory stimulation), but you may also feel fuller hours later throughout the day.⁴⁹²⁰ If you feed people at dinner boiled rye berries, which are the intact rye kernels before they're milled into rye bread, they eat less at *lunch* the next day, more than twelve hours later.⁴⁹²¹ You do not, however, see that same second-meal effect on long-term satiety—or, in this case, a *third-meal* effect—with the same amount of milled rye porridge made from rye flour. The researchers suspect the appetite-suppressing benefits of eating structurally intact foods derive from the afterparty effects in our colons from the bountiful abundance.⁴⁹²²

The Matrix

To claim “whole grain” on a label, the food just has to contain more than 51 percent whole-grain ingredients.⁴⁹²³ So a “whole grain” product could be nearly half white flour and straight sugar. This is why you see “whole grain” plastered across the likes of Froot Loops, Trix, Lucky Charms, and Cocoa Puffs. Even most “100 percent” whole-wheat flour these days starts out as white flour and then has some bran and germ added to approximate the proportions of the original grain.⁴⁹²⁴ Stone-ground flour, which really is just crushed grains, can be 100 percent whole grain though the cellular structure is still obliterated.

Nearly a half century ago, the *dietary fiber hypothesis* was proposed, suggesting that fiber was the reason that diets centered around whole plant foods were so protective against chronic disease.⁴⁹²⁵ Predictably, this gave rise to a multibillion-dollar fiber supplement market.⁴⁹²⁶ (People could just eat real food, but where’s the money in that?) The problem is it didn’t work.⁴⁹²⁷ Yes, fiber supplements can help with constipation, but all the other purported benefits didn’t seem to materialize. Studies associating high fiber intake with lower risk of disease and death relate only to fiber from *food* intake rather than from fiber isolates or supplements.⁴⁹²⁸ You can’t just take your magic bullet of Metamucil with your Wonder Bread. That’s not how fiber works.

Fiber is a smuggler.

Dietary fiber alone has certain benefits, but its primary role may be to encapsulate nutrients for special delivery to our gut microbiomes. If there’s one recurring theme in this book, it’s *wall off your calories*. Make sure as many of your calories as possible—your protein, your carbs, your fat—are encased in cell walls. Cell walls are made out of fiber, which acts as an indigestible physical barrier, so when you eat structurally intact plant foods, many of the calories remain trapped. Chew all you want—you’re still going to end up with calories completely surrounded by fiber, which then blunts the glycemic response, activates the ileal brake, and delivers sustenance to your friendly flora. That’s what nature intended to happen.

The primary *utility* of fiber may be more as a vehicle to transport cached calories and nutrients. Fiber is a ferry. Now you can see why apples, “contrary to expectations,” were found to be more satiating than apple juice enriched with an identical amount of added fiber.⁴⁹²⁹ You can’t just sprinkle on the fiber. That’s not how fiber works. Fiber is the carrier. Fiber is the matrix. The word *matrix* comes from the Latin *matricis*, derived from *mater*, meaning *mother*.⁴⁹³⁰ We should strive to preserve the matrix (the *blue* pill, Neo) by choosing not just whole grains but *intact* grains.

As one review title put it, “Food Structure Is Critical for Optimal Health.”⁴⁹³¹ We can preserve this “botanical integrity” of grains by sticking to whole kernels.⁴⁹³² I was amused to see a paper in a journal published by the Royal Society of Chemistry entitled “The Anti-Obesity Effect of Starch in a Whole Grain-Like Structural Form.”⁴⁹³³ Researchers at the Institute of Biotechnology and a food science lab found they could reduce weight gain in obese mice by embedding starch microspheres “in a biopolymer-based artificial matrix to form a whole g[r]ain-like structure.” If only Mother Nature had a ticker symbol on the stock exchange.

Broken Bread

Oil and sugar are examples of concentrated forms of “acellular” calories,⁴⁹³⁴ which have been blamed as a contributor to the obesity crisis.⁴⁹³⁵ Not only have the cells’ walls that once held them been ruptured, they’ve been removed completely. White flour is not far behind, with most of its fiber stripped away. Though 100 percent whole-wheat flour may have all its original fiber, the cellular structure has been disintegrated such that while the fiber is there, it’s not protectively wrapped around the starch. That’s why the glycemic

index of intact wheat kernels (wheatberries) or even cracked wheat (like bulgur found in tabbouleh) is down around 45, but whole-wheat bread is nearly as bad as white bread with both up about 70.⁴⁹³⁶ There's fiber floating around in that whole wheat, but the starch is still out there flapping in the breeze. (The sciency way of saying that is milling disrupts the "physical encapsulation of intracellular nutrients by cell walls of plant foods."⁴⁹³⁷)

Researchers funded with dough from Big Bread assert that white bread's weight-control concerns are "one of the most common mistakes and myths about nutrition."⁴⁹³⁸ But what does the conflict-of-interest-free science say? In that famous satiety index study where dozens of foods were tested, three slices of bread were found to be less satisfying than the same number of calories of all foods except croissants, cake, donuts, and candy bars. Even jelly beans appeared a bit more satiating.⁴⁹³⁹ Whole-wheat bread does appear to be more filling than white,⁴⁹⁴⁰ but do these results translate into changes in weight?

Ecological studies, such as country-by-country comparisons of per capita bread supply and obesity rates, show no clear link.⁴⁹⁴¹ They are considered a rather weak form of evidence, though, since data are analyzed at a population level, rather than an individual level. So while it's true that average bread consumption has been declining in some countries while obesity rates have been rising, that doesn't necessarily exonerate bread since we don't know if the particular individuals who are eating more or less bread are the ones losing or gaining more weight. You could do a cross-sectional study to see if, in a snapshot in time, those who ate more bread are thinner or fatter, but you'd never know which came first, like in the candy and diet soda studies where one's weight status may determine consumption, rather than the other way around.

Enter cohort studies, following individuals and their diets over time. Researchers in Spain found that over a period of four years, those who increased their white-bread consumption appeared to gain weight and abdominal fat, but no such effect was found for whole-grain bread.⁴⁹⁴² The challenge with cohort studies is confounding. Maybe people who cut down on white bread also made other dietary changes. Indeed, those who stopped eating so much bread also tended to stop eating so much meat and started eating more fruits and vegetables. So maybe the bread itself had nothing to do with it. Maybe it was skipping the bologna in the bologna sandwich.

Whole-grain consumers exhibit a variety of other healthy dietary behaviors as well,⁴⁹⁴³ but statistical tools used to adjust for some of these other factors suggest white-bread consumption does indeed have negative health consequences.⁴⁹⁴⁴ Consistent results were also found in two other cohort studies that looked into bread. White-bread consumption appeared to be associated with greater belly fat and a significantly higher risk of becoming overweight or obese, whereas no such relationship was found for whole-grain bread.^{4945,4946}

Aside from just whole-grain over white, which breads are better than others? From a glycemic-index standpoint, breads made from sprouted grains⁴⁹⁴⁷ or with added cracked wheat⁴⁹⁴⁸ are preferable. If you simply just must eat white bread, freezing and defrosting it lowers the blood sugar response, as does toasting⁴⁹⁴⁹ and the use of sourdough fermentation.⁴⁹⁵⁰ If you make your own bread at home, you can shorten the final rising time (proofing) to make a denser loaf, which has been found to lower the glycemic index and improve satiety.

Perhaps one way to test the healthfulness of a loaf is to see if it hurts if you drop it on your foot.

I was disappointed to learn that frozen bagels, even though the dough seems denser and they have the freeze-defrost cycle going for them, appear to cause the same exaggerated blood sugar spike as Wonder Bread.^{4951,4952}

Some breads don't just incorporate cracked grains but entire kernels. Bread with added wheatberries results in a lower glycemic index⁴⁹⁵³ and improved satiety compared to straight whole-wheat bread,⁴⁹⁵⁴ and pumpernickel bread, which often includes whole rye

kernels, has comparably blunted blood sugar and insulin responses.⁴⁹⁵⁵ I thought the glycemic index of wheatberries was low at 45.⁴⁹⁵⁶ Rye berries are even lower at 34, perhaps due to their higher fiber content,⁴⁹⁵⁷ which is down around legume territory. This may explain why those randomized to eat whole-grain rye products for six weeks lost significantly more weight than those given refined wheat, but those given whole-wheat products instead did not.⁴⁹⁵⁸

The Pasta Exception

There's no need to completely deflour your diet. Unlike bread, whose structure collapses into a slurry of starch that is rapidly absorbed,⁴⁹⁵⁹ the compact structure of pasta caused by the high-pressure compression during production slows down digestion.⁴⁹⁶⁰ The glycemic index of pasta is in the moderate range, at 55, compared to the glycemic index of even whole-wheat bread, which may exceed 70. Feed diabetics bread, and over the next five hours, their blood sugar curve is about 60 percent greater than had they had the same amount of carbohydrate in pasta form.⁴⁹⁶¹

We used to think it might be the type of wheat that's used. Pasta is typically made from harder varieties like durum wheat, which gets milled into coarser particles called *semolina*.⁴⁹⁶² But if a batch of bread is made from the exact same flour used to make a batch of pasta, there's still a dramatic difference in how our bodies react metabolically.⁴⁹⁶³ Another way to demonstrate that the structure is key is by testing "spaghetti porridge," a rather unappetizing-sounding concoction—blenderized spaghetti—dreamed up by researchers. Though the porridge may have spared research subjects some fork twirling, significantly higher blood sugar spikes were noted.

When you eat bread, the particles you swallow can be a thousand times smaller than when eating spaghetti. Bread tends to break down into particles under a millimeter, many of which are too microscopic to be seen by the naked eye. On the other hand, when subjects were instructed to chew some spaghetti, then spit it out instead of swallowing it, researchers found segments up to an inch long.⁴⁹⁶⁴ Our bodies' starch-munching enzymes can start superficially eroding the surface of these pieces, but it takes longer for spaghetti to get fully digested.

Is some pasta better than others? Macaroni is digested much quicker than spaghetti for some reason. Maybe we chew the elbows into smaller pieces? Thick linguini tested a bit better than thin.⁴⁹⁶⁵ Surprisingly, though, there was no glycemic difference between undercooked spaghetti boiled for five minutes and overcooked spaghetti boiled for fifteen.⁴⁹⁶⁶

Greater glycemic impact doesn't necessarily translate into reduced satiety, however. Remember how white potatoes took home the gold for the most satiating food on a calorie-for-calorie basis? Tested head-to-head, boiled and mashed potatoes beat out pasta for satiety, despite their bread-like glycemic index. Children consumed about 35 percent fewer calories at meals served with mashed potatoes than those served with pasta or rice.⁴⁹⁶⁷

Greater satiety also doesn't necessarily translate into reduced calorie consumption. People feel fuller eating whole-grain pasta compared to refined-grain pasta, but apparently not enough to affect subsequent meal intake hours later.⁴⁹⁶⁸ Similarly, people fed pasta for breakfast don't appear to eat any less at lunch than after a bready breakfast,⁴⁹⁶⁹ so do the short-term metabolic effects make any long-term difference?

Eating higher-glycemic-index diets is associated with a small to medium increase in breast cancer and colorectal cancer.⁴⁹⁷⁰ This is thought to be because regularly eating high-glycemic loads can cause a small increase in the blood of levels of IGF-1, the cancer-promoting growth hormone related to animal protein consumption I discussed in *How Not to Die*.⁴⁹⁷¹ Researchers zeroed in on bread versus pasta intake. Two case-control studies comparing the past diets of cancer cases to the diets of matched cancer-free controls

found that bread consumption was more strongly associated with cancer of the breast and colon than was the consumption of pasta.⁴⁹⁷² Pasta consumption is associated with other healthy habits, though, like greater tomato consumption. The studies were performed in Italy, so presumably they weren't eating Day-Glo mac 'n cheese out of a box.

These confounding factors also make it difficult to tease out the effects of pasta on body fat. Pasta consumers do tend to be slimmer,⁴⁹⁷³ but that could be due to related diet and lifestyle factors or possibly a chicken-or-the-egg phenomenon arising from overweight individuals disproportionately cutting down. You don't really know until you put it to the test.

Recently, two systematic reviews were published that compiled all the randomized controlled trials ever done on pasta and body weight.^{4974,4975} Neither found a single such trial. There aren't any randomized trials assessing the effects of pasta intake on any health parameter. All they could find were trials that tested pasta in the context of broader dietary patterns. There are dozens of studies randomizing people to low-glycemic-index diets that often include switching people from breads to pastas as a component. That swap is an easy way to change the glycemic index without changing the nutrient composition as much, so researchers can better isolate the glycemic effects. Though the switch to more pasta was just part of a constellation of dietary changes, when all those studies were put together, they did show significantly more weight loss compared to those randomized to higher-glycemic diets.

FOOD FOR THOUGHT

If you could only make one dietary change, getting rid of sugary beverages would be a good choice and one that is consistent with my advice to wall off your calories. That means eliminating soda sweetened with sugar or corn syrup, as well as other sugary drinks, both carbonated and uncarbonated, such as sports and energy drinks.

As I mentioned in the Fat Blockers section, I defined my Green Light category in *How Not to Die* as foods of plant origin to which nothing bad has been added and from which nothing good has been taken away. How is this different from my recommendation to wall off your calories, to ensure your protein, carbs, and fat are trapped within cell walls? After all, only plants have cell walls. (Animals are made up of cells with fluid membranes, requiring bones to hold them up, whereas plants have rigid cell walls made out of fiber.) So isn't walling off calories the same as saying choose whole plant foods? The difference becomes apparent with examples of formless foods like powdered whole grains. Imagine a whole-grain cream of wheat cereal with one ingredient: 100 percent whole wheat. Or almond butter with one ingredient: almonds. Green Light, right? Plant foods to which nothing bad has been added and from which nothing good has been taken away. But now we know something good *has* been taken away: the structure.

The reason I have always considered whole-grain pasta to be a Green Light food, but whole-grain bread, even if it's 100 percent whole grain, as a Yellow Light food, had nothing to do with the structure. It was all due to Green Light's "nothing bad added" caveat. Bread-makers add salt, making bread a leading contributor of sodium intake, second only to chicken for most American adults.⁴⁹⁷⁶ If we all just reduced our salt intake by about a half teaspoon a day, we could potentially prevent between 86,000 and 165,000 strokes and heart attacks and save 44,000 to 92,000 lives in the United States every year.⁴⁹⁷⁷

Eating whole grains is good, but eating whole-grain *kernel*s is better. Former Harvard nutrition chair Walter Willett has argued that the term *whole grain* should probably be reserved for only whole intact grain kernels.⁴⁹⁷⁸ So eat the wholiest of grains: intact grains, also known as *groats*.

Take oats, for example. They're found out in the fields as oat groats and then have their inedible outer husks removed during processing.⁴⁹⁷⁹ Groats can then be sliced into two to four pieces to make steel-cut (also known as *pinhead* or *Irish*) oats, coarsely ground into Scottish oatmeal, or steamed and flattened into "old-fashioned" rolled oats.⁴⁹⁸⁰ Quick-cooking oats are just old-fashioned oats rolled even thinner, and instant oats are steamed longer and rolled even more thinly.⁴⁹⁸¹ Then, at the bottom of the list, the most processed would be powdered oats, which you might find in oat-based breakfast cereals. Instead of buying boxed breakfast cereals, make oatmeal out of whole, intact oats. *They're gr-r-oat!*

I like to start my mornings with what I call my *BROL bowl*. *BROL* stands for *barley, rye, oats, and lentils*. Most people are only familiar with pearled barley, which is partially refined by having some of its bran polished off. You can buy barley groats, sold as hulled or hull-less barley. If your budget allows, go for purple barley, which naturally contains some of the antioxidant pigments found in berries as a bonus. Rye groats are typically sold as rye berries. Oat groats are just oat groats, though I've also seen the terms *hull-less* and *hulled oats*. And since I know I should probably check off a morning legume box on my Daily Dozen, I add black lentils, which are the most antioxidant-packed,⁴⁹⁸² sold as *beluga* lentils due to their resemblance to expensive caviar.

I have them all premixed in an unimaginative 1:1:1:1 ratio and then, in an electric pressure cooker, just cook one scoop of dry BROL to two scoops of water. There's probably a quicker way to do it, but I simply press a default one-

touch button for thirty minutes, and it comes out fine. Of course, that's just the base. It has a great texture but very little flavor. Depending on my mood, I go savory with greens and mushrooms or sweet with frozen dark red cherries, cocoa powder, dates, and walnuts, giving me more of a chocolate-covered-cherry sensation. I'll make sure to include a bunch of these recipes in my forthcoming cookbook.

With all the new data on the importance of food form, I'm starting to sour on flour, so I advise not living by bread alone. The new structure created by the pasta-making process can mediate these effects, though, so you don't have to say *basta* to pasta.

V. Dr. Greger's Twenty-One Tweaks

Too Much Food, Not Enough Calories

In *How Not to Die*, I compiled the healthiest of the Green Light foods into my Daily Dozen checklist of foods I encourage people to try to fit into their daily routines. I made it into a free app, Dr. Greger's Daily Dozen, available for iPhone and Android, so anyone and everyone can try to check off all the boxes every day and track their progress over time.

As the feedback poured in from people giving the app a try, two themes of complaints arose. The first was that it was just too much food. There was no way they could eat all that food in one day. In response, I explained that the Daily Dozen was aspirational, something to shoot for, just a tool to inspire people to include some of the healthiest of healthy foods into their daily diets. The vast volume of food I prescribed was on purpose. I was hoping that by telling people to eat so much healthy stuff, it would naturally crowd out some of the less-healthy stuff. After checking off all twenty-four servings in the Daily Dozen, there's only so much room left for a pepperoni pizza.

Ironically, the second major complaint we got is that it doesn't have enough calories. I had to explain that the Daily Dozen just represented the minimum I encourage people to eat, not the maximum, and that, certainly, training athletes requiring thousands more calories would have to eat much more. This all got me thinking, though. Too much food but too few calories? Sounds like the perfect weight-loss diet!

The Daily Dozen is by definition all Green Light foods, all whole plant foods, so that right there bakes in all seventeen of the ideal weight-loss diet ingredients listed [here](#). What about the calorie count? A systematic review of successful weight-loss strategies concluded that given the metabolic slowing and increased appetite that accompanies weight loss, to achieve *significant* weight loss, calorie counts may need to drop as low as 1,200 calories a day for women and 1,500 calories a day for men.⁴⁹⁸³ I set up a spreadsheet and tried a bunch of common foods in each of the categories, and what do you know: The Daily Dozen averages about 1,200 calories, with the higher-calorie food choices nailing 1,500 calories.

The Daily Dozen Diet

There are a number of tweaks necessary to optimize the Daily Dozen for weight loss. A typical breakfast of Green Light foods that would check off a few of the Daily Dozen boxes would be a big bowl of oatmeal sweetened with raisins. Based on what we learned in the Low in Calorie Density, High in Water-Rich Foods, Eating Rate, and Wall Off Your Calories sections, we could optimize that meal for weight loss by making the oatmeal from steel-cut or whole groats rather than rolled or instant, cooking it thick, and switching the dried fruit for fresh, for example, swapping in strawberries for the raisins. If we did want to use dried, as we learned in the Amping AMPK and Inflammation

Quenchers sections, barberries or gojis might be a better choice.

Similarly, when choosing vegetables, we can steer toward above-ground veggies highest on the water scale. Bell peppers have that nicotine edge I described in Amping AMPK, and uncooked vegetables in general offer more orosensory stimulation. If you want to go underground, based on what we learned about glycemic load, sweet potatoes would be preferable to white. We certainly want to mix it up, though, to take advantage of our built-in striving for variety, and since vegetables represent the healthiest class of foods with the fewest calories, we should aim to eat them earlier in the meal.

In the Appetite Suppression section, we learned yet another reason to include ground flaxseeds in our daily diets. Nuts are a great complement to greens to boost the absorption of fat-soluble nutrients, but they ideally should be eaten raw and whole or coarsely chopped rather than blended into butters. Miss the taste of peanut butter? A sprinkle of any one of the myriad powdered peanut butters on the market can help satisfy that craving. This is not to say something like almond butter or tahini is unhealthy by any stretch, but for weight-loss acceleration, structurally intact nuts and seeds would be better.

My free Dr. Greger's Daily Dozen app has become so popular that I decided to completely revamp it with new features for this book, so I've incorporated all these tweaks to the Daily Dozen to optimize it for weight control. You just have to switch over to the weight-loss setting. Now, you can not only track your progress, graphing your momentum day to day and month to month to see how well you're nailing each of the Daily Dozen, but since so many seemed to really appreciate having a list of reminders to check off throughout the day, I decided to add an entirely new checklist to

capture the weight-loss boosters I documented in part IV. With this new, expanded version of the app, you can toggle over to weight-loss mode and make a game out of how many of the new fat-busting boosters you can squeeze in every day, along with your Daily Dozen checkboxes.

Boxes of Tricks

Some of the weight-loss boosters are automatically taken care of with the Daily Dozen. For example, fat-blocking thylakoids and calcium are covered with my recommendation to eat lots of low-oxalate greens. But for the others, I've developed my Twenty-One Tweaks, practical takeaways from the boosters collected into one simple list on the next page.

You may have noticed that not all the strategies I covered in part IV are included in the list. Some only apply to certain individuals. For example, asking people to get into the NEAT habit of using steppers, fidget bars, or bouncing their knees during prolonged sitting may only apply to those with desk jobs. Other accelerants may be too risky for general consumption. For example, while the 25:5 modified fasting shows promise, you probably shouldn't drop below a thousand calories a day for more than twenty-four hours without medical supervision.⁴⁹⁸⁴ Finally, there are options that show theoretical promise but haven't been sufficiently vetted in clinical trials, such as pistachios for circadian synchronization or mixing peppermint oil into hand lotion to facilitate BAT activation.

So here's the list of strategies that made the cut—broadly applicable, relatively safe, and evidence-based. See how many of these easily actionable tweaks you can incorporate into your daily routine.

Dr. Greger's Twenty-One Tweaks

At Each Meal

- ✔✔✔ preload with water
- ✔✔✔ preload with “negative calorie” foods
- ✔✔✔ incorporate vinegar (2 tsp with each meal)
- ✔✔✔ enjoy undistracted meals
- ✔✔✔ follow the twenty-minute rule

Every Day

take your daily doses

- ✔ black cumin (¼ tsp)
- ✔ garlic powder (¼ tsp)
- ✔ ground ginger (1 tsp) or cayenne pepper (½ tsp)
- ✔ nutritional yeast (2 tsp)
- ✔✔ cumin (½ tsp with lunch and dinner)
- ✔✔✔ green tea (3 cups)
- ✔ stay hydrated
- ✔ deflower your diet
- ✔ front-load your calories
- ✔ time-restrict your eating
- ✔ optimize exercise timing
- ✔✔ weigh yourself twice a day
- ✔✔✔ complete your implementation intentions

Every Night

- ✔ fast after 7:00 p.m.
- ✔ get sufficient sleep
- ✔ experiment with mild trendelenburg

At Each Meal

Preload with Water

Time your metabolism-boosting two cups of cool or cold unflavored water before each meal to also take advantage of its preload benefits.

Preload with “Negative Calorie” Foods

As the first course, start each meal with an apple or a Green Light soup or salad containing fewer than one hundred calories per cup.

Incorporate Vinegar (2 tsp with each meal)

Never drink vinegar straight. Instead, flavor meals or dress a side salad with any of the sweet and savory vinegars out there. If you want to drink it, make sure to mix it in a glass of water and, afterward, be sure to rinse your mouth out with water to protect your tooth enamel.

Enjoy Undistracted Meals

Don't eat while watching TV or playing on your phone. Give yourself a check for each meal you're able to eat without distraction.

Follow the Twenty-Minute Rule

Whether through increasing viscosity or the number of chews, or decreasing bite size and eating rate, dozens of studies have demonstrated that no matter how we boost the amount of time food is in our mouths, it can result in lower caloric intake. So extend meal duration to at least twenty minutes to allow your natural satiety signals to take full effect. How? By choosing foods that

take longer to eat and eating them in a way that prolongs the time they stay in your mouth. Think bulkier, harder, chewier foods in smaller, well-chewed bites.

Every Day

Take Your Daily Doses

Black Cumin (Nigella sativa) (¼ tsp)

As noted in the Appetite Suppression section, a systematic review and meta-analysis of randomized, controlled weight-loss trials found that about a quarter teaspoon of black cumin powder every day appears to reduce body mass index within a span of a couple of months. Note that black cumin is different from regular cumin, for which the dosing is different. (See below.)

Garlic Powder (¼ tsp)

Randomized, double-blind, placebo-controlled studies have found that as little as a daily quarter teaspoon of garlic powder can reduce body fat at a cost of perhaps two cents a day.

Ground Ginger (1 tsp) or Cayenne Pepper (½ tsp)

Randomized controlled trials have found that ¼ teaspoon to 1½ teaspoons a day of ground ginger significantly decreased body weight for just pennies a day. It can be as easy as stirring the ground spice into a cup of hot water. Note: Ginger may work better in the morning than evening. Chai tea is a tasty way to combine the green tea and ginger tweaks into a single beverage.

Alternately, for BAT activation, you can add one raw jalapeño pepper or a half teaspoon of red pepper powder (or, presumably, crushed red pepper flakes)

into your daily diet. To help beat the heat, you can very thinly slice or finely chop the jalapeño to reduce its bite to little prickles, or mix the red pepper into soup or the whole-food vegetable smoothie I featured in one of my cooking videos on NutritionFacts.org.⁴⁹⁸⁵

Nutritional Yeast (2 tsp)

Two teaspoons of baker's, brewer's, or nutritional yeast contains roughly the amount of beta 1,3/1,6 glucans found in randomized, double-blind, placebo-controlled clinical trials to facilitate weight loss.

Cumin (Cuminum cyminum) (½ tsp with lunch and dinner)

Overweight women randomized to add a half teaspoon of cumin to their lunches and dinners beat out the control group by four more pounds and an extra inch off their waists. There is also evidence to support the use of the spice saffron, but a pinch a day would cost a dollar, whereas a teaspoon of cumin costs less than ten cents.

Green Tea (3 cups)

Drink three cups a day *between* meals (waiting at least an hour after a meal so as to not interfere with iron absorption). *During* meals, drink water, black coffee, or hibiscus tea mixed 6:1 with lemon verbena, but never exceed three cups of fluid an hour (important given my water preloading advice).

Take advantage of the reinforcing effect of caffeine by drinking your green tea along with something healthy you wish you liked more, but don't consume large amounts of caffeine within six hours of bedtime. Taking your tea without sweetener is best, but if you typically sweeten your tea with honey or sugar, try yacon syrup instead.

Stay Hydrated

Check this box if your urine never appeared darker than a pale yellow all day. Note that if you're eating riboflavin-fortified foods (such as nutritional yeast), then base this instead on getting nine cups of unsweetened beverages a day for women (which would be taken care of by the green tea and water preloading recommendations) or thirteen cups a day for men. If you have heart or kidney issues, don't increase fluid intake at all without first talking with your physician. Remember, diet soda may be calorie-free, but it's not consequence-free, as we learned in the Low in Added Sugar section.

Deflour Your Diet

Check this box every day your whole grain servings are in the form of intact grains. The powdering of even 100 percent whole grains robs our microbiomes of the starch that would otherwise be ferried down to our colons encapsulated in unbroken cell walls.

Front-Load Your Calories

There are metabolic benefits to distributing more calories to earlier in the day, so make breakfast (ideally) or lunch your largest meal of the day in true king/prince/pauper style.

Time-Restrict Your Eating

Confine eating to a daily window of time of your choosing under twelve hours in length that you can stick to consistently, seven days a week. Given the circadian benefits of reducing evening food intake, the window should end before 7:00 p.m.

Optimize Exercise Timing

The Daily Dozen's recommendation for optimum exercise duration for longevity is ninety minutes of moderately intense activity a day, which is also the optimum exercise duration for weight loss. Anytime is good, and the more the better, but there may be an advantage to exercising in a fasted state, at least six hours after your last meal. Typically, this would mean before breakfast, but if you timed it right, you could exercise midday before a late lunch or, if lunch is eaten early enough, before dinner. This is the timing for nondiabetics.

Diabetics and prediabetics should instead start exercising thirty minutes after the start of a meal and ideally go for at least an hour to completely straddle the blood sugar peak. If you had to choose a single meal to exercise after, it would be dinner, due to the circadian rhythm of blood sugar control that wanes throughout the day. Ideally, though, breakfast would be the largest meal of the day, and you'd exercise after that—or, even better, after every meal.

Weigh Yourself Twice a Day

Regular self-weighing is considered crucial for long-term weight control, but there is insufficient evidence to support a specific frequency of weighing. My recommendation is based on the one study that found that twice daily—upon waking and right before bed—appeared superior to once a day (about six versus two pounds of weight loss over twelve weeks).

Complete Your Implementation Intentions

Every two months, create three new implementation intentions—"if X, then Y" plans to perform a particular

behavior in a specific context—and check each one off as you complete them every day.

Every Night

Fast After 7:00 p.m.

Because of our circadian rhythms, food eaten at night is more fattening than the exact same food eaten earlier in the day, so fast every night for at least twelve hours starting before 7:00 p.m. The fewer calories after sundown, the better.

Get Sufficient Sleep

Check this box if you got at least seven hours of sleep at your regular bedtime.

Experiment with Mild Trendelenburg

Try spending at least four hours a night lying with your body tilted head-down six degrees by elevating the posts at the foot of your bed by eight inches (or by nine inches if you have a California king). Be *extremely* careful when you get out of bed, as this causes orthostatic intolerance in most people, even if you're young and healthy—meaning if you get up too fast, you can feel dizzy, faint, or light-headed and could fall and hurt yourself. So get up *slowly*. Drinking two cups of cold water thirty minutes before rising may also help prevent this potentially hazardous side effect.

IMPORTANT: Do not try this at home *at all* if you have any heart or lung issues, acid reflux, or problems with your brain (like head trauma) or eyes (even a family history of glaucoma disqualifies you). Also do not try this until you ask your physician if they think it's safe for you to sleep in mild Trendelenburg.

Tick All the Right Boxes

Between the twenty-four checkboxes in the Daily Dozen and the thirty-seven new checkboxes in the Tweaks, you may feel a bit overwhelmed, but it's easy to knock off a bunch at a time. For example, starting a meal with a tomato salad sprinkled with some black cumin, garlic powder, and balsamic vinegar hits five boxes right there, including the "Preload with 'Negative Calorie' Foods" tweak and the Daily Dozen box for "Other Vegetables." And if that was one of your implementation intentions, make that six! Ten percent of your boxes nailed with a single appetizer.

Of course, you don't have to hit all the booster boxes every day. You don't even have to hit any. A healthy diet, as encapsulated by the Daily Dozen, should be all you need to lose as much weight as you want, but the more of these extra tweaks you can hit, the more successful you may be. I'm working on an entire *How Not to Diet Cookbook* to try to fit as many of these combinations together into delicious recipes and hearty meal plans—but in the meanwhile, please feel free to download the free, updated Dr. Greger's Daily Dozen app on your Android or iPhone. Start experimenting with a few of the Twenty-One Tweaks and see which ones work for you. My goal is to provide you with the broadest palette of tools to choose from.

Remember, it's not what you eat today that matters, or tomorrow, or next week, but rather what you eat over the next months, years, and decades, so you have to find lifestyle changes that fit into your lifestyle.

VI. Conclusion

Joining *U.S. News & World Report's* expert panel to rank the “Best Diets” has been an eye-opening experience. Each year, we’re asked to score dozens of trending diets on a scale from one to five based on seven criteria—most of which, to my surprise, are weighted equally. For example, in ranking which diet is best, a diet that is given top marks for ease of compliance—a score of five for being “extremely easy” to follow, based on factors such as “taste appeal”—could rank just as a high (all other things being equal) as a diet that was ranked as “extremely effective” in reducing the risk of heart disease, the number-one killer of men and women. That’s like ranking bulletproof vest materials and concluding Kevlar does stop bullets better but, from a comfort standpoint, flannel wins the day.

After all, the Standard American Diet is easy to comply with—so much so it’s the *Standard American Diet*—but it’s killing us, more so than any other factor, including cigarettes.⁴⁹⁸⁶

For me, the best diet is the one that saves your life.

To *U.S. News's* credit, the “health risks” category is counted twice because, in its words, “no diet should be dangerous.”⁴⁹⁸⁷ But even with double counting, a diet rated as “extremely unsafe” but “extremely effective” (for short-term weight loss) and “extremely easy” (like popping

laxatives) would rank just as high (all else being equal) as a diet that was only moderately easy and effective but safe. How could “extremely unsafe” not disqualify a diet right off the bat? (Yes, cyanide is poisonous, but let’s not discount its fragrant almondy aroma.)

Nearly every year since the rankings started in 2011, Dr. Ornish’s plant-based diet has been ranked number one for heart health but has yet to be ranked number one overall. Isn’t the goal of a diet to achieve a long, healthy life? Once he proved back in 1990 that his diet could reverse our leading killer, it seems to me that the competition should have been over.

We should eat real food that grows out of the ground, natural foods that come from fields, not factories, and gardens, not garbage. The same diet that has been shown to prevent, treat, and reverse some of our leading killer diseases just so happens to be the one with the greatest potential for permanent weight loss. Inspired by my grandmother’s story, I went on this deep dive into the medical literature searching for an answer to the obesity epidemic and came full circle. Not only did I succeed in finding a plain solution to the crisis, I discovered the same solution: a diet centered around whole plant foods.

This may not be what people want to hear. This may not be what you want to hear. This certainly isn’t what the food industry wants to hear—or wants you to hear. But I believe everyone deserves at least access to this knowledge.

At the end of the day, it’s your body, your choice. As a physician and researcher, all I can do is share with you what I can discern from the best available balance of evidence at present, and the rest is up to you.

When I was in training, I remember witnessing a doctor grab a pack of cigarettes out of a patient’s shirt pocket and crumple it into the trash. I’m not here to grab anyone’s

cheeseburger, but I'm also not one to soft-pedal the message. It's true that a healthy diet is like exercise: It's by no means an all-or-nothing proposition, and every little bit helps. But I'm not going to shy away from sharing what the science says for fear it would be considered "impractical" or "unrealistic" (as the Sugar Association calls advice to reduce sugar intake).⁴⁹⁸⁸ When deciding how many daily servings of fruits and vegetables to recommend, dietary guidelines are advised to set "ambitious" goals but not recommend so many as to be "regarded as threatening."⁴⁹⁸⁹ (It doesn't help that ten of the fourteen members of the current U.S. Dietary Guidelines Advisory Committee apparently have financial conflicts of interest with meat, dairy, or processed food companies.⁴⁹⁹⁰) Rather than patronizing the public, I think they should just tell everyone the truth.

The healthiest commodities are the least profitable. It's that simple. This isn't some grand conspiracy to make us all fat. It's just how the system works. So it's up to us to reclaim our health destinies from companies that may not have the best interests of our families' health at heart.

Thankfully, the solution is simple. You don't need to follow any expensive plans, swallow any questionable pills, or undergo any surgical procedures. There are no magic-bullet infomercial gadgets "As Seen on TV." No meal replacements or meetings to attend. We don't have to compromise our health to lose weight, or our life spans. In fact, quite the opposite. The best diet for weight loss may just so happen to be the safest, cheapest way to eat for the longest, healthiest life.

References

The full list of citations follows. You can also go to www.nutritionfacts.org/books/how-not-to-diet/citations (or point your phone camera at the QR code below), where each cited source is hyperlinked so that you can read the original studies themselves.

Scan for cited sources:



Or visit:

www.bit.ly/citedsources

Notes

Preface

1. Westfall JM, Mold J, Fagnan L. Practice-based research—“Blue Highways” on the NIH roadmap. *JAMA*. 2007;297(4):403-6.
2. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. 1990;336(8708):129-33.
3. Allen J, Anderson DR, Baun B, et al. Reflections on developments in health promotion in the past quarter century from founding members of the American Journal of Health Promotion Editorial Board. *Am J Health Promot*. 2011;25(4):ei-eviii.
4. Shapin S. Expertise, common sense, and the Atkins Diet. In: Porter J, Phillips PWB, eds. *Public Science in Liberal Democracy*. Toronto: University of Toronto Press; 2007:175-93.
5. Mayer J, chair. *White House Conference on Food, Nutrition, and Health: final report*. Washington, D.C.;1969.
6. Mozaffarian D, Forouhi NG. Dietary guidelines and health—is nutrition science up to the task? *BMJ*. 2018;360:k822.
7. Kassirer J, Angell M. Losing weight—an ill-fated New Year’s resolution. *N Engl J Med*. 1998;338(1):52-4.
8. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *N Engl J Med*. 2013;368(5):446-54.

Introduction

9. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res.* 2009;43(8):2057-92.
10. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and extreme obesity among adults aged 20 and over: United States, 1960-1962 through 2013-2014. National Center for Health Statistics. Published July 18, 2016. Available at: https://www.cdc.gov/nchs/data/hestat/obesity_adult_13_14/obesity_adult_13_14.htm. Accessed June 9, 2019.
11. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA.* 2018;319(16):1723-5.
12. The Coca-Cola Co. Coming Together [Video]. YouTube.com. Published November 11, 2013. Available at: <https://www.youtube.com/watch?v=oV2D0Zq124g>. Accessed March 19, 2019.
13. Malik VS, Willett WC, Hu FB. The revised nutrition facts label: a step forward and more room for improvement. *JAMA.* 2016;316(6):583-4.
14. Ha V, Cozma AI, Choo VL, Mejia SB, Souza RJ, Sievenpiper JL. Do fructose-containing sugars lead to adverse health consequences? Results of recent systematic reviews and meta-analyses. *Adv Nutr.* 2015;6(4):504S-11S.
15. Viskaal-van Dongen M, Kok FJ, de Graaf C. Eating rate of commonly consumed foods promotes food and energy intake. *Appetite.* 2011;56(1):25-31.
16. Purnell JQ, Fair DA. Fructose ingestion and cerebral, metabolic, and satiety responses. *JAMA.* 2013;309(1):85-6.
17. Harris JL, Schwartz MB, Ustjanauskas A, Ohri-Vachaspati P, Brownell KD. Effects of serving high-sugar cereals on children's breakfast-eating behavior. *Pediatrics.* 2011;127(1):71-6.

Chapter 1

18. Regestein QR. The big, bad obesity pandemic. *Menopause*. 2018;25(2):129–32.
19. Katz D. Obesity ... be damned!: what it will take to turn the tide. *Harvard Health Policy Rev*. 2006;7(2):135–51.
20. National Center for Health Statistics. Table 53. Selected health conditions and risk factors, by age: United States, selected years 1988–1994 through 2015–2016. 2017. Available at: <https://www.cdc.gov/nchs/data/hus/2017/053.pdf>. Accessed March 19, 2019.
21. Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of obesity in adults: latest trends. *Curr Obes Rep*. 2018;7(4):276–88.
22. Ludwig DS. Epidemic childhood obesity: not yet the end of the beginning. *Pediatrics*. 2018;141(3):1–4.
23. Skinner AC, Ravanbakht SN, Skelton JA, et al. Prevalence of obesity and severe obesity in US children, 1999–2016. *Pediatrics*. 2018;141(3):e20173459.
24. Helmchen LA, Henderson RM. Changes in the distribution of body mass index of white US men, 1890–2000. *Ann Hum Biol*. 2004;31(2):174–81.
25. Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of obesity in adults: latest trends. *Curr Obes Rep*. 2018;7(4):276–88.
26. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804–14.
27. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804–14.
28. Frank LD, Andresen MA, Schmid TL. Obesity relationships with community design, physical activity, and time spent in cars. *Am J Prev Med*. 2004;27(2):87–96.
29. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804–14.
30. European Association for the Study of Obesity. Obesity: perception and policy—multi-country review and survey of policymakers 2014. 2014. Available at: https://web.archive.org/web/20180722003601/http://easo.org/wp-content/uploads/2014/05/C3_EASO_Survey_A4_Web-FINAL.pdf. Accessed March 19, 2019.
31. Rodgers A, Woodward A, Swinburn B, Dietz WH. Prevalence trends tell us what did not precipitate the US obesity epidemic. *Lancet Public Health*. 2018;3(4):e162–3.
32. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768–73.
33. Mangalindan J. PepsiCo CEO: “if all consumers exercised ... obesity wouldn’t exist.” *Fortune*. Published April 27, 2010. Available at: http://archive.fortune.com/2010/04/27/news/companies/indra_nooyi_pepsico.fortune/index.htm. Accessed March 19, 2019.
34. Barlow P, Seródio P, Ruskin G, McKee M, Stuckler D. Science organisations and Coca-Cola’s “war” with the public health community: insights from an internal industry document. *J Epidemiol Community Health*. 2018;72(9):761–3.
35. Karnani A, McFerran B, Mukhopadhyay A. Leanwashing: a hidden factor in the obesity crisis. *Calif Manage Rev*. 2014;56(4):5–30.
36. Scrinis G. Big Food corporations and the nutritional marketing and regulation of processed foods. *Canadian Food Studies*. 2015;2(2):136–45.
37. What is Nestlé doing about obesity? Nestle.com. Available at: <https://www.nestle.com/ask-nestle/health-nutrition/answers/what-is-nestle-doing-about-obesity>. Accessed March 19, 2019.
38. Karnani A, McFerran B, Mukhopadhyay A. Leanwashing: a hidden factor in the obesity crisis. *Calif Manage Rev*. 2014;56(4):5–30.
39. Flatt JP. Issues and misconceptions about obesity. *Obesity (Silver Spring)*. 2011;19(4):676–86.
40. McFerran B, Mukhopadhyay A. Lay theories of obesity predict actual body mass. *Psychol Sci*. 2013;24(8):1428–36.
41. Flatt JP. Issues and misconceptions about obesity. *Obesity (Silver Spring)*. 2011;19(4):676–86.
42. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation*. 2012;126(1):126–32.
43. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453–6.
44. Vandevijvere S, Chow CC, Hall KD, Umali E, Swinburn BA. Increased food energy supply as a major driver of the obesity epidemic: a global analysis. *Bull World Health Organ*. 2015;93(7):446–56.
45. Westerterp KR, Speakman JR. Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. *Int J Obes (Lond)*. 2008;32(8):1256–63.
46. Church T, Martin CK. The obesity epidemic: a consequence of reduced energy expenditure and the uncoupling of energy intake? *Obesity (Silver Spring)*. 2018;26(1):14–6.
47. Bleich S, Cutler D, Murray C, Adams A. Why is the developed world obese? *Annu Rev Public Health*. 2008;29:273–95.
48. Tataranni PA, Harper IT, Snitker S, et al. Body weight gain in free-living Pima Indians: effect of energy intake vs expenditure. *Int J Obes Relat Metab Disord*. 2003;27(12):1578–83.
49. McFerran B, Mukhopadhyay A. Lay theories of obesity predict actual body mass. *Psychol Sci*. 2013;24(8):1428–36.
50. McFerran B, Mukhopadhyay A. Lay theories of obesity predict actual body mass. *Psychol Sci*. 2013;24(8):1428–36.
51. McFerran B, Mukhopadhyay A. Lay theories of obesity predict actual body mass. *Psychol Sci*. 2013;24(8):1428–36.
52. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197–206.
53. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat Rev Endocrinol*. 2014;10(1):51–61.
54. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937–48.
55. Karra E, O’Daly OG, Choudhury AI, et al. A link between FTO, ghrelin, and impaired brain food-cue responsivity. *J Clin Invest*. 2013;123(8):3539–51.

56. Cheung MK, Yeo GS. FTO biology and obesity: why do a billion of us weigh 3 kg more? *Front Endocrinol (Lausanne)*. 2011;2:4.
57. Tedstone AE. Obesity treatment—are personalised approaches missing the point? *BMJ*. 2016;354:i4980.
58. Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011;378(9793):826–37.
59. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. *Nat Rev Endocrinol*. 2014;10(1):51–61.
60. Li S, Zhao JH, Luan J, et al. Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *Am J Clin Nutr*. 2010;91(1):184–90.
61. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. 2011;8(11):e1001116.
62. Corella D, Arnett DK, Tucker KL, et al. A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. *J Nutr*. 2011;141(12):2219–25.
63. Livingstone KM, Celis-Morales C, Papandonatos GD, et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. *BMJ*. 2016;354:i4707.
64. Celis-Morales C, Marsaux CF, Livingstone KM, et al. Can genetic-based advice help you lose weight? Findings from the Food4Me European randomized controlled trial. *Am J Clin Nutr*. 2017;105(5):1204–13.
65. Meisel SF, Walker C, Wardle J. Psychological responses to genetic testing for weight gain: a vignette study. *Obesity (Silver Spring)*. 2012;20(3):540–6.
66. Centre for Economic Performance. Vertical transmission of overweight: evidence from English adoptees. Published October 2016. Available at: <http://cep.lse.ac.uk/pubs/download/dp1324.pdf>. Accessed March 19, 2019.
67. Knowler WC, Pettitt DJ, Saad MF, et al. Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr*. 1991;53(6 Suppl):1543S–51S.
68. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev*. 1990;6(1):1–27.
69. Ravussin E. Energy metabolism in obesity. Studies in the Pima Indians. *Diabetes Care*. 1993;16(1):232–8.
70. Ravussin E. Energy metabolism in obesity. Studies in the Pima Indians. *Diabetes Care*. 1993;16(1):232–8.
71. Boyce VL, Swinburn BA. The traditional Pima Indian diet. Composition and adaptation for use in a dietary intervention study. *Diabetes Care*. 1993;16(1):369–71.
72. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. *Nutr Rev*. 2001;59(5):129–39.
73. Schulz LO, Bennett PH, Ravussin E, et al. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care*. 2006;29(8):1866–71.
74. Dobzhansky T. Nothing in biology makes sense except in the light of evolution. *Am Biol Teach*. 1973;35(3):125–9.
75. Neel JV. Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? *Am J Hum Genet*. 1962;14:353–62.
76. Genné-Bacon EA. Thinking evolutionarily about obesity. *Yale J Biol Med*. 2014;87(2):99–112.
77. Anderson RM, Brackenridge BP. Polar bears in the jungle: reflections on obesity and overeating. *Diabetes Educ*. 1999;25(4):521–3.
78. Egger G, Swinburn B. An “ecological” approach to the obesity pandemic. *BMJ*. 1997;315(7106):477–80.
79. Pimentel GD, Ganeshan K, Carvalheira JB. Hypothalamic inflammation and the central nervous system control of energy homeostasis. *Mol Cell Endocrinol*. 2014;397(1–2):15–22.
80. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the “drifty gene” hypothesis. *Int J Obes (Lond)*. 2008;32(11):1611–7.
81. Myslobodsky M, Ingraham LJ. Managing the pandemic of obesity: siding with the fox or the hedgehog? *Obes Facts*. 2009;2(6):384–92.
82. Neel JV. Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? *Am J Hum Genet*. 1962;14:353–62.
83. Genné-Bacon EA. Thinking evolutionarily about obesity. *Yale J Biol Med*. 2014;87(2):99–112.
84. American Medical Association’s Council on Science and Public Health. American Medical Association’s Council on Science and Public Health report 420 (A-13). 2013. Available at: <https://www.npr.org/documents/2013/jun/ama-resolution-obesity.pdf>. Accessed March 19, 2019.
85. The Council on Science and Public Health. Report of the Council on Science and Public Health: CSAPH report 3-A-13. 2013. Available at: <https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/about-ama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf>. Accessed March 19, 2019.
86. Katz D. Obesity ... be damned!: what it will take to turn the tide. *Harvard Health Policy Rev*. 2006;7(2):135–51.
87. Rutter H. Where next for obesity? *Lancet*. 2011;378(9793):746–7.
88. National Center for Health Statistics. Table 53. Selected health conditions and risk factors, by age: United States, selected years 1988–1994 through 2015–2016. 2017. Available at: <https://www.cdc.gov/nchs/data/hus/2017/053.pdf>. Accessed March 19, 2019.
89. Newburgh LH, Johnston MW. The nature of obesity. *J Clin Invest*. 1930;8(2):197–213.
90. Swinburn BA. Obesity prevention: the role of policies, laws and regulations. *Aust New Zealand Health Policy*. 2008;5(12):1–7.
91. Brunstrom JM, Drake ACL, Forde CG, Rogers PJ. Undervalued and ignored: are humans poorly adapted to energy-dense foods? *Appetite*. 2018;120:589–95.
92. Gibson EL, Wardle J. Energy density predicts preferences for fruit and vegetables in 4-year-old children. *Appetite*. 2003;41(1):97–8.
93. Laska M, Hernandez Salazar LT, Luna ER. Food preferences and nutrient composition in captive spider monkeys, *Ateles geoffroyi*. *Int J Primatol*. 2000;21(4):671–3.
94. Brunstrom JM, Drake ACL, Forde CG, Rogers PJ. Undervalued and ignored: are humans poorly adapted to energy-dense foods? *Appetite*. 2018;120:589–95.
95. United States Department of Agriculture. USDA food composition databases. Available at: <https://ndb.nal.usda.gov/ndb>. Accessed March 19, 2019.

96. Novick J. Added oils: the elephant in the room. Dr. McDougall's Health & Medical Center. Published February 28, 2018. Available at: <https://us4.campaign-archive.com/?e=fa8b8ba4e0&u=5e58f59d97611f910916b6276&id=cc2c77335d>. Accessed March 19, 2019.
97. Inland J, Preuss HG, Marcus MT, Rourke KM, Taylor W, Theresa Wright H. Clearing the confusion around processed food addiction. *J Am Coll Nutr*. 2015;34(3):240-3.
98. Fortuna JL. The obesity epidemic and food addiction: clinical similarities to drug dependence. *J Psychoactive Drugs*. 2012;44(1):56-63.
99. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry*. 2011;68(8):808-16.
100. Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. *Am J Psychiatry*. 1999;156(1):11-8.
101. Schneider F, Habel U, Wagner M, et al. Subcortical correlates of craving in recently abstinent alcoholic patients. *Am J Psychiatry*. 2001;158(7):1075-83.
102. Schulte EM, Smeal JK, Gearhardt AN. Foods are differentially associated with subjective effect report questions of abuse liability. *PLoS ONE*. 2017;12(8):e0184220.
103. Altmann J, Schoeller D, Altmann S, Muruthi P, Sapolsky R. Body size and fatness of free-living baboons reflect food availability and activity levels. *Am J Primatol*. 1993;30(2):149-61.
104. Rubio-Ruiz ME, Peredo-Escárcega AE, Cano-Martínez A, Guarner-Lans V. An evolutionary perspective of nutrition and inflammation as mechanisms of cardiovascular disease. *Int J Evol Biol*. 2015;2015:179791.
105. Jenkins DJ, Jenkins AL, Kendall CW, Vuksan V, Vidgen E. The garden of Eden: implications for cardiovascular disease prevention. *Asia Pac J Clin Nutr*. 2000;9 Suppl 1:S1-3.
106. Regestein QR. The big, bad obesity pandemic. *Menopause*. 2018;25(2):129-32.
107. Aronne LJ. Treatment of obesity in the primary care setting. In: Wadden TA, Stunkard AJ, eds. *Handbook of Obesity Treatment*. New York: The Guilford Press; 2002:383-94.
108. Battle EK, Brownell KD. Confronting a rising tide of eating disorders and obesity: treatment vs. prevention and policy. *Addict Behav*. 1996;21(6):755-65.
109. Maffetone PB, Laursen PB. The prevalence of overfat adults and children in the US. *Front Public Health*. 2017;5:290.
110. National Center for Health Statistics. Table 53. Selected health conditions and risk factors, by age: United States, selected years 1988-1994 through 2015-2016. 2017. Available at: <https://www.cdc.gov/nchs/data/hestats/2017/053.pdf>. Accessed March 19, 2019.
111. Friedman JM. A war on obesity, not the obese. *Science*. 2003;299(5608):856-8.
112. Bouchard C, Tremblay A, Després JP, et al. The response to long-term overfeeding in identical twins. *N Engl J Med*. 1990;322(21):1477-82.
113. Bouchard C, Tremblay A, Després JP, et al. The response to exercise with constant energy intake in identical twins. *Obes Res*. 1994;2(5):400-10.
114. Campbell MK. Biological, environmental, and social influences on childhood obesity. *Pediatr Res*. 2016;79(1-2):205-11.
115. Brooks AA, Johnson MR, Steer PJ, Pawson ME, Abdalla HI. Birth weight: nature or nurture? *Early Hum Dev*. 1995;42(1):29-35.
116. Waterland RA. Epigenetic mechanisms affecting regulation of energy balance: many questions, few answers. *Annu Rev Nutr*. 2014;34:337-55.
117. Smith J, Cianflone K, Biron S, et al. Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J Clin Endocrinol Metab*. 2009;94(11):4275-83.
118. McAllister EJ, Dhurandhar NV, Keith SW, et al. Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr*. 2009;49(10):868-913.
119. Waterland RA. Epigenetic mechanisms affecting regulation of energy balance: many questions, few answers. *Annu Rev Nutr*. 2014;34:337-55.
120. McAllister EJ, Dhurandhar NV, Keith SW, et al. Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr*. 2009;49(10):868-913.
121. Finch CE, Loehlin JC. Environmental influences that may precede fertilization: a first examination of the prezygotic hypothesis from maternal age influences on twins. *Behav Genet*. 1998;28(2):101-6.
122. Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obes (Lond)*. 2006;30(11):1585-94.
123. Katzmarzyk PT, Barlow S, Bouchard C, et al. An evolving scientific basis for the prevention and treatment of pediatric obesity. *Int J Obes (Lond)*. 2014;38(7):887-905.
124. Smith J, Cianflone K, Biron S, et al. Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J Clin Endocrinol Metab*. 2009;94(11):4275-83.
125. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
126. Vandevijvere S, Chow CC, Hall KD, Umali E, Swinburn BA. Increased food energy supply as a major driver of the obesity epidemic: a global analysis. *Bull World Health Organ*. 2015;93(7):446-56.
127. Bleich S, Cutler D, Murray C, Adams A. Why is the developed world obese? *Annu Rev Public Health*. 2008;29:273-95.
128. Gerrior S, Bente L, Hiza H. Nutrient content of the U.S. food supply, 1909-2000. *Home Economics Research Report No. 56*. United States Department of Agriculture, Center for Nutrition Policy and Promotion. Published November 2004. Available at: https://www.cnpp.usda.gov/sites/default/files/nutrient_content_of_the_us_food_supply/FoodSupply1909-2000.pdf. Accessed March 19, 2019.
129. Gerrior S, Bente L, Hiza H. Nutrient content of the U.S. food supply, 1909-2000. *Home Economics Research Report No. 56*. United States Department of Agriculture, Center for Nutrition Policy and Promotion. Published November 2004. Available at: https://www.cnpp.usda.gov/sites/default/files/nutrient_content_of_the_us_food_supply/FoodSupply1909-2000.pdf. Accessed March 19, 2019.

130. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-14.
131. Cutler D, Glaeser E, Shapiro J. Why have Americans become more obese? *J Econ Perspect*. 2003;17(3):93-118.
132. Cutler D, Glaeser E, Shapiro J. Why have Americans become more obese? *J Econ Perspect*. 2003;17(3):93-118.
133. Moodie R, Stuckler D, Monteiro C, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. 2013;381(9867):670-9.
134. Scrinis G. Big Food corporations and the nutritional marketing and regulation of processed foods. *Canadian Food Studies*. 2015;2(2):136-45.
135. Cutler D, Glaeser E, Shapiro J. Why have Americans become more obese? *J Econ Perspect*. 2003;17(3):93-118.
136. Cutler D, Glaeser E, Shapiro J. Why have Americans become more obese? *J Econ Perspect*. 2003;17(3):93-118.
137. Cutler D, Glaeser E, Shapiro J. Why have Americans become more obese? *J Econ Perspect*. 2003;17(3):93-118.
138. Perry CL, Creamer MR. The childhood obesity epidemic: lessons learned from tobacco. *J Pediatr*. 2014;164(1):178-85.
139. Centers for Disease Control and Prevention. Tobacco use—United States, 1900-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48(43):986-93.
140. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
141. Siegel KR, McKeever Bullard K, Imperatore G, et al. Association of higher consumption of foods derived from subsidized commodities with adverse cardiometabolic risk among US adults. *JAMA Intern Med*. 2016;176(8):1124-32.
142. Franck C, Grandi SM, Eisenberg MJ. Agricultural subsidies and the American obesity epidemic. *Am J Prev Med*. 2013;45(3):327-33.
143. Siegel KR, McKeever Bullard K, Imperatore G, et al. Association of higher consumption of foods derived from subsidized commodities with adverse cardiometabolic risk among US adults. *JAMA Intern Med*. 2016;176(8):1124-32.
144. Popkin BM. Contemporary nutritional transition: determinants of diet and its impact on body composition. *Proc Nutr Soc*. 2011;70(1):82-91.
145. Nestle M. Utopian dream: a new farm bill. *Dissent*. 2012;59(2):15-9.
146. Popkin BM. Agricultural policies, food and public health. *EMBO Rep*. 2011;12(1):11-8.
147. Popkin BM. Contemporary nutritional transition: determinants of diet and its impact on body composition. *Proc Nutr Soc*. 2011;70(1):82-91.
148. Franck C, Grandi SM, Eisenberg MJ. Agricultural subsidies and the American obesity epidemic. *Am J Prev Med*. 2013;45(3):327-33.
149. Harvie A, Wise TA. Sweetening the pot: implicit subsidies to corn sweeteners and the US obesity epidemic. Global Development and Environment Institute. Published February 2009. Available at: <http://www.ase.tufts.edu/gdae/Pubs/rp/PB09-01SweeteningPotFeb09.pdf>. Accessed March 19, 2019.
150. Wise TA, Starmer E. Industrial livestock companies' gains from low feed prices, 1997-2005. Global Development and Environment Institute. Published February 2007. Available at: <http://www.ase.tufts.edu/gdae/Pubs/rp/CompanyFeedSvgsFeb07.pdf>. Accessed March 19, 2019.
151. Putnam J, Allshouse J, Kantor LS. U.S. per capita food supply trends: more calories, refined carbohydrates, and fats. *FoodReview*. 2002;25(3):2-15.
152. King DE, Mainous AG, Carnemolla M, Everett CJ. Adherence to healthy lifestyle habits in US adults, 1988-2006. *Am J Med*. 2009;122(6):528-34.
153. Winson A. Bringing political economy into the debate on the obesity epidemic. *Agric Human Values*. 2004;21(4):299-312.
154. Winson A. Bringing political economy into the debate on the obesity epidemic. *Agric Human Values*. 2004;21(4):299-312.
155. Siegel KR, McKeever Bullard K, Imperatore G, et al. Association of higher consumption of foods derived from subsidized commodities with adverse cardiometabolic risk among US adults. *JAMA Intern Med*. 2016;176(8):1124-32.
156. Putnam J, Allshouse J, Kantor LS. U.S. per capita food supply trends: more calories, refined carbohydrates, and fats. *FoodReview*. 2002;25(3):2-15.
157. Putnam J, Allshouse J, Kantor LS. U.S. per capita food supply trends: more calories, refined carbohydrates, and fats. *FoodReview*. 2002;25(3):2-15.
158. Gerritor S, Bente L, Hiza H. Nutrient content of the U.S. food supply, 1909-2000. *Home Economics Research Report No. 56*. United States Department of Agriculture, Center for Nutrition Policy and Promotion. Published November 2004. Available at: https://www.cnpp.usda.gov/sites/default/files/nutrient_content_of_the_us_food_supply/FoodSupply1909-2000.pdf. Accessed March 19, 2019.
159. Rehkamp S. A look at calorie sources in the American diet. Economic Research Service, United States Department of Agriculture. Published December 5, 2016. Available at: <https://www.ers.usda.gov/amber-waves/2016/december/a-look-at-calorie-sources-in-the-american-diet>. Accessed March 31, 2019.
160. Nestle M. Utopian dream: a new farm bill. *Dissent*. 2012;59(2):15-9.
161. Morris B. Tearing up the Jack Welch playbook. *Fortune*. Published July 14, 2006. Available at: https://money.cnn.com/sales/executive_resource_center/articles2/rules.fortune/index.htm. Accessed March 19, 2019.
162. Nestle M. Interview with Marion Nestle. *Health Promot Pract*. 2008;9(1):16-8.
163. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
164. Consumers Union. Out of balance: marketing of soda, candy, snacks and fast foods drowns out healthful messages. California Pan-Ethnic Health Network. Published September 2005. Available at: https://cpehn.org/sites/default/files/resource_files/outofbalance.pdf. Accessed May 4, 2019.
165. Vranica S. McDonald's to review its \$2 billion global media buying account. *Wall Street Journal*. Published October 26, 2017. Available at: <https://www.wsj.com/articles/mcdonalds-to-review-its-2-billion-global-media-buying-account-1509036600>. Accessed March 19, 2019.
166. Winson A. Bringing political economy into the debate on the obesity epidemic. *Agric Human Values*. 2004;21(4):299-312.

167. Nestle M. Utopian dream: a new farm bill. *Dissent*. 2012;59(2):15-9.
168. Horgen KB, Brownell KD. Confronting the toxic environment: environmental, public health actions in a world crisis. In: Wadden TA, Stunkard AJ, eds. *Handbook of Obesity Treatment*. New York: The Guilford Press; 2002:95-106.
169. Lapierre MA, Fleming-Milici F, Rozendaal E, McAlister AR, Castonguay J. The effect of advertising on children and adolescents. *Pediatrics*. 2017;140(Suppl 2):S152-6.
170. Harris JL, Pomeranz JL, Lobstein T, Brownell KD. A crisis in the marketplace: how food marketing contributes to childhood obesity and what can be done. *Annu Rev Public Health*. 2009;30:211-25.
171. Harris JL, Pomeranz JL, Lobstein T, Brownell KD. A crisis in the marketplace: how food marketing contributes to childhood obesity and what can be done. *Annu Rev Public Health*. 2009;30:211-25.
172. James P. All-of-government approach needed to tackle obesity. Interview by Fiona Fleck. *Bull World Health Organ*. 2013;91(8):551-2.
173. Bond ME, Crammond BR, Loff B. It's not about choice: the supermarket and obesity. *Med J Aust*. 2012;197(7):371.
174. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
175. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
176. Katz D. Obesity ... be dammed!: what it will take to turn the tide. *Harvard Health Policy Rev*. 2006;7(2):135-51.
177. Institute of Medicine. Food marketing to children and youth: threat or opportunity? National Academies Press. 2006. Available at: <https://www.nap.edu/catalog/11514/food-marketing-to-children-and-youth-threat-or-opportunity>. Accessed on March 19, 2019.
178. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
179. Nestle M, Jacobson MF. Halting the obesity epidemic: a public health policy approach. *Public Health Rep*. 2000;115(1):12-24.
180. Fersht A. The most influential journals: Impact Factor and Eigenfactor. *Proc Natl Acad Sci USA*. 2009;106(17):6883-4.
181. North AC, Hargreaves DJ, McKendrick J. In-store music affects product choice. *Nature*. 1997;390(132):132.
182. North AC, Hargreaves DJ, McKendrick J. In-store music affects product choice. *Nature*. 1997;390(132):132.
183. Nestle M, Jacobson MF. Halting the obesity epidemic: a public health policy approach. *Public Health Rep*. 2000;115(1):12-24.
184. Stanton RA. Food retailers and obesity. *Curr Obes Rep*. 2015;4(1):54-9.
185. Muris TJ, Thompson MW, Swindle O, Leary TB, Jones HP. Slotting allowances in the retail grocery industry: select case studies in five product categories. Federal Trade Commission. Published November 2003. Available at: <https://www.ftc.gov/sites/default/files/documents/reports/use-slotting-allowances-retail-grocery-industry/slottingallowancerpt031114.pdf>. Accessed on March 21, 2019.
186. Collier R. Call to reduce junk food at checkouts. *CMAJ*. 2015;187(1):E14.
187. Cohen DA, Lesser LI. Obesity prevention at the point of purchase. *Obes Rev*. 2016;17(5):389-96.
188. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
189. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
190. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
191. Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. *Psychol Rev*. 1956;63(2):81-97.
192. Shiv B, Fedorikhin A. Heart and mind in conflict: the interplay of affect and cognition in consumer decision-making. *J Consum Res*. 1999;26(3):278-92.
193. Zimmerman FJ, Shimoga SV. The effects of food advertising and cognitive load on food choices. *BMC Public Health*. 2014;14:342.
194. Zimmerman FJ, Shimoga SV. The effects of food advertising and cognitive load on food choices. *BMC Public Health*. 2014;14:342.
195. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
196. Nestle M. Utopian dream: a new farm bill. *Dissent*. 2012;59(2):15-9.
197. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
198. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-14.
199. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
200. Williams KJ, Wu X. Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward. *Atherosclerosis*. 2016;247:225-82.
201. Poti JM, Duffey KJ, Popkin BM. The association of fast food consumption with poor dietary outcomes and obesity among children: is it the fast food or the remainder of the diet? *Am J Clin Nutr*. 2014;99(1):162-71.
202. Alh riti re A, Montois S, Galinski M, Tazarourte K, Lapostolle F. Worldwide relation between the number of McDonald's restaurants and the prevalence of obesity. *J Intern Med*. 2013;274(6):610-1.
203. Poti JM, Duffey KJ, Popkin BM. The association of fast food consumption with poor dietary outcomes and obesity among children: is it the fast food or the remainder of the diet? *Am J Clin Nutr*. 2014;99(1):162-71.
204. Young LR, Nestle M. Portion sizes and obesity: responses of fast-food companies. *J Public Health Policy*. 2007;28(2):238-48.
205. Rolls BJ. The supersizing of America: portion size and the obesity epidemic. *Nutr Today*. 2003;38(2):42-53.
206. Young LR, Nestle M. Expanding portion sizes in the US marketplace: implications for nutrition counseling. *J Am Diet Assoc*. 2003;103(2):231-4.

207. Rolls BJ. The supersizing of America: portion size and the obesity epidemic. *Nutr Today*. 2003;38(2):42-53.
208. Rolls BJ. The supersizing of America: portion size and the obesity epidemic. *Nutr Today*. 2003;38(2):42-53.
209. Herman CP, Polivy J, Vartanian LR, Pliner P. Are large portions responsible for the obesity epidemic? *Physiol Behav*. 2016;156:177-81.
210. Livingstone MB, Pourshahidi LK. Portion size and obesity. *Adv Nutr*. 2014;5(6):829-34.
211. Almiron-Roig E, Tsiountsioura M, Lewis HB, Wu J, Solis-Trapala I, Jebb SA. Large portion sizes increase bite size and eating rate in overweight women. *Physiol Behav*. 2015;139:297-302.
212. Rolls BJ, Roe LS, Meengs JS. The effect of large portion sizes on energy intake is sustained for 11 days. *Obesity (Silver Spring)*. 2007;15(6):1535-43.
213. van Kleef E, Bruggers I, de Vet E. Encouraging vegetable intake as a snack among children: the influence of portion and unit size. *Public Health Nutr*. 2015;18(15):2736-41.
214. Rolls BJ. What is the role of portion control in weight management? *Int J Obes (Lond)*. 2014;38 Suppl 1:S1-8.
215. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
216. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. *Diabetes*. 2008;57(7):1768-73.
217. Taillie LS, Ng SW, Popkin BM. Global growth of "big box" stores and the potential impact on human health and nutrition. *Nutr Rev*. 2016;74(2):83-97.
218. Nestle M. Counting the cost of calories. Interview by Ben Jones. *Bull World Health Organ*. 2012;90(8):566-7.
219. Duffey KJ, Popkin BM. Energy density, portion size, and eating occasions: contributions to increased energy intake in the United States, 1977-2006. *PLoS Med*. 2011;8(6):e1001050.
220. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
221. Ludwig DS. Childhood obesity—the shape of things to come. *N Engl J Med*. 2007;357(23):2325-7.
222. Bonnet J, George A, Evans P, Silberberg M, Dolinsky D. Rethinking obesity counseling: having the French Fry Discussion. *J Obes*. 2014;2014:525021.
223. Grummer-Strawn LM, Scanlon KS, Fein SB. Infant feeding and feeding transitions during the first year of life. *Pediatrics*. 2008;122 Suppl 2:S36-42.
224. Katz D. Obesity ... be damned!: what it will take to turn the tide. *Harvard Health Policy Rev*. 2006;7(2):135-51.
225. Perry CL, Creamer MR. The childhood obesity epidemic: lessons learned from tobacco. *J Pediatr*. 2014;164(1):178-85.
226. McCrory MA, Suen VM, Roberts SB. Biobehavioral influences on energy intake and adult weight gain. *J Nutr*. 2002;132(12):3830S-4S.
227. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
228. McCrory MA, Suen VM, Roberts SB. Biobehavioral influences on energy intake and adult weight gain. *J Nutr*. 2002;132(12):3830S-4S.
229. Scrinis G. Big Food corporations and the nutritional marketing and regulation of processed foods. *Canadian Food Studies*. 2015;2(2):136-45.
230. Sacks G, Swinburn BA, Cameron AJ, Ruskin G. How food companies influence evidence and opinion—straight from the horse's mouth. *Crit Public Health*. 2018;28(2):253-6.
231. Moodie R, Stuckler D, Monteiro C, et al. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. 2013;381(9867):670-9.
232. Lobbying spending database food & beverage, 2009. Center for Responsive Politics. Available at: <http://www.opensecrets.org/lobby/indusclient.php?id=n01&year=2009>. Accessed March 22, 2019.
233. *Citizens United v. Federal Election Commission*. 130 S.Ct. 876 08-205 (Roberts Court 2010).
234. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-14.
235. Steier G. Dead people don't eat: food governmentenomics and conflicts-of-interest in the USDA and FDA. *J Environ Public Health*. 2012;7(1):1-77.
236. Brownell KD. Thinking forward: the quicksand of appeasing the food industry. *PLoS Med*. 2012;9(7):e1001254.
237. Swinburn B, Vandevijvere S. WHO report on ending childhood obesity echoes earlier recommendations. *Public Health Nutr*. 2016;19(1):1-2.
238. Liggett & Myers Tobacco Company Campaign: Doctor ordered. Tobacco.Stanford.edu. Available at: <https://stanford.io/2BfDHPx>. Accessed March 21, 2019.
239. Kirk SF, Penney TL, Freedhoff Y. Running away with the facts on food and fatness. *Public Health Nutr*. 2010;13(1):147-8.
240. Our mission. HealthyChildren.org. Published 2009. Available at: <https://web.archive.org/web/20120310054653/http://www.healthychildren.org:80/english/our-mission/sponsors/pages/default.aspx>. Accessed March 21, 2019.
241. Murray JL. Coke and the AAFP—the real thing or a dangerous liaison? *Fam Med*. 2010;42(1):57-8.
242. Yanamadala S, Bragg MA, Roberto CA, Brownell KD. Food industry front groups and conflicts of interest: the case of Americans against food taxes. *Public Health Nutr*. 2012;15(8):1331-2.
243. About. Americans for Food and Beverage Choice. Available at: <https://www.yourcartyourchoice.com/about-us>. Accessed March 21, 2019.
244. Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. *J Health Polit Policy Law*. 1996;21(3):515-42.
245. Mialon M, Mialon J. Corporate political activity of the dairy industry in France: an analysis of publicly available information. *Public Health Nutr*. 2017;20(13):2432-9.
246. Perry CL, Creamer MR. The childhood obesity epidemic: lessons learned from tobacco. *J Pediatr*. 2014;164(1):178-85.
247. Schleifer D. We spent a million bucks and then we had to do something: the unexpected implications of industry involvement in trans fat research. *Bull Sci Technol Soc*. 2011;31(6):460-71.
248. Perry CL, Creamer MR. The childhood obesity epidemic: lessons learned from tobacco. *J Pediatr*. 2014;164(1):178-85.

249. Schleifer D. We spent a million bucks and then we had to do something: the unexpected implications of industry involvement in trans fat research. *Bull Sci Technol Soc*. 2011;31(6):460-71.
250. Beaglehole R, Bonita R, Horton R, et al. Priority actions for the non-communicable disease crisis. *Lancet*. 2011;377(9775):1438-47.
251. Chan M. WHO Director-General addresses health promotion conference. World Health Organization. Published June 10, 2013. Available at: https://www.who.int/dg/speeches/2013/health_promotion_20130610/en. Accessed March 21, 2019.
252. Chan M. Obesity and diabetes: the slow-motion disaster. *Milbank Q*. 2017;95(1):11-4.
253. Chan M. Obesity and diabetes: the slow-motion disaster. Keynote address at the 47th meeting of the National Academy of Medicine. World Health Organization. Published October 17, 2016. Available at: <https://www.who.int/dg/speeches/2016/obesity-diabetes-disaster/en>. Accessed March 21, 2019.
254. Ortiz SE, Zimmerman FJ, Gilliam FD. Weighing in: the taste-engineering frame in obesity expert discourse. *Am J Public Health*. 2015;105(3):554-9.
255. Zimmerman FJ. Using marketing muscle to sell fat: the rise of obesity in the modern economy. *Annu Rev Public Health*. 2011;32:285-306.
256. Brownell KD, Warner KE. The perils of ignoring history: Big Tobacco played dirty and millions died. How similar is Big Food? *Milbank Q*. 2009;87(1):259-94.
257. Lifshitz F, Lifshitz JZ. Globesity: the root causes of the obesity epidemic in the USA and now worldwide. *Pediatr Endocrinol Rev*. 2014;12(1):17-34.
258. Ortiz SE, Zimmerman FJ, Gilliam FD. Weighing in: the taste-engineering frame in obesity expert discourse. *Am J Public Health*. 2015;105(3):554-9.
259. Hall KD, Guo J, Dore M, Chow CC. The progressive increase of food waste in America and its environmental impact. *PLoS ONE*. 2009;4(11):e7940.
260. Hastings G. Why corporate power is a public health priority. *BMJ*. 2012;345:e5124.
261. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-14.
262. Nestle M. The ironic politics of obesity. *Science*. 2003;299(5608):781.
263. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27.
264. Liu Y, Hazlewood GS, Kaplan GG, Eksteen B, Barnabe C. Impact of obesity on remission and disease activity in rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2017;69(2):157-65.
265. Aune D, Norat T, Vatten LJ. Body mass index and the risk of gout: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Nutr*. 2014;53(8):1591-601.
266. Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology (Oxford)*. 2015;54(4):588-600.
267. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22-8.
268. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22-8.
269. Baudart P, Louati K, Marcelli C, Berenbaum F, Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. *RMD Open*. 2017;3(2):e000442.
270. Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology (Oxford)*. 2015;54(4):588-600.
271. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. Framingham Study. *Ann Intern Med*. 1992;116(7):535-9.
272. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthr Cartil*. 2005;13(1):20-7.
273. Bernstein J. Not the last word: safety alert: one in 200 knee replacement patients die within 90 days of surgery. *Clin Orthop Relat Res*. 2017;475(2):318-23.
274. Bernstein J. Not the last word: safety alert: one in 200 knee replacement patients die within 90 days of surgery. *Clin Orthop Relat Res*. 2017;475(2):318-23.
275. Bernstein J. Not the last word: safety alert: one in 200 knee replacement patients die within 90 days of surgery. *Clin Orthop Relat Res*. 2017;475(2):318-23.
276. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. 2010;468(1):57-63.
277. Zhang TT, Liu Z, Liu YL, Zhao JJ, Liu DW, Tian QB. Obesity as a risk factor for low back pain: a meta-analysis. *Clin Spine Surg*. 2018;31(1):22-7.
278. Shiri R, Lallukka T, Karppinen J, Viikari-Juntura E. Obesity as a risk factor for sciatica: a meta-analysis. *Am J Epidemiol*. 2014;179(8):929-37.
279. Xu X, Li X, Wu W. Association between overweight or obesity and lumbar disk diseases. *J Spinal Disord Tech*. 2015;28(10):370-6.
280. Shiri R, Lallukka T, Karppinen J, Viikari-Juntura E. Obesity as a risk factor for sciatica: a meta-analysis. *Am J Epidemiol*. 2014;179(8):929-37.
281. Xu X, Li X, Wu W. Association between overweight or obesity and lumbar disk diseases. *J Spinal Disord Tech*. 2015;28(10):370-6.
282. Kauppila LI. Atherosclerosis and disc degeneration/low-back pain—a systematic review. *Eur J Vasc Endovasc Surg*. 2009;37(6):661-70.
283. Naumnik B, Myśliwiec M. Renal consequences of obesity. *Med Sci Monit*. 2010;16(8):RA163-70.
284. Arena R, Daugherty J, Bond S, Lavie CJ, Phillips S, Borghi-Silva A. The combination of obesity and hypertension: a highly unfavorable phenotype requiring attention. *Curr Opin Cardiol*. 2016;31(4):394-401.
285. Poorolajal J, Hooshmand E, Bahrami M, Ameri P. How much excess weight loss can reduce the risk of hypertension? *J Public Health (Oxf)*. 2017;39(3):e95-102.

286. Jackson SL, King SM, Zhao L, Cogswell ME. Prevalence of excess sodium intake in the United States—NHANES, 2009–2012. *MMWR Morb Mortal Wkly Rep.* 2016;64(52):1393–7.
287. He FJ, Li J, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev.* 2013;(4):CD004937.
288. Semlitsch T, Jeitler K, Berghold A, et al. Long-term effects of weight-reducing diets in people with hypertension. *Cochrane Database Syst Rev.* 2016;3:CD008274.
289. Gulland A. Three in four are unaware of obesity link to cancer, says charity. *BMJ.* 2016;354:i4898.
290. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer—viewpoint of the IARC working group. *N Engl J Med.* 2016;375(8):794–8.
291. Kolb R, Sutterwala FS, Zhang W. Obesity and cancer: inflammation bridges the two. *Curr Opin Pharmacol.* 2016;29:77–89.
292. Poloz Y, Stambolic V. Obesity and cancer, a case for insulin signaling. *Cell Death Dis.* 2015;6:e2037.
293. O'Rourke RW. Obesity and cancer: at the crossroads of cellular metabolism and proliferation. *Surg Obes Relat Dis.* 2014;10(6):1208–19.
294. Cleland WH, Mendelson CR, Simpson ER. Effects of aging and obesity on aromatase activity of human adipose cells. *J Clin Endocrinol Metab.* 1985;60(1):174–7.
295. Cauley JA, Gutai JP, Kuller LH, Ledonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol.* 1989;129(6):1120–31.
296. Goodwin PJ, Stambolic V. Impact of the obesity epidemic on cancer. *Annu Rev Med.* 2015;66:281–96.
297. Carpenter CL, Duvall K, Jardack P, et al. Weight loss reduces breast ductal fluid estrogens in obese postmenopausal women: a single arm intervention pilot study. *Nutr J.* 2012;11:102.
298. Zhang X, Zhou G, Sun B, et al. Impact of obesity upon prostate cancer-associated mortality: a meta-analysis of 17 cohort studies. *Oncol Lett.* 2015;9(3):1307–12.
299. Barnes KT, McDowell BD, Button A, Smith BJ, Lynch CF, Gupta A. Obesity is associated with increased risk of invasive penile cancer. *BMC Urol.* 2016;16(1):42.
300. Sjöström L, Gummesson A, Sjöström CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol.* 2009;10(7):653–62.
301. Tao W, Konings P, Hull MA, Adami HO, Mattsson F, Lagergren J. Colorectal cancer prognosis following obesity surgery in a population-based cohort study. *Obes Surg.* 2017;27(5):1233–9.
302. Tao W, Konings P, Hull MA, Adami HO, Mattsson F, Lagergren J. Colorectal cancer prognosis following obesity surgery in a population-based cohort study. *Obes Surg.* 2017;27(5):1233–9.
303. Kant P, Sainsbury A, Reed KR, et al. Rectal epithelial cell mitosis and expression of macrophage migration inhibitory factor are increased 3 years after Roux-en-Y gastric bypass (RYGB) for morbid obesity: implications for long-term neoplastic risk following RYGB. *Gut.* 2011;60(7):893–901.
304. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. *Diabet Med.* 2007;24(5):451–63.
305. Centers for Disease Control and Prevention. About diabetes. CDC.gov. Published June 1, 2017. Available at: <https://www.cdc.gov/diabetes/basics/diabetes.html>. Accessed March 22, 2019.
306. Lau DC, Teoh H. Impact of current and emerging glucose-lowering drugs on body weight in type 2 diabetes. *Can J Diabetes.* 2015;39 Suppl 5:S148–54.
307. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. *Age Ageing.* 2016;45(1):14–21.
308. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring).* 2013;21(1):E51–5.
309. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev.* 2018;84:225–44.
310. McCrady-Spitzer SK, Levine JA. Nonexercise activity thermogenesis: a way forward to treat the worldwide obesity epidemic. *Surg Obes Relat Dis.* 2012;8(5):501–6.
311. Willette AA, Kapogiannis D. Does the brain shrink as the waist expands? *Ageing Res Rev.* 2015;20:86–97.
312. Walthers K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp.* 2010;31(7):1052–64.
313. Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. *Obes Rev.* 2015;16(4):273–81.
314. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev.* 2018;84:225–44.
315. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2017;72:87–94.
316. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2017;72:87–94.
317. Best D, Avenell A, Bhattacharya S. How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. *Hum Reprod Update.* 2017;23(6):681–705.
318. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update.* 2013;19(3):221–31.
319. Davidson LM, Millar K, Jones C, Fatum M, Coward K. Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. *Hum Fertil (Camb).* 2015;18(3):184–93.
320. Eriksson J, Haring R, Grarup N, et al. Causal relationship between obesity and serum testosterone status in men: a bi-directional Mendelian randomization analysis. *PLoS ONE.* 2017;12(4):e0176277.
321. Cavayero CT, Cooper MA, Harlin SL. Adult-acquired hidden penis in obese patients: a critical survey of the literature. *J Am Osteopath Assoc.* 2015;115(3):150–6.
322. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. *Lancet.* 2006;368(9531):230–9.

323. Alexander HC, Bartlett AS, Wells CI, et al. Reporting of complications after laparoscopic cholecystectomy: a systematic review. *HPB (Oxford)*. 2018;20(9):786-94.
324. Pucher PH, Brunt LM, Davies N, et al. Outcome trends and safety measures after 30 years of laparoscopic cholecystectomy: a systematic review and pooled data analysis. *Surg Endosc*. 2018;32(5):2175-83.
325. Isherwood J, Oakland K, Khanna A. A systematic review of the aetiology and management of post cholecystectomy syndrome. *Surgeon*. 2019;17(1):33-42.
326. Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. *Lancet*. 2006;368(9531):230-9.
327. Pradhan SB, Joshi MR, Vaidya A. Prevalence of different types of gallstone in the patients with cholelithiasis at Kathmandu Medical College, Nepal. *Kathmandu Univ Med J (KUMJ)*. 2009;7(27):268-71.
328. McConnell TJ, Appleby PN, Key TJ. Vegetarian diet as a risk factor for symptomatic gallstone disease. *Eur J Clin Nutr*. 2017;71(6):731-5.
329. Chang CM, Chiu THT, Chang CC, Lin MN, Lin CL. Plant-based diet, cholesterol, and risk of gallstone disease: a prospective study. *Nutrients*. 2019;11(2):335.
330. Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Elevated body mass index as a causal risk factor for symptomatic gallstone disease: a Mendelian randomization study. *Hepatology*. 2013;58(6):2133-41.
331. Cruz-Monserrate Z, Conwell DL, Krishna SG. The impact of obesity on gallstone disease, acute pancreatitis, and pancreatic cancer. *Gastroenterol Clin North Am*. 2016;45(4):625-37.
332. Stampfer MJ, Maclure KM, Colditz GA, Manson JE, Willett WC. Risk of symptomatic gallstones in women with severe obesity. *Am J Clin Nutr*. 1992;55(3):652-8.
333. Weinsier RL, Wilson LJ, Lee J. Medically safe rate of weight loss for the treatment of obesity: a guideline based on risk of gallstone formation. *Am J Med*. 1995;98(2):115-7.
334. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Long-term intake of dietary fiber and decreased risk of cholecystectomy in women. *Am J Gastroenterol*. 2004;99(7):1364-70.
335. Sulaberidze G, Okujava M, Liliashvili K, Tughushi M, Bezarashvili S. Dietary fiber's benefit for gallstone disease prevention during rapid weight loss in obese patients. *Georgian Med News*. 2014;(231):95-9.
336. Hampel H, Abraham N, El-Serag H. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med*. 2005;143(3):199-211.
337. Giri A, Hartmann KE, Hellwege JN, Velez Edwards DR, Edwards TL. Obesity and pelvic organ prolapse: a systematic review and meta-analysis of observational studies. *Am J Obstet Gynecol*. 2017;217(1):11-26.e3.
338. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27.
339. Hägg S, Fall T, Ploner A, et al. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. *Int J Epidemiol*. 2015;44(2):578-86.
340. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273(3):219-34.
341. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273(3):219-34.
342. Jahn J, Spielau M, Brandsch C, et al. Decreased NK cell functions in obesity can be reactivated by fat mass reduction. *Obesity (Silver Spring)*. 2015;23(11):2233-41.
343. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev*. 2011;17:6-63.
344. Mokry LE, Ross S, Timpson NJ, Sawcer S, Davey Smith G, Richards JB. Obesity and multiple sclerosis: a Mendelian randomization study. *PLoS Med*. 2016;13(6):e1002053.
345. Chen S, Akbar SM, Miyake T, et al. Diminished immune response to vaccinations in obesity: role of myeloid-derived suppressor and other myeloid cells. *Obes Res Clin Pract*. 2015;9(1):35-44.
346. Gallacher J, McPherson S. Practical diagnosis and staging of nonalcoholic fatty liver disease: a narrative review. *EMJ*. 2018;3(2):108-18.
347. Gallacher J, McPherson S. Practical diagnosis and staging of nonalcoholic fatty liver disease: a narrative review. *EMJ*. 2018;3(2):108-18.
348. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology*. 2012;142(7):1592-609.
349. Calzadilla Bertot L, Adams LA. The natural course of non-alcoholic fatty liver disease. *Int J Mol Sci*. 2016;17(5):774.
350. Nouredin M, Vipani A, Bresee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol*. 2018;113(11):1649-59.
351. Kovesdy CP, Furth SL, Zoccali C. Obesity and kidney disease: hidden consequences of the epidemic. *Am J Nephrol*. 2017;45:283-91.
352. Forno E, Han YY, Mullen J, Celedón JC. Overweight, obesity, and lung function in children and adults—a meta-analysis. *J Allergy Clin Immunol Pract*. 2018;6(2):570-81.e10.
353. Zafar U, Khaliq S, Ahmad HU, Manzoor S, Lone KP. Metabolic syndrome: an update on diagnostic criteria, pathogenesis, and genetic links. *Hormones (Athens)*. 2018;17(3):299-313.
354. Hogerzeil DP, Hartholt KA, de Vries MR. Xiphoidectomy: a surgical intervention for an underdocumented disorder. *Case Rep Surg*. 2016;2016:9306262.
355. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. *Value Health*. 2016;19(5):602-13.
356. Thompson D, Edelsberg J, Colditz GA, Bird AP, Oster G. Lifetime health and economic consequences of obesity. *Arch Intern Med*. 1999;159(18):2177-83.
357. Bhattacharya J, Bundorf MK. The incidence of the healthcare costs of obesity. *J Health Econ*. 2009;28(3):649-58.
358. Hamilton D, Dee A, Perry IJ. The lifetime costs of overweight and obesity in childhood and adolescence: a systematic review. *Obes Rev*. 2018;19(4):452-63.
359. Kim DD, Basu A. Estimating the medical care costs of obesity in the United States: systematic review, meta-analysis, and empirical analysis. *Value Health*. 2016;19(5):602-13.

360. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378(9793):815-25.
361. Waters H, DeVol R. Weighing down America: the health and economic impact of obesity. Milken Institute. Published November 2016. Available at: <https://assets1b.milkeninstitute.org/assets/publication/researchreport/pdf/weighing-down-america-web.pdf>. Accessed March 21, 2019.
362. Under Secretary of Defense (Comptroller), Chief Financial Officer. Defense Budget Overview. United States Department of Defense. Published May 12, 2017. Available at: https://comptroller.defense.gov/portals/45/documents/defbudget/fy2018/fy2018_budget_request_overview_book.pdf. Accessed March 22, 2019.
363. van Baal PH, Polder JJ, de Wit GA, et al. Lifetime medical costs of obesity: prevention no cure for increasing health expenditure. *PLoS Med*. 2008;5(2):e29.
364. King, ML Jr. *Stride Toward Freedom: The Montgomery Story*. New York: Harper; 1958.
365. Mathers JC. Obesity and mortality: is childhood obesity shortening life expectancy? *Maturitas*. 2015;81(1):1-2.
366. Ludwig DS. Lifespan weighed down by diet. *JAMA*. 2016;315(21):2269-70.
367. Mathers JC. Obesity and mortality: is childhood obesity shortening life expectancy? *Maturitas*. 2015;81(1):1-2.
368. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352(11):1138-45.
369. Ludwig DS. Lifespan weighed down by diet. *JAMA*. 2016;315(21):2269-70.
370. Mann CC. Public health. Provocative study says obesity may reduce U.S. life expectancy. *Science*. 2005;307(5716):1716-7.
371. Tobias DK, Hu FB. Does being overweight really reduce mortality? *Obesity (Silver Spring)*. 2013;21(9):1746-9.
372. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011-2014. *Vital Health Stat 3*. 2016;(39):1-46.
373. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82.
374. National Health Service. Overweight people "live longer" study claims. NHS.uk. Published January 2, 2013. Available at: <https://www.nhs.uk/news/obesity/overweight-people-live-longer-study-claims>. Accessed March 21, 2019.
375. Beck M. A few extra pounds won't kill you—really. *Wall Street Journal*. Published January 1, 2013. Available at: <https://www.wsj.com/articles/SB10001424127887323635504578215801377387088>. Accessed March 21, 2019.
376. Aubrey A. Research: a little extra fat may help you live longer. National Public Radio. Published January 2, 2013. Available at: <https://www.npr.org/sections/health-shots/2013/01/02/168437030/research-a-little-extra-fat-may-help-you-live-longer>. Accessed March 21, 2019.
377. Hughes V. The big fat truth. *Nature*. Published May 22, 2013. Available at: <https://www.nature.com/news/the-big-fat-truth-1.13039>. Accessed March 21, 2019.
378. Aubrey A. Research: a little extra fat may help you live longer. National Public Radio. Published January 2, 2013. Available at: <https://www.npr.org/sections/health-shots/2013/01/02/168437030/research-a-little-extra-fat-may-help-you-live-longer>. Accessed March 21, 2019.
379. Hughes V. The big fat truth. *Nature*. Published May 22, 2013. Available at: <https://www.nature.com/news/the-big-fat-truth-1.13039>. Accessed March 21, 2019.
380. Flegal KM, Ioannidis JPA. The obesity paradox: a misleading term that should be abandoned. *Obesity (Silver Spring)*. 2018;26(4):629-30.
381. Stokes A, Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. *Obesity (Silver Spring)*. 2015;23(12):2485-90.
382. Hennekens CH, Andreotti F. Leading avoidable cause of premature deaths worldwide: case for obesity. *Am J Med*. 2013;126(2):97-8.
383. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med*. 1999;341(6):427-34.
384. National Center for Health Statistics. Trend Tables, National Health and Nutrition Examination Survey. Appendix I. Centers for Disease Control and Prevention. Published August 9, 2018. Available at: <https://www.cdc.gov/nchs/hus/contents2017.htm#053>. Accessed March 18, 2019.
385. Willett WC, Hu FB, Thun M. Overweight, obesity, and all-cause mortality. *JAMA*. 2013;309(16):1681.
386. Berrigan D, Troiano RP, Graubard BI. BMI and mortality: the limits of epidemiological evidence. *Lancet*. 2016;388(10046):734-6.
387. Di Angelantonio E, Bhupathiraju SN, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388(10046):776-86.
388. Stokes A, Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. *Obesity (Silver Spring)*. 2015;23(12):2485-90.
389. Obesity paradox? Just a myth. *Harv Heart Lett*. 2014;24(8):8.
390. Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. A systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. *Ann Surg*. 2011;253(3):484-7.
391. Kritchevsky SB, Beavers KM, Miller ME, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS ONE*. 2015;10(3):e0121993.
392. Barry VW, Caputo JL, Kang M. The joint association of fitness and fatness on cardiovascular disease mortality: a meta-analysis. *Prog Cardiovasc Dis*. 2018;61(2):136-41.
393. Shea MK, Houston DK, Nicklas BJ, et al. The effect of randomization to weight loss on total mortality in older overweight and obese adults: the ADAPT Study. *J Gerontol A Biol Sci Med Sci*. 2010;65(5):519-25.
394. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211-9.
395. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27.
396. Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156.

397. Fontana L, Hu FB. Optimal body weight for health and longevity: bridging basic, clinical, and population research. *Aging Cell*. 2014;13(3):391-400.
398. Thorogood M, Appleby PN, Key TJ, Mann J. Relation between body mass index and mortality in an unusually slim cohort. *J Epidemiol Community Health*. 2003;57(2):130-3.
399. Kitahara CM, Flint AJ, Berrington de Gonzalez A, et al. Association between class III obesity (BMI of 40-59 kg/m²) and mortality: a pooled analysis of 20 prospective studies. *PLoS Med*. 2014;11(7):e1001673.
400. Gard M. Truth, belief and the cultural politics of obesity scholarship and public health policy. *Crit Public Health*. 2011;21(1):37-48.
401. Saguy AC, Riley KW. Weighing both sides: morality, mortality, and framing contests over obesity. *J Health Polit Policy Law*. 2005;30(5):869-921.
402. Saguy AC, Riley KW. Weighing both sides: morality, mortality, and framing contests over obesity. *J Health Polit Policy Law*. 2005;30(5):869-921.
403. Gurrieri L, Cherrier H. Queering beauty: fatshionistas in the fatosphere. *Qual Market Res Int J*. 2013;16(3):276-95.
404. Santos-Lozano A, Pareja-Galeano H, Fuku N, et al. Implications of obesity in exceptional longevity. *Ann Transl Med*. 2016;4(20):416.
405. Brown RE, Kuk JL. Consequences of obesity and weight loss: a devil's advocate position. *Obes Rev*. 2015;16(1):77-87.
406. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758-69.
407. Appleton SL, Seaborn CJ, Visvanathan R, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care*. 2013;36(8):2388-94.
408. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes Rev*. 2014;15(6):504-15.
409. Chang Y, Jung HS, Cho J, et al. Metabolically healthy obesity and the development of nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2016;111(8):1133-40.
410. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758-69.
411. Hill JO, Wyatt HR. The myth of healthy obesity. *Ann Intern Med*. 2013;159(11):789-90.
412. Puhl R, Brownell KD. Bias, discrimination, and obesity. *Obes Res*. 2001;9(12):788-805.
413. Seacat JD, Dougal SC, Roy D. A daily diary assessment of female weight stigmatization. *J Health Psychol*. 2016;21(2):228-40.
414. Puhl RM, Andreyeva T, Brownell KD. Perceptions of weight discrimination: prevalence and comparison to race and gender discrimination in America. *Int J Obes (Lond)*. 2008;32(6):992-1000.
415. Cramer P, Steinwert T. Thin is good, fat is bad: how early does it begin? *J Appl Dev Psychol*. 1998;19(3):429-51.
416. Richardson S, Goodman N, Hastorf A, Dornbusch S. Cultural uniformity in reaction to physical disabilities. *Am Sociol Rev*. 1961;26(2):241.
417. Latner JD, Stunkard AJ. Getting worse: the stigmatization of obese children. *Obes Res*. 2003;11(3):452-6.
418. Andreyeva T, Puhl RM, Brownell KD. Changes in perceived weight discrimination among Americans, 1995-1996 through 2004-2006. *Obesity (Silver Spring)*. 2008;16(5):1129-34.
419. Neumark-Sztainer D, Story M, Harris T. Beliefs and attitudes about obesity among teachers and school health care providers working with adolescents. *J Nutr Educ Behav*. 1999;31(1):3-9.
420. Crandall C. Do parents discriminate against their heavyweight daughters? *Pers Soc Psychol Bull*. 1995;21(7):724-35.
421. Puhl R, Brownell KD. Bias, discrimination, and obesity. *Obes Res*. 2001;9(12):788-805.
422. Foster GD, Wadden TA, Makris AP, et al. Primary care physicians' attitudes about obesity and its treatment. *Obes Res*. 2003;11(10):1168-77.
423. Bagley CR, Conklin DN, Isherwood RT, Pechulis DR, Watson LA. Attitudes of nurses toward obesity and obese patients. *Percept Mot Skills*. 1989;68(3 Pt 1):954.
424. Poorolajal J, Jenabi E. The association between BMI and cervical cancer risk: a meta-analysis. *Eur J Cancer Prev*. 2016;25(3):232-8.
425. Adams CH, Smith NJ, Wilbur DC, Grady KE. The relationship of obesity to the frequency of pelvic examinations: do physician and patient attitudes make a difference? *Women Health*. 1993;20(2):45-57.
426. Hernandez-Boussard T, Ahmed SM, Morton JM. Obesity disparities in preventive care: findings from the National Ambulatory Medical Care Survey, 2005-2007. *Obesity (Silver Spring)*. 2012;20(8):1639-44.
427. LaMendola B. Overweight women: some ob-gyns in South Florida turn away overweight women. *Sun Sentinel*. Published May 16, 2011. Available at: http://articles.sun-sentinel.com/2011-05-16/health/fl-hk-no-obesity-doc-20110516_1_gyn-ob-gyn-obese-patients. Accessed April 17, 2019.
428. Hebl MR, Xu J. Weighing the care: physicians' reactions to the size of a patient. *Int J Obes Relat Metab Disord*. 2001;25(8):1246-52.
429. Guzdune KA, Beach MC, Roter DL, Cooper LA. Physicians build less rapport with obese patients. *Obesity (Silver Spring)*. 2013;21(10):2146-52.
430. Guzdune KA, Huizinga MM, Beach MC, Cooper LA. Obese patients overestimate physicians' attitudes of respect. *Patient Educ Couns*. 2012;88(1):23-8.
431. Sutin AR, Terracciano A. Perceived weight discrimination and obesity. *PLoS ONE*. 2013;8(7):e70048.
432. Vartanian LR, Novak SA. Internalized societal attitudes moderate the impact of weight stigma on avoidance of exercise. *Obesity (Silver Spring)*. 2011;19(4):757-62.
433. Ball K, Crawford D, Owen N. Too fat to exercise? Obesity as a barrier to physical activity. *Aust N Z J Public Health*. 2000;24(3):331-3.
434. Robertson N, Vohora R. Fitness vs. fatness: implicit bias towards obesity among fitness professionals and regular exercisers. *Psychol Sport Exerc*. 2008;9(4):547-57.
435. Vartanian LR, Novak SA. Internalized societal attitudes moderate the impact of weight stigma on avoidance of exercise. *Obesity (Silver Spring)*. 2011;19(4):757-62.

436. Robinson E, Sutin A, Daly M. Perceived weight discrimination mediates the prospective relation between obesity and depressive symptoms in U.S. and U.K. adults. *Health Psychol.* 2017;36(2):112-21.
437. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Perceived weight discrimination and C-reactive protein. *Obesity (Silver Spring)*. 2014;22(9):1959-61.
438. Tomiyama AJ, Epel ES, McClatchey TM, et al. Associations of weight stigma with cortisol and oxidative stress independent of adiposity. *Health Psychol.* 2014;33(8):862-7.
439. Sutin AR, Stephan Y, Terracciano A. Weight discrimination and risk of mortality. *Psychol Sci.* 2015;26(11):1803-11.
440. Callahan D. Obesity: chasing an elusive epidemic. *Hastings Cent Rep.* 2013;43(1):34-40.
441. Puhl R, Luedicke J, Lee Peterson J. Public reactions to obesity-related health campaigns: a randomized controlled trial. *Am J Prev Med.* 2013;45(1):36-48.
442. Grinberg E. Georgia's child obesity ads aim to create movement out of controversy. *CNN*. Published February 7, 2012. Available at: <https://www.cnn.com/2012/02/07/health/atlanta-child-obesity-ads/index.html>. Accessed April 17, 2019.
443. Hunger JM, Tomiyama AJ. Weight labeling and obesity: a longitudinal study of girls aged 10 to 19 years. *JAMA Pediatr.* 2014;168(6):579-80.
444. Churchill J, Ward E. Communicating with pet owners about obesity: roles of the veterinary health care team. *Vet Clin North Am Small Anim Pract.* 2016;46(5):899-911.
445. Perrin EM, Skinner AC, Steiner MJ. Parental recall of doctor communication of weight status: national trends from 1999 through 2008. *Arch Pediatr Adolesc Med.* 2012;166(4):317-22.
446. Callahan D. Obesity: chasing an elusive epidemic. *Hastings Cent Rep.* 2013;43(1):34-40.
447. Rose SA, Poynter PS, Anderson JW, Noar SM, Conigliaro J. Physician weight loss advice and patient weight loss behavior change: a literature review and meta-analysis of survey data. *Int J Obes (Lond)*. 2013;37(1):118-28.
448. Pool AC, Kraschnewski JL, Cover LA, et al. The impact of physician weight discussion on weight loss in US adults. *Obes Res Clin Pract.* 2014;8(2):e131-9.
449. Bleich SN, Bennett WL, Gudzone KA, Cooper LA. Impact of physician BMI on obesity care and beliefs. *Obesity (Silver Spring)*. 2012;20(5):999-1005.
450. Berry AC, Berry NA, Myers TS, Reznicek J, Berry BB. Physician body mass index and bias toward obesity documentation patterns. *Ochsner J.* 2018;18(1):66-71.
451. Bleich SN, Gudzone KA, Bennett WL, Jarlenski MP, Cooper LA. How does physician BMI impact patient trust and perceived stigma? *Prev Med.* 2013;57(2):120-4.
452. Kraschnewski JL, Sciamanna CN, Stuckey HL, et al. A silent response to the obesity epidemic: decline in US physician weight counseling. *Med Care.* 2013;51(2):186-92.
453. Smith AW, Borowski LA, Liu B, et al. U.S. primary care physicians' diet-, physical activity-, and weight-related care of adult patients. *Am J Prev Med.* 2011;41(1):33-42.
454. Foster GD, Wadden TA, Makris AP, et al. Primary care physicians' attitudes about obesity and its treatment. *Obes Res.* 2003;11(10):1168-77.
455. Adler NE, Stewart J. Reducing obesity: motivating action while not blaming the victim. *Milbank Q.* 2009;87(1):49-70.
456. Tomiyama AJ, Mann T. If shaming reduced obesity, there would be no fat people. *Hastings Cent Rep.* 2013;43(3):4-5.
457. Rand CS, MacGregor AM. Successful weight loss following obesity surgery and the perceived liability of morbid obesity. *Int J Obes.* 1991;15(9):577-9.
458. Wright B. Sensitizing outsiders to the position of the insider. *Rehabil Psychol.* 1975;22(2):129-35.
459. Rand CS, Macgregor AM. Successful weight loss following obesity surgery and the perceived liability of morbid obesity. *Int J Obes.* 1991;15(9):577-9.
460. Pellagra: secondary to antiobesity diet. *Postgrad Med.* 1955;17(3):37.
461. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med.* 2017;377(1):13-27.
462. Zheng Y, Manson JE, Yuan C, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. *JAMA.* 2017;318(3):255-69.
463. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. *Int J Obes (Lond)*. 2008;32(4):619-28.
464. Warkentin LM, Majumdar SR, Johnson JA, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. *BMC Med.* 2014;12:175.
465. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity (Silver Spring)*. 2015;23(12):2319-20.
466. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006;29(9):2102-7.
467. Mackie GM, Samocha-Bonet D, Tam CS. Does weight cycling promote obesity and metabolic risk factors? *Obes Res Clin Pract.* 2017;11(2):131-9.
468. Mehta T, Smith DL, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. *Obes Rev.* 2014;15(11):870-81.
469. Brownell KD, Greenwood MR, Stellar E, Shrager EE. The effects of repeated cycles of weight loss and regain in rats. *Physiol Behav.* 1986;38(4):459-64.
470. Mehta T, Smith DL, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. *Obes Rev.* 2014;15(11):870-81.
471. Smith DL, Yang Y, Nagy TR, et al. Weight cycling increases longevity compared with sustained obesity in mice. *Obesity (Silver Spring)*. 2018;26(11):1733-9.
472. Syngal S, Coakley EH, Willett WC, Byers T, Williamson DF, Colditz GA. Long-term weight patterns and risk for cholecystectomy in women. *Ann Intern Med.* 1999;130(6):471-7.
473. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. Weight cycling and risk of gallstone disease in men. *Arch Intern Med.* 2006;166(21):2369-74.
474. Mehta T, Smith DL, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. *Obes Rev.* 2014;15(11):870-81.

475. Di Germanio C, Di Francesco A, Bernier M, de Cabo R. Yo-yo dieting is better than none. *Obesity (Silver Spring)*. 2018;26(11):1673.
476. Afshin A, Reitsma MB, Murray CJL. Health effects of overweight and obesity in 195 countries. *N Engl J Med*. 2017;377(15):1496-7.
477. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)*. 2008;32(6):959-66.
478. Ortega FB, Sui X, Lavie CJ, Blair SN. Body mass index, the most widely used but also widely criticized index: would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality? *Mayo Clin Proc*. 2016;91(4):443-55.
479. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)*. 2008;32(6):959-66.
480. Dickey RA, Bartuska DG, Bray GW, et al. AACE/ACE position statement on the prevention, diagnosis, and treatment of obesity (1998 revision). *Endocr Pract*. 1998;4(5):300-30.
481. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. *Nutr Today*. 2015;50(3):117-28.
482. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis*. 2014;56(4):426-33.
483. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)*. 2008;32(6):959-66.
484. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)*. 2008;32(6):959-66.
485. Ortega FB, Sui X, Lavie CJ, Blair SN. Body mass index, the most widely used but also widely criticized index: would a criterion standard measure of total body fat be a better predictor of cardiovascular disease mortality? *Mayo Clin Proc*. 2016;91(4):443-55.
486. Wells JC. Commentary: the paradox of body mass index in obesity assessment: not a good index of adiposity, but not a bad index of cardio-metabolic risk. *Int J Epidemiol*. 2014;43(3):672-4.
487. Gwartzney D, Allison A, Pastuszak AW, et al. MP47-17: rates of mortality are higher among professional male bodybuilders. *J Urology*. 2016;195(4S):e633.
488. Frati P, Busardò FP, Cipolloni L, Dominicis ED, Fineschi V. Anabolic androgenic steroid (AAS) related deaths: autopsic, histopathological and toxicological findings. *Curr Neuroparmacol*. 2015;13(1):146-59.
489. Schemmel R, Vaghefi S, Bowman B, Olaf Mickelsen (July 29, 1912 to August 8, 1999). *J Nutr*. 2001;131(2):205-10.
490. Blackburn H, Jacobs D. Commentary: origins and evolution of body mass index (BMI): continuing saga. *Int J Epidemiol*. 2014;43(3):665-9.
491. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. *J Clin Invest*. 2015;125(5):1790-2.
492. Flegal KM, Graubard BI. Estimates of excess deaths associated with body mass index and other anthropometric variables. *Am J Clin Nutr*. 2009;89(4):1213-9.
493. Cerhan JR, Moore SC, Jacobs EJ, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc*. 2014;89(3):335-45.
494. Sahakyan KR, Somers VK, Rodriguez-Escudero JP, et al. Normal-weight central obesity: implications for total and cardiovascular mortality. *Ann Intern Med*. 2015;163(11):827-35.
495. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii,1-253.
496. Working group of the North American Association for the Study of Obesity, National Heart, Lung, and Blood Institute, and the American Society for Bariatric Surgery. Practical guide to the identification, evaluation and treatment of overweight and obesity in adults. National Institutes of Health. Published October 2000. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf. Accessed March 21, 2019.
497. Rao G, Powell-Wiley TM, Ancheta I, et al. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American Heart Association. *Circulation*. 2015;132(5):457-72.
498. Rubin R. Postmenopausal women with a "normal" BMI might be overweight or even obese. *JAMA*. 2018;319(12):1185-7.
499. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii,1-253.
500. IDF Task Force on Epidemiology and Prevention Writing Group. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation. Published 2006. Available at: <https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definition-of-the-metabolic-syndrome>. Accessed March 21, 2019.
501. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii,1-253.
502. Cerhan JR, Moore SC, Jacobs EJ, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc*. 2014;89(3):335-45.
503. Brown RE, Randhawa AK, Canning KL, et al. Waist circumference at five common measurement sites in normal weight and overweight adults: which site is most optimal? *Clin Obes*. 2018;8(1):21-9.
504. Brown RE, Randhawa AK, Canning KL, et al. Waist circumference at five common measurement sites in normal weight and overweight adults: which site is most optimal? *Clin Obes*. 2018;8(1):21-9.
505. Shi W, Neubeck L, Gallagher R. Measurement matters: a systematic review of waist measurement sites for determining central adiposity. *Collegian*. 2016;24(5):513-23.
506. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS ONE*. 2017;12(5):e0177175.
507. Yoo EG. Waist-to-height ratio as a screening tool for obesity and cardiometabolic risk. *Korean J Pediatr*. 2016;59(11):425-31.
508. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS ONE*. 2017;12(5):e0177175.

509. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev*. 2012;13(3):275–86.
510. Martin-Calvo N, Moreno-Galarraga L, Martinez-Gonzalez MA. Association between body mass index, waist-to-height ratio and adiposity in children: a systematic review and meta-analysis. *Nutrients*. 2016;8(8):512.
511. Carmienke S, Freitag MH, Pischon T, et al. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. *Eur J Clin Nutr*. 2013;67(6):573–85.
512. Frank A. Futility and avoidance: medical professionals in the treatment of obesity. *JAMA*. 1993;269(16):2132–3.
513. Astwood EB. The heritage of corpulence. *Endocrinology*. 1962;71:337–41.
514. Garrow JS. Treatment of obesity. *Lancet*. 1992;340(8816):409–13.
515. Frank A. Futility and avoidance: medical professionals in the treatment of obesity. *JAMA*. 1993;269(16):2132–3.
516. Chaiton M, Diemert L, Cohen JE, et al. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open*. 2016;6(6):e011045.
517. Garrow JS. Treatment of obesity. *Lancet*. 1992;340(8816):409–13.
518. Vallgård S. Childhood obesity policies—mighty concerns, meek reactions. *Obes Rev*. 2018;19(3):295–301.
519. Vallgård S. Childhood obesity policies—mighty concerns, meek reactions. *Obes Rev*. 2018;19(3):295–301.
520. Biltekoff C. The terror within: obesity in post 9/11 U.S. life. *American Studies*. 2007;48(3):29–48.
521. European Commission. EU action plan on childhood obesity 2014–2020. EC.Europa.eu. Published February 24, 2014. Available at: https://ec.europa.eu/health/sites/health/files/nutrition_physical_activity/docs/childhoodobesity_actionplan_2014_2020_en.pdf. Accessed March 21, 2019.
522. Hill JO. Can a small-changes approach help address the obesity epidemic? A report of the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. *Am J Clin Nutr*. 2009;89(2):477–84.
523. Hill JO. Can a small-changes approach help address the obesity epidemic? A report of the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. *Am J Clin Nutr*. 2009;89(2):477–84.
524. Guth E. Counting calories as an approach to achieve weight control. *JAMA*. 2018;319(3):225–6.
525. Guth E. Counting calories as an approach to achieve weight control. *JAMA*. 2018;319(3):225–6.
526. Sterodimas A, Boriani F, Magarakis E, Nicaretta B, Pereira LH, Illouz YG. Thirtyfour years of liposuction: past, present and future. *Eur Rev Med Pharmacol Sci*. 2012;16(3):393–406.
527. Grazer FM, De jong RH. Fatal outcomes from liposuction: census survey of cosmetic surgeons. *Plast Reconstr Surg*. 2000;105(1):436–46.
528. Bellini E, Grieco MP, Raposio E. A journey through liposuction and liposculture: review. *Ann Med Surg (Lond)*. 2017;24:53–60.
529. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med*. 2004;350(25):2549–57.
530. Blackburn G. Effect of degree of weight loss on health benefits. *Obes Res*. 1995;3 Suppl 2:211s–6s.
531. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med*. 2004;350(25):2549–57.
532. Scopinaro N. The IFSO and obesity surgery throughout the world. *Obes Surg*. 1998;8(1):3–8.
533. American Society for Metabolic and Bariatric Surgery. Estimate of bariatric surgery numbers, 2011–2017. ASMBS.org. Published June 2018. Available at: <https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers>. Accessed March 21, 2019.
534. DiBaise J, Parrish C, Thompson J. *Short Bowel Syndrome: Practical Approach to Management*. 1st ed. Boca Raton, FL: CRC Press; 2016.
535. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S89–96.
536. Celio AC, Pories WJ. A history of bariatric surgery: the maturation of a medical discipline. *Surg Clin North Am*. 2016;96(4):655–67.
537. Dixon JB, Logue J, Komesaroff PA. Promises and ethical pitfalls of surgical innovation: the case of bariatric surgery. *Obes Surg*. 2013;23(10):1698–702.
538. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S89–96.
539. Celio AC, Pories WJ. A history of bariatric surgery: the maturation of a medical discipline. *Surg Clin North Am*. 2016;96(4):655–67.
540. Drenick EJ, Simmons F, Murphy JF. Effect on hepatic morphology of treatment of obesity by fasting, reducing diets and small-bowel bypass. *N Engl J Med*. 1970;282(15):829–34.
541. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S89–96.
542. Dartmouth Atlas Working Group. Variation in the care of surgical conditions: obesity. Dartmouth Institute for Health Policy & Clinical Practice. Published September 2014. Available at: https://www.researchgate.net/publication/283298425_Variation_in_the_Care_of_Surgical_Conditions_Obesity. Accessed March 21, 2019.
543. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short-and long-term mortality after bariatric surgery: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(9):1223–32.
544. Ozsoy Z, Demir E. Which bariatric procedure is the most popular in the world? A bibliometric comparison. *Obes Surg*. 2018;28(8):2339–52.
545. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S89–96.
546. Garrow JS. Treatment of obesity. *Lancet*. 1992;340(8816):409–13.
547. English WJ, Demaria EJ, Brethauer SA, Mattar SG, Rosenthal RJ, Morton JM. American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. *Surg Obes Relat Dis*. 2018;14(3):259–63.
548. Beaulac J, Sandre D. Critical review of bariatric surgery, medically supervised diets, and behavioural interventions for weight management in adults. *Perspect Public Health*. 2017;137(3):162–72.

549. Golzarand M, Toolabi K, Farid R. The bariatric surgery and weight losing: a meta-analysis in the long-and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. *Surg Endosc*. 2017;31(11):4331-45.
550. Panagiotou OA, Markozannes G, Adam GP, et al. Comparative effectiveness and safety of bariatric procedures in Medicare-eligible patients: a systematic review. *JAMA Surg*. 2018;153(11):e183326.
551. De Ville K. Bariatric surgery, ethical obligation, and the life cycle of medical innovation. *Am J Bioeth*. 2010;10(12):22-4.
552. Dixon JB, Logue J, Komesaroff PA. Promises and ethical pitfalls of surgical innovation: the case of bariatric surgery. *Obes Surg*. 2013;23(10):1698-702.
553. English WJ, Demaria EJ, Brethauer SA, Mattar SG, Rosenthal RJ, Morton JM. American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. *Surg Obes Relat Dis*. 2018;14(3):259-63.
554. Pinto-Bastos A, Conceição EM, Machado PPP. Reoperative bariatric surgery: a systematic review of the reasons for surgery, medical and weight loss outcomes, relevant behavioral factors. *Obes Surg*. 2017;27(10):2707-15.
555. Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. *Lancet*. 2016;387(10031):1947-56.
556. Shehab H. Enteral stents in the management of post-bariatric surgery leaks. *Surg Obes Relat Dis*. 2018;14(3):393-403.
557. Pinto-Bastos A, Conceição EM, Machado PPP. Reoperative bariatric surgery: a systematic review of the reasons for surgery, medical and weight loss outcomes, relevant behavioral factors. *Obes Surg*. 2017;27(10):2707-15.
558. Birkmeyer JD, Finks JF, O'Reilly A, et al. Surgical skill and complication rates after bariatric surgery. *N Engl J Med*. 2013;369(15):1434-42.
559. Birkmeyer JD, Finks JF, O'Reilly A, et al. Surgical skill and complication rates after bariatric surgery. *N Engl J Med*. 2013;369(15):1434-42.
560. Doumouras AG, Saleh F, Anvari S, Gmora S, Anvari M, Hong D. Mastery in bariatric surgery: the long-term surgeon learning curve of Roux-en-Y gastric bypass. *Ann Surg*. 2018;267(3):489-94.
561. Azagury D, Morton JM. Bariatric surgery outcomes in US accredited vs non-accredited centers: a systematic review. *J Am Coll Surg*. 2016;223(3):469-77.
562. Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. *Lancet*. 2016;387(10031):1947-56.
563. Trilk JL, Kennedy AB. Using lifestyle medicine in U.S. health care to treat obesity: too many bariatric surgeries? *Curr Sports Med Rep*. 2015;14(2):96-9.
564. Pories WJ. Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab*. 2008;93(11 Suppl 1):S89-96.
565. Rapoport Y, Lavin PJ. Nutritional optic neuropathy caused by copper deficiency after bariatric surgery. *J Neuroophthalmol*. 2016;36(2):178-81.
566. Oudman E, Wijnia JW, van Dam M, Biter LU, Postma A. Preventing Wernicke encephalopathy after bariatric surgery. *Obes Surg*. 2018;28(7):2060-8.
567. Bohan PK, Yonge J, Connelly C, Watson JJ, Friedman E, Fielding G. Wernicke encephalopathy after restrictive bariatric surgery. *Am Surg*. 2016;82(4):E73-5.
568. Sherf Dagan S, Goldenshluger A, Globus I, et al. Nutritional recommendations for adult bariatric surgery patients: clinical practice. *Adv Nutr*. 2017;8(2):382-94.
569. Banerjee A, Ding Y, Mikami DJ, Needleman BJ. The role of dumping syndrome in weight loss after gastric bypass surgery. *Surg Endosc*. 2013;27(5):1573-8.
570. Hofmann B. Parachutes for diabetes: bariatric surgery beyond evidence? *Diabetes Res Clin Pract*. 2012;98(3):406-7.
571. Amouyal C, Andreelli F. What is the evidence for metabolic surgery for type 2 diabetes? A critical perspective. *Diabetes Metab*. 2017;43(1):9-17.
572. Taylor R. Calorie restriction and reversal of type 2 diabetes. *Expert Rev Endocrinol Metab*. 2016;11(6):521-8.
573. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311(22):2297-304.
574. Pop LM, Mari A, Zhao TJ, et al. Roux-en-Y gastric bypass compared with equivalent diet restriction: mechanistic insights into diabetes remission. *Diabetes Obes Metab*. 2018;20(7):1710-21.
575. Taylor R. Calorie restriction and reversal of type 2 diabetes. *Expert Rev Endocrinol Metab*. 2016;11(6):521-8.
576. Hall TC, Pellen MG, Sedman PC, Jain PK. Preoperative factors predicting remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery for obesity. *Obes Surg*. 2010;20(9):1245-50.
577. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest*. 2008;118(7):2583-91.
578. Korer J, Conroy R, Febres G, et al. Randomized double-blind placebo-controlled study of leptin administration after gastric bypass. *Obesity (Silver Spring)*. 2013;21(5):951-6.
579. Lips MA, van Klinken JB, Pijl H, et al. Weight loss induced by very low calorie diet is associated with a more beneficial systemic inflammatory profile than by Roux-en-Y gastric bypass. *Metab Clin Exp*. 2016;65(11):1614-20.
580. Young L, Nor Hanipah Z, Brethauer SA, Schauer PR, Aminian A. Long-term impact of bariatric surgery in diabetic nephropathy. *Surg Endosc*. 2019;33(5):1654-60.
581. Cheung D, Switzer NJ, Ehmann D, Rudnisky C, Shi X, Karmali S. The impact of bariatric surgery on diabetic retinopathy: a systematic review and meta-analysis. *Obes Surg*. 2015;25(9):1604-9.
582. Chen Y, Laybourne JP, Sandinha MT, et al. Does bariatric surgery prevent progression of diabetic retinopathy? *Eye (Lond)*. 2017;31(8):1131-9.
583. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145-54.
584. Kempner W. Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet. *Ann Intern Med*. 1949;31(5):821-56, illust.
585. Kempner W, Peschel RL, Schlayer C. Effect of rice diet on diabetes mellitus associated with vascular disease. *Postgrad Med*. 1958;24(4):359-71.
586. Mozetic V, Daou JP, Martimbianco AL, Riera R. What do Cochrane systematic reviews say about diabetic retinopathy? *Sao Paulo Med J*. 2017;135(1):79-87.

587. Alasil T, Waheed NK. Pan retinal photocoagulation for proliferative diabetic retinopathy: pattern scan laser versus argon laser. *Curr Opin Ophthalmol*. 2014;25(3):164-70.
588. Kempner W, Newborg BC, Peschel RL, Skyler JS. Treatment of massive obesity with rice/reduction diet program. An analysis of 106 patients with at least a 45-kg weight loss. *Arch Intern Med*. 1975;135(12):1575-84.
589. Kempner W. The Treatment of Retinopathy in Kidney Disease and Hypertensive and Arteriosclerotic Vascular Disease with the Rice Diet. *Revista dos Tribunais*; 1951.
590. Katz DL. Perspective: obesity is not a disease. *Nature*. 2014;508(7496):S57.
591. Magro DO, Geloneze B, Delfini R, Pareja BC, Callejas F, Pareja JC. Long-term weight regain after gastric bypass: a 5-year prospective study. *Obes Surg*. 2008;18(6):648-51.
592. Shukla AP, He D, Saunders KH, Andrew C, Aronne LJ. Current concepts in management of weight regain following bariatric surgery. *Expert Rev Endocrinol Metab*. 2018;13(2):67-76.
593. Ghaferi AA, Varban OA. Setting appropriate expectations after bariatric surgery: evaluating weight regain and clinical outcomes. *JAMA*. 2018;320(15):1543-4.
594. Pizato N, Botelho PB, Gonçalves VSS, Dutra ES, de Carvalho KMB. Effect of grazing behavior on weight regain post-bariatric surgery: a systematic review. *Nutrients*. 2017;9(12).
595. Kruseman M, Leimgruber A, Zumbach F, Golay A. Dietary, weight, and psychological changes among patients with obesity, 8 years after gastric bypass. *J Am Diet Assoc*. 2010;110(4):527-34.
596. van Geelen SM, Bolt IL, van der Baan-Slootweg OH, van Summeren MJ. The controversy over pediatric bariatric surgery: an explorative study on attitudes and normative beliefs of specialists, parents, and adolescents with obesity. *J Bioeth Inq*. 2013;10(2):227-37.
597. Groven KS, Braithwaite J. Happily-ever-after: personal narratives in weight-loss surgery advertising. *Health Care Women Int*. 2016;37(11):1221-38.
598. Rouleau CR, Rash JA, Mothersill KJ. Ethical issues in the psychosocial assessment of bariatric surgery candidates. *J Health Psychol*. 2016;21(7):1457-71.
599. Lin HC, Tsao LI. Living with my small stomach: the experiences of post-bariatric surgery patients within 1 year after discharge. *J Clin Nurs*. 2018;27(23-24):4279-89.
600. Velapati SR, Shah M, Kuchkuntla AR, et al. Weight regain after bariatric surgery: prevalence, etiology, and treatment. *Curr Nutr Rep*. 2018;7(4):329-34.
601. Lu CW, Chang YK, Lee YH, et al. Increased risk for major depressive disorder in severely obese patients after bariatric surgery—a 12-year nationwide cohort study. *Ann Med*. 2018;50(7):605-12.
602. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery—a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-33.
603. Sarwer DB, Polonsky HM. The psychosocial burden of obesity. *Endocrinol Metab Clin North Am*. 2016;45(3):677-88.
604. Neovius M, Bruze G, Jacobson P, et al. Risk of suicide and non-fatal self-harm after bariatric surgery: results from two matched cohort studies. *Lancet Diabetes Endocrinol*. 2018;6(3):197-207.
605. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery—a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-33.
606. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery—a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-33.
607. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery—a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-33.
608. Castaneda D, Popov VB, Wander P, Thompson CC. Risk of suicide and self-harm is increased after bariatric surgery—a systematic review and meta-analysis. *Obes Surg*. 2019;29(1):322-33.
609. Courcoulas A. Who, why, and how? Suicide and harmful behaviors after bariatric surgery. *Ann Surg*. 2017;265(2):253-4.
610. Sarwer DB, Polonsky HM. The psychosocial burden of obesity. *Endocrinol Metab Clin North Am*. 2016;45(3):677-88.
611. Steffen KJ, Engel SG, Pollert GA, Li C, Mitchell JE. Blood alcohol concentrations rise rapidly and dramatically after Roux-en-Y gastric bypass. *Surg Obes Relat Dis*. 2013;9(3):470-3.
612. King WC, Chen JY, Mitchell JE, et al. Prevalence of alcohol use disorders before and after bariatric surgery. *JAMA*. 2012;307(23):2516-25.
613. Canetti L, Bachar E, Bonne O. Deterioration of mental health in bariatric surgery after 10 years despite successful weight loss. *Eur J Clin Nutr*. 2016;70(1):17-22.
614. Trainer S, Benjamin T. Elective surgery to save my life: rethinking the “choice” in bariatric surgery. *J Adv Nurs*. 2017;73(4):894-904.
615. Trainer S, Brewis A, Wutich A. Not “taking the easy way out”: reframing bariatric surgery from low-effort weight loss to hard work. *Anthropol Med*. 2017;24(1):96-110.
616. Mattingly B, Stambush M, Hill A. Shedding the pounds but not the stigma: negative attributions as a function of a target’s method of weight loss. *J Appl Biobehav Res*. 2010;14(3):128-44.
617. Pinkney JH, Johnson AB, Gale EA. The big fat bariatric bandwagon. *Diabetologia*. 2010;53(9):1815-22.
618. Katz D. Obesity ... be damned!: what it will take to turn the tide. *Harvard Health Policy Rev*. 2006;7(2):135-51.
619. Oliver JE. The politics of pathology: how obesity became an epidemic disease. *Perspect Biol Med*. 2006;49(4):611-27.
620. Hofmann B. Bariatric surgery for obese children and adolescents: a review of the moral challenges. *BMC Med Ethics*. 2013;14:18.
621. Alqahtani AR, Antonisamy B, Alamri H, Elahmedi M, Zimmerman VA. Laparoscopic sleeve gastrectomy in 108 obese children and adolescents aged 5 to 21 years. *Ann Surg*. 2012;256(2):266-73.
622. Sarr MG. The problem of obesity: how are we going to address it? *Am J Bioeth*. 2010;10(12):12-3.
623. Ortiz SE, Kawachi I, Boyce AM. The medicalization of obesity, bariatric surgery, and population health. *Health (Lond)*. 2017;21(5):498-518.
624. van Geelen SM, Bolt IL, van der Baan-Slootweg OH, van Summeren MJ. The controversy over pediatric bariatric surgery: an explorative study on attitudes and normative beliefs of specialists, parents, and adolescents with obesity. *J Bioeth Inq*. 2013;10(2):227-37.

625. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA*. 2003;289(2):187-93.
626. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short-and long-term mortality after bariatric surgery: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(9):1223-32.
627. Trainer S, Benjamin T. Elective surgery to save my life: rethinking the “choice” in bariatric surgery. *J Adv Nurs*. 2017;73(4):894-904.
628. Vittal H, Raju GS. Endoscopic bubble: can it bust the obesity bubble? *Gastroenterology*. 2005;129(3):1130-2.
629. Ross S, Robert M, Harvey MA, et al. Ethical issues associated with the introduction of new surgical devices, or just because we can, doesn't mean we should. *J Obstet Gynaecol Can*. 2008;30(6):508-13.
630. Twardzik M, Wiewiora M, Glück M, Piecuch J. Mechanical intestinal obstruction caused by displacement of a stomach balloon—case report. *Wideochir Inne Tech Maloinwazyjne*. 2018;13(2):278-81.
631. Lindor KD, Hughes RW, Ilstrup DM, Jensen MD. Intra-gastric balloons in comparison with standard therapy for obesity—a randomized, double-blind trial. *Mayo Clin Proc*. 1987;62(11):992-6.
632. Benjamin SB, Maher KA, Cattau EL, et al. Double-blind controlled trial of the Garren-Edwards gastric bubble: an adjunctive treatment for exogenous obesity. *Gastroenterology*. 1988;95(3):581-8.
633. Tate CM, Geliebter A. Intra-gastric balloon treatment for obesity: review of recent studies. *Adv Ther*. 2017;34(8):1859-75.
634. English WJ, Demaria EJ, Brethauer SA, Mattar SG, Rosenthal RJ, Morton JM. American Society for Metabolic and Bariatric Surgery estimation of metabolic and bariatric procedures performed in the United States in 2016. *Surg Obes Relat Dis*. 2018;14(3):259-63.
635. Ziai K, Pigazzi A, Smith BR, et al. Association of compensation from the surgical and medical device industry to physicians and self-declared conflict of interest. *JAMA Surg*. 2018;153(11):997-1002.
636. Camp MW, Mattingly DA, Gross AE, Nousiainen MT, Alman BA, McKneally MF. Patients' views on surgeons' financial conflicts of interest. *J Bone Joint Surg Am*. 2013;95(2):e9(1-8).
637. Ziai K, Pigazzi A, Smith BR, et al. Association of compensation from the surgical and medical device industry to physicians and self-declared conflict of interest. *JAMA Surg*. 2018;153(11):997-1002.
638. United States Food and Drug Administration. Update: potential risks with liquid-filled intra-gastric balloons—letter to health care providers. FDA.gov. Published August 10, 2017. Available at: <https://www.fda.gov/medicaldevices/safety/letterstohealthcareproviders/ucm570707.htm>. Accessed March 22, 2019.
639. Ashraffian H, Monnich M, Braby TS, Smellie J, Bonanomi G, Efthimiou E. Intra-gastric balloon outcomes in super-obesity: a 16-year city center hospital series. *Surg Obes Relat Dis*. 2018;14(11):1691-9.
640. Trang J, Lee SS, Miller A, et al. Incidence of nausea and vomiting after intra-gastric balloon placement in bariatric patients—a systematic review and meta-analysis. *Int J Surg*. 2018;57:22-9.
641. Vellante P, Carnevale A, D'Ovidio C. An autopsy case of misdiagnosed Wernicke's Syndrome after intra-gastric balloon therapy. *Case Rep Gastrointest Med*. 2018;2018:1510850.
642. Saunders KH, Igel LI, Saumoy M, Sharaiha RZ, Aronne LJ. Devices and endoscopic bariatric therapies for obesity. *Curr Obes Rep*. 2018;7(2):162-71.
643. United States Food and Drug Administration. The FDA alerts health care providers about potential risks with liquid-filled intra-gastric balloons. FDA.gov. Published February 9, 2017. Available at: <https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm540655.htm>. Accessed March 22, 2019.
644. de Quadros LG, Dos Passos Galvão Neto M, Grecco E, et al. Intra-gastric balloon hyperinsufflation as a cause of acute obstructive abdomen. *ACG Case Rep J*. 2018;5:e69.
645. Landon J, DiGregorio V. The phenomenon of the spontaneously autoinflating breast implant. Northeastern Society of Plastic Surgeons. 2014. Available at: <http://meeting.nesps.org/abstracts/2014/54.cgi>. Accessed March 21, 2019.
646. Landon J, DiGregorio V. The phenomenon of the spontaneously autoinflating breast implant. Northeastern Society of Plastic Surgeons. 2014. Available at: <http://meeting.nesps.org/abstracts/2014/54.cgi>. Accessed March 21, 2019.
647. Robinson OG, Benos DJ, Mazzochi C. Spontaneous autoinflation of saline mammary implants: further studies. *Aesthet Surg J*. 2005;25(6):582-6.
648. Hogan RB, Johnston JH, Long BW, et al. A double-blind, randomized, sham-controlled trial of the gastric bubble for obesity. *Gastrointest Endosc*. 1989;35(5):381-5.
649. Ali MR, Moustarah F, Kim JJ. American Society for Metabolic and Bariatric Surgery position statement on intra-gastric balloon therapy endorsed by the Society of American Gastrointestinal and Endoscopic Surgeons. *Surg Obes Relat Dis*. 2016;12(3):462-7.
650. Maffulli N. We are operating too much. *J Orthop Traumatol*. 2017;18(4):289-92.
651. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*. 2002;347(2):81-8.
652. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med*. 2013;369(26):2515-24.
653. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40.
654. McCormack RG, Hutchinson MR. Rocking the shoulder surgeon's world. *Br J Sports Med*. 2017;51(24):1727.
655. Hogan RB, Johnston JH, Long BW, et al. A double-blind, randomized, sham-controlled trial of the gastric bubble for obesity. *Gastrointest Endosc*. 1989;35(5):381-5.
656. Martinez-Brocca MA, Belda O, Parejo J, et al. Intra-gastric balloon-induced satiety is not mediated by modification in fasting or postprandial plasma ghrelin levels in morbid obesity. *Obes Surg*. 2007;17(5):649-57.
657. Genco A, Cipriano M, Bacci V, et al. BioEnterics Intra-gastric Balloon (BIB): a short-term, double-blind, randomised, controlled, crossover study on weight reduction in morbidly obese patients. *Int J Obes (Lond)*. 2006;30(1):129-33.
658. Dumonceau JM, François E, Hittelet A, Mehdi AI, Barea M, Deviere J. Single vs repeated treatment with the intra-gastric balloon: a 5-year weight loss study. *Obes Surg*. 2010;20(6):692-7.
659. Martinez-Brocca MA, Belda O, Parejo J, et al. Intra-gastric balloon-induced satiety is not mediated by modification in fasting or postprandial plasma ghrelin levels in morbid obesity. *Obes Surg*. 2007;17(5):649-57.

660. Thorlund JB. Deconstructing a popular myth: why knee arthroscopy is no better than placebo surgery for degenerative meniscal tears. *Br J Sports Med*. 2017;51(22):1630-1.
661. Rongen JJ, Rovers MM, van Tienen TG, Buma P, Hannink G. Increased risk for knee replacement surgery after arthroscopic surgery for degenerative meniscal tears: a multi-center longitudinal observational study using data from the osteoarthritis initiative. *Osteoarthr Cartil*. 2017;25(1):23-9.
662. Orchard J, Moen MH. Has reimbursement for knee osteoarthritis treatments now reached “postfact” status? *Br J Sports Med*. 2017;51(21):1510-1.
663. Xia Y, Kelton CM, Guo JJ, Bian B, Heaton PC. Treatment of obesity: pharmacotherapy trends in the United States from 1999 to 2010. *Obesity (Silver Spring)*. 2015;23(8):1721-8.
664. Halpern B, Halpern A. Why are anti-obesity drugs stigmatized? *Expert Opin Drug Saf*. 2015;14(2):185-9.
665. McGee S. Getting unstuck: rubber bands and public health. *Am J Bioeth*. 2010;10(12):1-2.
666. Wharton S, Serodio KJ. Next generation of weight management medications: implications for diabetes and CVD risk. *Curr Cardiol Rep*. 2015;17(5):35.
667. Colman E. Dinitrophenol and obesity: an early twentieth-century regulatory dilemma. *Regul Toxicol Pharmacol*. 2007;48(2):115-7.
668. Rodin FH. Cataracts following the use of dinitrophenol: a summary of thirty-two cases. *Cal West Med*. 1936;44(4):276-9.
669. Center for Drug Evaluation and Research 2002. Defendant pleads guilty in internet drug case. United States Food and Drug Administration. Available at: <https://www.fda.gov/iceci/enforcementactions/enforcementstory/enforcementstoryarchive/ucm103554.htm>. Accessed March 22, 2019.
670. Miranda EJ, McIntyre IM, Parker DR, Gary RD, Logan BK. Two deaths attributed to the use of 2,4-dinitrophenol. *J Anal Toxicol*. 2006;30(3):219-22.
671. Ahmsbrak R, Bose J, Hedden SL, Lipari RN, Park-Lee E. Key substance use and mental health indicators in the United States: results from the 2016 national survey on drug use and health. Substance Abuse and Mental Health Services Administration. Published September 2017. Available at: <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>. Accessed March 22, 2019.
672. Rasmussen N. America’s first amphetamine epidemic 1929–1971: a quantitative and qualitative retrospective with implications for the present. *Am J Public Health*. 2008;98(6):974-85.
673. Rasmussen N. America’s first amphetamine epidemic 1929–1971: a quantitative and qualitative retrospective with implications for the present. *Am J Public Health*. 2008;98(6):974-85.
674. Graham J. Amphetamine politics on Capitol Hill. *Society*. 1972;9(3):14-22.
675. McGee M, Whitehead N, Martin J, Collins N. Drug-associated pulmonary arterial hypertension. *Clin Toxicol (Phila)*. 2018;56(9):801-9.
676. Kassirer JP, Angell M. Losing weight—an ill-fated New Year’s resolution. *N Engl J Med*. 1998;338(1):52-4.
677. Connolly HM, Cray JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337(9):581-8.
678. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905-17.
679. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007;370(9600):1706-13.
680. Lagerros YT, Rössner S. Obesity management: what brings success? *Therap Adv Gastroenterol*. 2013;6(1):77-88.
681. Haslam D. Weight management in obesity—past and present. *Int J Clin Pract*. 2016;70(3):206-17.
682. Chawla A, Carls G, Deng E, Tuttle E. The expected net present value of developing weight management drugs in the context of drug safety litigation. *Pharmacoeconomics*. 2015;33(7):749-63.
683. Diet, drugs, devices, and surgery for weight management. *Med Lett Drugs Ther*. 2018;60(1548):91-8.
684. Woloshin S, Schwartz LM. The new weight-loss drugs, lorcaserin and phentermine-topiramate: slim pickings? *JAMA Intern Med*. 2014;174(4):615-9.
685. Nuffer W, Trujillo JM, Megyeri J. A comparison of new pharmacological agents for the treatment of obesity. *Ann Pharmacother*. 2016;50(5):376-88.
686. Rodríguez JE, Campbell KM. Past, present, and future of pharmacologic therapy in obesity. *Prim Care*. 2016;43(1):61-7.viii.
687. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22.
688. Igel LI, Kumar RB, Saunders KH, Aronne LJ. Practical use of pharmacotherapy for obesity. *Gastroenterology*. 2017;152(7):1765-79.
689. Igel LI, Kumar RB, Saunders KH, Aronne LJ. Practical use of pharmacotherapy for obesity. *Gastroenterology*. 2017;152(7):1765-79.
690. Shepherd RW. No evidence for benefit of medication for obesity. *Can Fam Physician*. 2017;63(4):276.
691. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care*. 1998;21(8):1288-94.
692. Schroll JB, Penninga EI, Gøtzsche PC. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of orlistat: a document analysis. *PLoS Med*. 2016;13(8):e1002101.
693. Bourns L, Shiao J. Rebuttal: should family physicians prescribe medication for obesity? YES. *Can Fam Physician*. 2017;63(2):e82.
694. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord*. 2002;26(2):262-73.
695. Rodríguez JE, Campbell KM. Past, present, and future of pharmacologic therapy in obesity. *Prim Care*. 2016;43(1):61-7.viii.
696. Hemo B, Endevelt R, Porath A, Stampfer MJ, Shai I. Adherence to weight loss medications; post-marketing study from HMO pharmacy data of one million individuals. *Diabetes Res Clin Pract*. 2011;94(2):269-75.

697. Glauser TA, Roepke N, Stevenin B, Dubois AM, Ahn SM. Physician knowledge about and perceptions of obesity management. *Obes Res Clin Pract*. 2015;9(6):573-83.
698. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-62.
699. Yeh JS, Kushner RF, Schiff GD. Obesity and management of weight loss. *N Engl J Med*. 2016;375(12):1187-9.
700. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-62.
701. Brauer P, Connor Gorber S, Shaw E, et al. Recommendations for prevention of weight gain and use of behavioural and pharmacologic interventions to manage overweight and obesity in adults in primary care. *CMAJ*. 2015;187(3):184-95.
702. Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Burton SL, Wadden TA. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity (Silver Spring)*. 2008;16(4):790-6.
703. Austin SB, Yu K, Liu SH, Dong F, Tefft N. Household expenditures on dietary supplements sold for weight loss, muscle building, and sexual function: disproportionate burden by gender and income. *Prev Med Rep*. 2017;6:236-41.
704. Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Burton SL, Wadden TA. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity (Silver Spring)*. 2008;16(4):790-6.
705. United States Government Accountability Office. Dietary supplements: FDA should take further actions to improve oversight and consumer understanding. GAO.gov. Published January 29, 2009. Available at: <https://www.gao.gov/products/GAO-09-250>. Accessed March 22, 2019.
706. Marcus DM. Dietary supplements: what's in a name? What's in the bottle? *Drug Test Anal*. 2016;8(3-4):410-2.
707. Starfield B. Is US health really the best in the world? *JAMA*. 2000;284(4):483-5.
708. Center for Drug Evaluation and Research. Drug approval process. United States Food and Drug Administration. Available at: <https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf>. Accessed March 22, 2019.
709. Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL. An herbal supplement containing Ma Huang-Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord*. 2001;25(3):316-24.
710. Statement of Marcia Crosse. Dietary supplements containing ephedra: health risks and FDA's oversight. United States Government Accountability Office. Published July 23, 2003. Available at: <https://www.gao.gov/products/GAO-03-1042T>. Accessed March 22, 2019.
711. Long J. FDA GMP inspectors cite 70% of dietary supplement firms. *Natural Products INSIDER*. Published May 20, 2013. Available at: <https://www.naturalproductsinsider.com/fda-gmp-inspectors-cite-70-dietary-supplement-firms>. Accessed March 22, 2019.
712. Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med*. 2013;11:222.
713. Vilanova-Sanchez A, Gasior AC, Toocheck N, et al. Are *Senna* based laxatives safe when used as long term treatment for constipation in children? *J Pediatr Surg*. 2018;53(4):722-7.
714. Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med*. 2013;11:222.
715. O'Connor A. New York attorney general targets supplements at major retailers. *New York Times*. Published February 3, 2015. Available at: <https://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers>. Accessed March 22, 2019.
716. Marcus DM. Dietary supplements: what's in a name? What's in the bottle? *Drug Test Anal*. 2016;8(3-4):410-2.
717. Hachem R, Assemat G, Martins N, et al. Proton NMR for detection, identification and quantification of adulterants in 160 herbal food supplements marketed for weight loss. *J Pharm Biomed Anal*. 2016;124:34-47.
718. Moreira AP, Motta MJ, Dal Molin TR, Viana C, de Carvalho LM. Determination of diuretics and laxatives as adulterants in herbal formulations for weight loss. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2013;30(7):1230-7.
719. Eichner S, Maguire M, Shea LA, Fete MG. Banned and discouraged-use ingredients found in weight loss supplements. *J Am Pharm Assoc (2003)*. 2016;56(5):538-43.
720. Mathews NM. Prohibited contaminants in dietary supplements. *Sports Health*. 2018;10(1):19-30.
721. Chen SP, Tang MH, Ng SW, Poon WT, Chan AY, Mak TW. Psychosis associated with usage of herbal slimming products adulterated with sibutramine: a case series. *Clin Toxicol (Phila)*. 2010;48(8):832-8.
722. Ozdemir B, Sahin I, Kapucu H, et al. How safe is the use of herbal weight-loss products sold over the internet? *Hum Exp Toxicol*. 2013;32(1):101-6.
723. Cohen PA, Maller G, Desouza R, Neal-Kababick J. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA*. 2014;312(16):1691-3.
724. Marcus DM. Dietary supplements: what's in a name? What's in the bottle? *Drug Test Anal*. 2016;8(3-4):410-2.
725. Petróczi A, Ocampo JA, Shah I, et al. Russian roulette with unlicensed fat-burner drug 2,4-dinitrophenol (DNP): evidence from a multidisciplinary study of the internet, bodybuilding supplements and DNP users. *Subst Abuse Treat Prev Policy*. 2015;10:39.
726. Slomski A. A trip on "bath salts" is cheaper than meth or cocaine but much more dangerous. *JAMA*. 2012;308(23):2445-7.
727. Mathews NM. Prohibited contaminants in dietary supplements. *Sports Health*. 2018;10(1):19-30.
728. Archer JR, Dargan PI, Lostia AM, et al. Running an unknown risk: a marathon death associated with the use of 1,3-dimethylamylamine (DMAA). *Drug Test Anal*. 2015;7(5):433-8.
729. Young C, Oladipo O, Frasier S, Putko R, Chronister S, Marovich M. Hemorrhagic stroke in young healthy male following use of sports supplement Jack3d. *Mil Med*. 2012;177(12):1450-4.
730. Cohen PA, Travis JC, Keizers PHJ, Deuster P, Venhuis BJ. Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA). *Clin Toxicol (Phila)*. 2018;56(6):421-6.
731. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA*. 2003;289(12):1537-45.

732. Mullin GE. Supplements for weight loss: hype or help for obesity? Part III. *Nutr Clin Pract*. 2015;30(3):446-9.
733. Gibson-Moore H. Do slimming supplements work? *Nutr Bull*. 2010;34(4):300-3.
734. Onakpoya IJ, Wider B, Pittler MH, Ernst E. Food supplements for body weight reduction: a systematic review of systematic reviews. *Obesity (Silver Spring)*. 2011;19(2):239-44.
735. Poddar K, Kolge S, Bezman L, Mullin GE, Cheskin LJ. Nutraceutical supplements for weight loss: a systematic review. *Nutr Clin Pract*. 2011;26(5):539-52.
736. Chang YY, Chiou WB. The liberating effect of weight loss supplements on dietary control: a field experiment. *Nutrition*. 2014;30(9):1007-10.
737. Chiou WB, Wan CS, Wu WH, Lee KT. A randomized experiment to examine unintended consequences of dietary supplement use among daily smokers: taking supplements reduces self-regulation of smoking. *Addiction*. 2011;106(12):2221-8.
738. Chiou WB, Yang CC, Wan CS. Ironic effects of dietary supplementation: illusory invulnerability created by taking dietary supplements licenses health-risk behaviors. *Psychol Sci*. 2011;22(8):1081-6.
739. Chang YY, Chiou WB. The liberating effect of weight loss supplements on dietary control: a field experiment. *Nutrition*. 2014;30(9):1007-10.
740. Chang YY, Chiou WB. Taking weight-loss supplements may elicit liberation from dietary control. A laboratory experiment. *Appetite*. 2014;72:8-12.
741. Chiou WB, Yang CC, Wan CS. Ironic effects of dietary supplementation: illusory invulnerability created by taking dietary supplements licenses health-risk behaviors. *Psychol Sci*. 2011;22(8):1081-6.
742. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Published 2013. Available at: https://www.who.int/nmh/events/ncd_action_plan/en. Accessed March 22, 2019.
743. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
744. Neal B. Fat chance for physical activity. *Popul Health Metr*. 2013;11(1):9.
745. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
746. Murray S. The world's biggest industry. *Forbes*. Published November 15, 2007. Available at: https://www.forbes.com/2007/11/11/growth-agriculture-business-forbeslife-food07-cx_sm_1113bigfood.html. Accessed March 22, 2019.
747. Packaged food market is expected to reach \$3.03 trillion, globally, by 2020. Allied Market Research. 2015. Available at: <https://www.alliedmarketresearch.com/press-release/packaged-food-market-is-expected-to-reach-3.03-trillion-worldwide-by-2020-allied-market-research.html>. Accessed March 22, 2019.
748. Neal B. Fat chance for physical activity. *Popul Health Metr*. 2013;11(1):9.
749. Marlow M. Weight loss nudges: market test or government guess? Mercatus Center at George Mason University. Published September 2014. Available at: <https://www.mercatus.org/system/files/Marlow-Weight-Loss-Nudges.pdf>. Accessed March 22, 2019.
750. Marlow M. Weight loss nudges: market test or government guess? Mercatus Center at George Mason University. Published September 2014. Available at: <https://www.mercatus.org/system/files/Marlow-Weight-Loss-Nudges.pdf>. Accessed March 22, 2019.
751. Kirkwood K. Lipids, liberty, and the integrity of free actions. *Am J Bioeth*. 2010;10(3):45-6.
752. Popkin BM. Agricultural policies, food and public health. *EMBO Rep*. 2011;12(1):11-8.
753. Brownell KD, Warner KE. The perils of ignoring history: Big Tobacco played dirty and millions died. How similar is Big Food? *Milbank Q*. 2009;87(1):259-94.
754. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debaquey Cardiovasc J*. 2009;5(4):46-50.
755. Jamal A, Phillips E, Gentzke AS, et al. Current cigarette smoking among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(2):53-9.
756. Mokdad AH, Ballesteros K, Echko M, et al. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444-72.
757. Lagerros YT, Rössner S. Obesity management: what brings success? *Therap Adv Gastroenterol*. 2013;6(1):77-88.
758. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debaquey Cardiovasc J*. 2009;5(4):46-50.
759. Biener L, Aseltine RH, Cohen B, Anderka M. Reactions of adult and teenaged smokers to the Massachusetts tobacco tax. *Am J Public Health*. 1998;88(9):1389-91.
760. World Health Organization. WHO report on the global tobacco epidemic, 2008. Published 2008. Available at: https://www.who.int/tobacco/mpower/gtcr_download/en. Accessed March 22, 2019.
761. Smith A. *An Inquiry into the Nature and Causes of the Wealth of Nations*. Methuen and Co Ltd; 1904.
762. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debaquey Cardiovasc J*. 2009;5(4):46-50.
763. Graff SK, Kappagoda M, Wooten HM, McGowan AK, Ashe M. Policies for healthier communities: historical, legal, and practical elements of the obesity prevention movement. *Annu Rev Public Health*. 2012;33:307-24.
764. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debaquey Cardiovasc J*. 2009;5(4):46-50.
765. Marshall T. Exploring a fiscal food policy: the case of diet and ischaemic heart disease. *BMJ*. 2000;320(7230):301-5.
766. Thow AM, Downs S, Jan S. A systematic review of the effectiveness of food taxes and subsidies to improve diets: understanding the recent evidence. *Nutr Rev*. 2014;72(9):551-65.
767. Marshall T. Exploring a fiscal food policy: the case of diet and ischaemic heart disease. *BMJ*. 2000;320(7230):301-5.
768. Marshall T. Exploring a fiscal food policy: the case of diet and ischaemic heart disease. *BMJ*. 2000;320(7230):301-5.
769. Koh HK. An analysis of the successful 1992 Massachusetts tobacco tax initiative. *Tob Control*. 1996;5(3):220-5.
770. Smith KE, Savell E, Gilmore AB. What is known about tobacco industry efforts to influence tobacco tax? A systematic review of empirical studies. *Tob Control*. 2013;22(2):144-53.

771. Waterlander WE, Steenhuis IH, de Boer MR, Schuit AJ, Seidell JC. The effects of a 25% discount on fruits and vegetables: results of a randomized trial in a three-dimensional web-based supermarket. *Int J Behav Nutr Phys Act*. 2012;9:11.
772. Ananthapavan J, Peterson A, Sacks G. Paying people to lose weight: the effectiveness of financial incentives provided by health insurers for the prevention and management of overweight and obesity—a systematic review. *Obes Rev*. 2018;19(5):605-13.
773. An R, Patel D, Segal D, Sturm R. Eating better for less: a national discount program for healthy food purchases in South Africa. *Am J Health Behav*. 2013;37(1):56-61.
774. Ananthapavan J, Peterson A, Sacks G. Paying people to lose weight: the effectiveness of financial incentives provided by health insurers for the prevention and management of overweight and obesity—a systematic review. *Obes Rev*. 2018;19(5):605-13.
775. Yancy WS, Shaw PA, Wesby L, et al. Financial incentive strategies for maintenance of weight loss: results from an internet-based randomized controlled trial. *Nutr Diabetes*. 2018;8(1):33.
776. Cawley J. Does anything work to reduce obesity? (Yes, modestly). *J Health Polit Policy Law*. 2016;41(3):463-72.
777. Rahkovsky I, Gregory CA. Food prices and blood cholesterol. *Econ Hum Biol*. 2013;11(1):95-107.
778. Cash S, Sunding D, Zilberman D. Fat taxes and thin subsidies: prices, diet, and health outcomes. *Acta Agr Scand C*. 2005;2(3-4):167-74.
779. Hanks A, Wansink B, Just D, et al. From Coke to Coors: a field study of a fat tax and its unintended consequences. *J Nutr Educ Behav*. 2013;45(4):S40. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
780. Jue JJ, Press MJ, McDonald D, et al. The impact of price discounts and calorie messaging on beverage consumption: a multi-site field study. *Prev Med*. 2012;55(6):629-33.
781. Brown AW, Allison DB. Unintended consequences of obesity-targeted health policy. *Virtual Mentor*. 2013;15(4):339-46.
782. Richardson MB, Williams MS, Fontaine KR, Allison DB. The development of scientific evidence for health policies for obesity: why and how? *Int J Obes (Lond)*. 2017;41(6):840-8.
783. Folkvord F, Anshütz DJ, Buijzen M, Valkenburg PM. The effect of playing advergames that promote energy-dense snacks or fruit on actual food intake among children. *Am J Clin Nutr*. 2013;97(2):239-45.
784. At a glance. Reducing tobacco use: a report of the Surgeon General—2000. *Oncology (Williston Park, NY)*. 2000;14(12):1671,1675,1764-5.
785. Bolton L, Cohen J, Bloom P. Does marketing products as remedies create “get out of jail free cards”? *J Consum Res*. 2006;33(1):71-81.
786. Bolton L, Cohen J, Bloom P. Does marketing products as remedies create “get out of jail free cards”? *J Consum Res*. 2006;33(1):71-81.
787. Burgers triumph over baguettes in French fast food wars. *Local*. Published March 20, 2018. Available at: <https://www.thelocal.fr/20180320/burgers-triumph-against-baguettes-in-french-fast-food-wars>. Accessed March 22, 2019.
788. Hawkes C. Regulating and litigating in the public interest: regulating food marketing to young people worldwide: trends and policy drivers. *Am J Public Health*. 2007;97(11):1962-73.
789. Arrêté du 27 février 2007 fixant les conditions relatives aux informations à caractère sanitaire devant accompagner les messages publicitaires ou promotionnels en faveur de certains aliments et boissons. Légifrance. Published February 27, 2007. Available at: <https://www.legifrance.gouv.fr/eli/arrrete/2007/2/27/SANP0720073A/jo/texte>. Accessed March 22, 2019.
790. Werle C, Cuny C. The boomerang effect of mandatory sanitary messages to prevent obesity. *Mark Lett*. 2012;23(3):883-91.
791. Werle C, Cuny C. The boomerang effect of mandatory sanitary messages to prevent obesity. *Mark Lett*. 2012;23(3):883-91.
792. Werle C, Cuny C. The boomerang effect of mandatory sanitary messages to prevent obesity. *Mark Lett*. 2012;23(3):883-91.
793. Caraher M, Cowburn G. Guest commentary: fat and other taxes, lessons for the implementation of preventive policies. *Prev Med*. 2015;77:204-6.
794. Moore M, Yeatman H, Davey R. Which nanny—the state or industry? Wowers, teetotalers and the fun police in public health advocacy. *Public Health*. 2015;129(8):1030-7.
795. Gostin LO. Bloomberg's health legacy: urban innovator or meddling nanny? *Hastings Cent Rep*. 2013;43(5):19-25.
796. Mejia P, Dorfman L, Cheyne A, et al. The origins of personal responsibility rhetoric in news coverage of the tobacco industry. *Am J Public Health*. 2014;104(6):1048-51.
797. Gostin LO, Gostin KG. A broader liberty: J.S. Mill, paternalism and the public's health. *Public Health*. 2009;123(3):214-21.
798. Gostin LO, Gostin KG. A broader liberty: J.S. Mill, paternalism and the public's health. *Public Health*. 2009;123(3):214-21.
799. Hoek J. Informed choice and the nanny state: learning from the tobacco industry. *Public Health*. 2015;129(8):1038-45.
800. Gostin LO, Gostin KG. A broader liberty: J.S. Mill, paternalism and the public's health. *Public Health*. 2009;123(3):214-21.
801. World Health Organization. WHO Director-General addresses health promotion conference. Published June 10, 2013. Available at: http://www.who.int/dg/speeches/2013/health_promotion_20130610/en. Accessed March 22, 2019.
802. Brown & Williamson. Smoking and health proposal. 1969. Available at: <https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=jryf0138>. Accessed March 22, 2019.
803. Ibrahim JK, Glantz SA. The rise and fall of tobacco control media campaigns, 1967-2006. *Am J Public Health*. 2007;97(8):1383-96.
804. Weimholt J. “Bringing a butter knife to a gun fight”? Salience, disclosure, and FDA's differing approaches to the tobacco use and obesity epidemics. *Food Drug Law J*. 2015;70(4):501-51.i.

805. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debakey Cardiovasc J*. 2009;5(4):46-50.
806. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debakey Cardiovasc J*. 2009;5(4):46-50.
807. Watson E. Front-of-pack nutrition labels prompt surprise swing in sales. *Food Manufacture*. Published May 1, 2006. Available at: <https://www.foodmanufacture.co.uk/Article/2006/05/02/Front-of-pack-nutrition-labels-prompt-surprise-swing-in-sales>. Accessed March 22, 2019.
808. Mindell JS, Reynolds L, Cohen DL, McKee M. All in this together: the corporate capture of public health. *BMJ*. 2012;345:e8082.
809. Bleich SN, Wolfson JA, Jarlenski MP, Block JP. Restaurants with calories displayed on menus had lower calorie counts compared to restaurants without such labels. *Health Aff (Millwood)*. 2015;34(11):1877-84.
810. Dumanovsky T, Huang CY, Nonas CA, Matte TD, Bassett MT, Silver LD. Changes in energy content of lunchtime purchases from fast food restaurants after introduction of calorie labelling: cross sectional customer surveys. *BMJ*. 2011;343:d4464.
811. Berry C, Burton S, Howlett E. The effects of voluntary versus mandatory menu calorie labeling on consumers' retailer-related responses. *J Retailing*. 2017;94(1):73-88.
812. Strom S. McDonald's to start posting calorie counts. *New York Times*. Published September 12, 2012. Available at: <https://www.nytimes.com/2012/09/13/business/mcdonalds-to-start-posting-calorie-counts.html>. Accessed March 22, 2019.
813. Wilcox K, Vallen B, Block L, Fitzsimons G. Vicarious goal fulfillment: when the mere presence of a healthy option leads to an ironically indulgent decision. *J Consum Res*. 2009;36(3):380-93.
814. Wilcox K, Vallen B, Block L, Fitzsimons G. Vicarious goal fulfillment: when the mere presence of a healthy option leads to an ironically indulgent decision. *J Consum Res*. 2009;36(3):380-93.
815. Chernev A. The dieter's paradox. *J Consum Psychol*. 2011;21(2):178-83.
816. Chandon P, Wansink B. The biasing health halos of fast-food restaurant health claims: lower calorie estimates and higher side-dish consumption intentions. *J Consum Res*. 2007;34(3):301-14. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
817. Werle C, Cuny C. The boomerang effect of mandatory sanitary messages to prevent obesity. *Mark Lett*. 2012;23(3):883-91.
818. Wilcox K, Vallen B, Block L, Fitzsimons G. Vicarious goal fulfillment: when the mere presence of a healthy option leads to an ironically indulgent decision. *J Consum Res*. 2009;36(3):380-93.
819. Lagerros YT, Rössner S. Obesity management: what brings success? *Therap Adv Gastroenterol*. 2013;6(1):77-88.
820. Chopra M, Darnton-Hill I. Tobacco and obesity epidemics: not so different after all? *BMJ*. 2004;328(7455):1558-60.
821. Institute of Medicine. Food marketing to children and youth: threat or opportunity? National Academies Press. 2006. Available at: <https://www.nap.edu/catalog/11514/food-marketing-to-children-and-youth-threat-or-opportunity>. Accessed March 22, 2019.
822. Lyons R. Ban on sugary-cereal TV ads urged. *New York Times*. Published March 6, 1973. Available at: <https://www.nytimes.com/1973/03/06/archives/ban-on-sugarycereal-tv-ads-urged-sugarcoated-nothings-115-pounds-of.html>. Accessed March 22, 2019.
823. Congress of the United States Hearings Before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-Second Congress, Second Session. Nutrition Education—1972. Part 1—Overview; Consultants' Recommendations. Washington, D.C., December 6, 1972. Washington, D.C.; 1972:1-191.
824. Congress of the United States Hearings Before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-Third Congress, First Session. Nutrition Education—1973. Parts 3, 4, and 5—TV Advertising of Food to Children. Washington, D.C., March 5, 6, and 12, 1973. Washington, D.C.; 1973:1-546.
825. Congress of the United States Hearings Before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-Third Congress, First Session. Nutrition Education—1973. Parts 3, 4, and 5—TV Advertising of Food to Children. Washington, D.C., March 5, 6, and 12, 1973. Washington, D.C.; 1973:1-546.
826. Congress of the United States Hearings Before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-Third Congress, First Session. Nutrition Education—1973. Parts 3, 4, and 5—TV Advertising of Food to Children. Washington, D.C., March 5, 6, and 12, 1973. Washington, D.C.; 1973:1-546.
827. Children's Food & Beverage Advertising Initiative. White paper on CFBAI's uniform nutrition criteria. Council of Better Business Bureaus. Published July 2011. Available at: <https://www.bbb.org/us/storage/0/Shared%20Documents/White%20Paper%20on%20CFBAI%20Uniform%20Nutrition%20Criteria%20July%202011.pdf>. Accessed March 22, 2019.
828. Harris JL, LoDolce M, Dembek C, Schwartz MB. Sweet promises: candy advertising to children and implications for industry self-regulation. *Appetite*. 2015;95:585-92.
829. LoDolce ME, Harris JL, Schwartz MB. Sugar as part of a balanced breakfast? What cereal advertisements teach children about healthy eating. *J Health Commun*. 2013;18(11):1293-309.
830. Dietz WH. New strategies to improve food marketing to children. *Health Aff (Millwood)*. 2013;32(9):1652-8.
831. Pestano P, Yeshua E, Houlihan J. Sugar in children's cereals: popular brands pack more sugar than snack cakes and cookies. Environmental Working Group. Published December 2011. Available at: https://www.foodpolitics.com/wp-content/uploads/CEREALSevg_press_cereal_report.pdf. Accessed March 22, 2019.
832. Harris JL, Schwartz MB, Brownell KD, et al. Cereal FACTS 2012: limited progress in the nutrition quality and marketing of children's cereals. Rudd Center for Food Policy & Obesity. Published June 2012. Available at: http://www.cerealfacts.org/media/cereal_facts_report_2012_7.12.pdf. Accessed March 22, 2019.
833. Westen T. Government regulation of food marketing to children: the Federal Trade Commission and the Kid-Vid controversy. *Loyola Los Angel Law Rev*. Published May 1, 2006. Available at: <https://digitalcommons.lmu.edu/llr/vol39/iss1/4>. Accessed March 22, 2019.
834. Dietz WH. New strategies to improve food marketing to children. *Health Aff (Millwood)*. 2013;32(9):1652-8.

835. Federal Trade Commission. Interagency Working Group seeks input on proposed voluntary principles for marketing food to children. FTC.gov. Published April 28, 2011. Available at: <https://www.ftc.gov/news-events/press-releases/2011/04/interagency-working-group-seeks-input-proposed-voluntary>. Accessed March 22, 2019.
836. Federal Trade Commission. Interagency Working Group on food marketed to children. Preliminary proposed nutrition principles to guide industry self-regulatory efforts. Available at: https://www.ftc.gov/sites/default/files/documents/public_events/food-marketed-children-forum-interagency-working-group-proposal/110428foodmarketproposedguide.pdf. Accessed March 22, 2019.
837. Harris JL, Schwartz MB, Brownell KD, et al. Cereal FACTS 2012: limited progress in the nutrition quality and marketing of children's cereals. Rudd Center for Food Policy & Obesity. Published June 2012. Available at: http://www.cerealfacts.org/media/cereal_facts_report_2012_7.12.pdf. Accessed March 22, 2019.
838. General Mills. Re: Interagency Working Group on Food Marketed to Children: FTC Project No. P094513 Comments on Proposed Nutrition Principles and General Comments and Proposed Marketing Definitions. Washington, D.C. Published July 14, 2011.
839. Jackson T. Dear Chairman Leibowitz. Ohio Grocers Association. 2011.
840. General Mills. Re: Interagency Working Group on Food Marketed to Children: FTC Project No. P094513 Comments on Proposed Nutrition Principles and General Comments and Proposed Marketing Definitions. Washington, D.C. Published July 14, 2011.
841. Vladeck D. What's on the table. Federal Trade Commission. Published July 1, 2011. Available at: <https://www.ftc.gov/news-events/blogs/business-blog/2011/07/whats-table>. Accessed March 22, 2019.
842. Dietz WH. New strategies to improve food marketing to children. *Health Aff (Millwood)*. 2013;32(9):1652-8.
843. Wilson D, Roberts J. Special report: how Washington went soft on childhood obesity. *Reuters*. Published April 27, 2012. Available at: <https://www.reuters.com/article/us-usa-foodlobby/special-report-how-washington-went-soft-on-childhood-obesity-idUSBRE83Q0ED20120427>. Accessed March 22, 2019.
844. Wilson D, Roberts J. Special report: how Washington went soft on childhood obesity. *Reuters*. Published April 27, 2012. Available at: <https://www.reuters.com/article/us-usa-foodlobby/special-report-how-washington-went-soft-on-childhood-obesity-idUSBRE83Q0ED20120427>. Accessed March 22, 2019.
845. Wilson D, Roberts J. Special report: how Washington went soft on childhood obesity. *Reuters*. Published April 27, 2012. Available at: <https://www.reuters.com/article/us-usa-foodlobby/special-report-how-washington-went-soft-on-childhood-obesity-idUSBRE83Q0ED20120427>. Accessed March 22, 2019.
846. Wilson D, Roberts J. Special report: how Washington went soft on childhood obesity. *Reuters*. Published April 27, 2012. Available at: <https://www.reuters.com/article/us-usa-foodlobby/special-report-how-washington-went-soft-on-childhood-obesity-idUSBRE83Q0ED20120427>. Accessed March 22, 2019.
847. Gerberding JL. Safer fats for healthier hearts: the case for eliminating dietary artificial trans fat intake. *Ann Intern Med*. 2009;151(2):137-8.
848. Galizzi MM. Label, nudge or tax? A review of health policies for risky behaviours. *J Public Health Res*. 2012;1(1):14-21.
849. Mozaffarian D, Rogoff KS, Ludwig DS. The real cost of food: can taxes and subsidies improve public health? *JAMA*. 2014;312(9):889-90.
850. Barragan NC, Noller AJ, Robles B, et al. The "sugar pack" health marketing campaign in Los Angeles County, 2011-2012. *Health Promot Pract*. 2014;15(2):208-16.
851. Processed meat is the next public health crisis. Physicians Committee for Responsible Medicine. Published March 20, 2012. Available at: <https://www.pcrm.org/news/blog/processed-meat-next-public-health-crisis>. Accessed November 26, 2018.
852. Willett WC, Stampfer MJ, Manson JE, et al. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet*. 1993;341(8845):581-5.
853. Astrup A. The trans fatty acid story in Denmark. *Atheroscler Suppl*. 2006;7(2):43-6.
854. McCarthy M. US moves to ban trans fats. *BMJ*. 2013;347:f6749.
855. Gerberding JL. Safer fats for healthier hearts: the case for eliminating dietary artificial trans fat intake. *Ann Intern Med*. 2009;151(2):137-8.
856. Cohen JT. FDA's proposed ban on trans fats: how do the costs and benefits stack up? *Clin Ther*. 2014;36(3):322-7.
857. Angell SY, Silver LD, Goldstein GP, et al. Cholesterol control beyond the clinic: New York City's trans fat restriction. *Ann Intern Med*. 2009;151(2):129-34.
858. European Dairy Association. Trans fatty acids: questions & answers. EDA.Euromilk.org. Published 2015. Available at: http://eda.euromilk.org/fileadmin/user_upload/Public_Documents/Nutrition_Factsheets/EDA-Nutrition_fact_sheet_Q_A_On_Trans_Fatty_Acids.pdf. Accessed March 22, 2019.
859. Reeves RM. Effect of dietary trans fatty acids on cholesterol levels. *N Engl J Med*. 1991;324(5):338-40.
860. Brownell KD, Pomeranz JL. The trans-fat ban—food regulation and long-term health. *N Engl J Med*. 2014;370(19):1773-5.
861. Resnik D. Trans fat bans and human freedom. *Am J Bioeth*. 2010;10(3):27-32.
862. Ferrara P. Rise of food fascism. *Washington Times*. Published May 31, 2003. Available at: <https://www.washingtontimes.com/news/2003/may/31/20030531-092643-1371r>. Accessed March 22, 2019.
863. Ross GL. Determining the benefits of the New York City trans fat ban. *Ann Intern Med*. 2010;152(3):194.
864. Gostin LO. Bloomberg's health legacy: urban innovator or meddling nanny? *Hastings Cent Rep*. 2013;43(5):19-25.
865. *National Federation of Independent Business, et al. v. Sebelius, Secretary of Health and Human Services, et al.* 567 U.S. 519 11-393 (Roberts Court 2011).
866. Bork R. *The Tempting of America*. New York: Free Press; 1997.
867. Angell SY, Silver LD, Goldstein GP, et al. Cholesterol control beyond the clinic: New York City's trans fat restriction. *Ann Intern Med*. 2009;151(2):129-34.
868. Restrepo BJ, Rieger M. Trans fat and cardiovascular disease mortality: evidence from bans in restaurants in New York. *J Health Econ*. 2016;45:176-96.
869. Coombes R. Trans fats: chasing a global ban. *BMJ*. 2011;343:d5567.
870. Kirkwood K. Lipids, liberty, and the integrity of free actions. *Am J Bioeth*. 2010;10(3):45-6.

871. Golan E, Kuchler F, Krissow B. Do food labels make a difference? Sometimes. United States Department of Agriculture. Published November 1, 2007. Available at: <https://www.ers.usda.gov/amber-waves/2007/november/do-food-labels-make-a-difference-sometimes>. Accessed March 22, 2019.
872. *Hoyte v. Yum! Brands, Inc.* 567 U.S. 519 06-1127 (United States District Court, District of Columbia, 2006).
873. Brownell KD, Warner KE. The perils of ignoring history: Big Tobacco played dirty and millions died. How similar is Big Food? *Milbank Q.* 2009;87(1):259-94.
874. Jargon J. The gluten-free craze: is it healthy? *Wall Street Journal*. Published June 22, 2014. Available at: <https://www.wsj.com/articles/how-we-eat-the-gluten-free-craze-is-it-healthy-1403491041>. Accessed March 22, 2019.
875. "Gluten free" claims in the marketplace. Agriculture and Agri-Food Canada. Published April 2014. Available at: <http://www.agr.gc.ca/eng/industry-markets-and-trade/canadian-agri-food-sector-intelligence/processed-food-and-beverages/trends-and-market-opportunities-for-the-food-processing-sector/gluten-free-claims-in-the-marketplace>. Accessed March 22, 2019.
876. Jargon J. The gluten-free craze: is it healthy? *Wall Street Journal*. Published June 22, 2014. Available at: <https://www.wsj.com/articles/how-we-eat-the-gluten-free-craze-is-it-healthy-1403491041>. Accessed March 22, 2019.
877. Fry L, Madden AM, Fallaize R. An investigation into the nutritional composition and cost of gluten-free versus regular food products in the UK. *J Hum Nutr Diet.* 2018;31(1):108-20.
878. Elliott C. The nutritional quality of gluten-free products for children. *Pediatrics.* 2018;142(2):e20180525.
879. He FJ, Pombo-Rodrigues S, MacGregor GA. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. *BMJ Open.* 2014;4(4):e004549.
880. Dunford E, Webster J, Woodward M, et al. The variability of reported salt levels in fast foods across six countries: opportunities for salt reduction. *CMAJ.* 2012;184(9):1023-8.
881. Coyne KJ, Baldrige AS, Huffman MD, Jenner K, Xavier D, Dunford EK. Differences in the sodium content of bread products in the USA and UK: implications for policy. *Public Health Nutr.* 2018;21(3):632-6.
882. Wyness LA, Buttriss JL, Stanner SA. Reducing the population's sodium intake: the UK Food Standards Agency's salt reduction programme. *Public Health Nutr.* 2012;15(2):254-61.
883. Roehr B. US tops salty fast food league table. *BMJ.* 2012;344:e2769.
884. Ma Y, He FJ, Yin Y, Hashem KM, MacGregor GA. Gradual reduction of sugar in soft drinks without substitution as a strategy to reduce overweight, obesity, and type 2 diabetes: a modelling study. *Lancet Diabetes Endocrinol.* 2016;4(2):105-14.
885. Hill JO. Can a small-changes approach help address the obesity epidemic? A report of the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. *Am J Clin Nutr.* 2009;89(2):477-84.
886. Brownell KD. Government intervention and the nation's diet: the slippery slope of inaction. *Am J Bioeth.* 2010;10(3):1-2.

Chapter 2

887. Katz DL. Diets, diatribes, and a dearth of data. *Circ Cardiovasc Qual Outcomes*. 2014;7(6):809-11.
888. Amazon.com: weight loss: books. Amazon.com. Available at: <https://amzn.to/2EK547G>. Accessed March 31, 2019.
889. Mishkin B, Mishkin S. Dietary fads and gut mysteries versus nutrition with a grain of common sense. *Can J Gastroenterol*. 1997;11(4):371-5.
890. Yoder S. The Big Fat Surprise: a critical review; part 2. Science of Nutrition. Published June 30, 2014. Available at: <https://thescienceofnutrition.wordpress.com/2014/06/30/the-big-fat-surprise-a-critical-review-part-2>. Accessed March 31, 2019.
891. Yoder S. The Big Fat Surprise: a critical review; part 1. Science of Nutrition. Published August 10, 2014. Available at: <https://thescienceofnutrition.wordpress.com/2014/08/10/the-big-fat-surprise-a-critical-review-part-1/>. Accessed August 20, 2019.
892. Goff SL, Foody JM, Inzucchi S, Katz D, Mayne ST, Krumholz HM. Brief report: nutrition and weight loss information in a popular diet book: is it fact, fiction, or something in between? *J Gen Intern Med*. 2006;21(7):769-74.
893. Carroll AE. Obesity interventions can improve more than just body mass index. *JAMA Pediatr*. 2013;167(11):1002-3.
894. Gudzone KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med*. 2015;162(7):501-12.
895. Rabasca Roepe L. The diet industry. SAGE Business Researcher. Published March 5, 2018. Available at: <http://businessresearcher.sagepub.com/sbr-1946-105904-2881576/20180305/the-diet-industry>. Accessed March 31, 2019.
896. Freedhoff Y. From plunger to *Punkt-roller*: a century of weight-loss quackery. *CMAJ*. 2009;180(4):432-3.
897. Winter G. Fraudulent marketers capitalize on demand for sweat-free diets. *New York Times*. Published October 29, 2000. Available at: <https://www.nytimes.com/2000/10/29/business/fraudulent-marketers-capitalize-on-demand-for-sweat-free-diets.html>. Accessed March 3, 2019.
898. Ware L. *Selling It*. New York: Norton; 2002.
899. Blast up to 49 pounds off you in only 29 days! *Working Mother*. 1996;(11):73.
900. Kicklighter JR. Update on congressional hearings on the diet industry. *Nutrition*. 1991;7(4):297-9.
901. Cleland RL, Gross WC, Koss LD, Daynard M, Muoio KM. Weight-loss advertising: an analysis of current trends. Federal Trade Commission. 2002:1-58.
902. Gross JE. The First Amendment and diet industry advertising: how puffery in weight-loss advertisements has gone too far. *JLH*. 2007;20(2):325-55.
903. Nguyen ES. Weight loss testimonials: a critique of potential FTC restrictions on diet advertising. *Food Drug Law J*. 2008;63(2):493-507.
904. Gardner D. Numbers are nice, but stories matter. *CMAJ*. 2008;179(1):108.
905. Small D, Loewenstein G, Slovic P. Sympathy and callousness: the impact of deliberative thought on donations to identifiable and statistical victims. *Organ Behav Hum Decis Process*. 2007;102(2):143-53.
906. Polivy J, Herman CP. If at first you don't succeed. False hopes of self-change. *Am Psychol*. 2002;57(9):677-89.
907. Gardner D. Numbers are nice, but stories matter. *CMAJ*. 2008;179(1):108.
908. Vakili RM, Chaudhry ZW, Doshi RS, Clark JM, Gudzone KA. Commercial programs' online weight-loss claims compared to results from randomized controlled trials. *Obesity (Silver Spring)*. 2017;25(11):1885-93.
909. Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. *JAMA*. 2003;289(14):1792-8.
910. Vakili RM, Chaudhry ZW, Doshi RS, Clark JM, Gudzone KA. Commercial programs' online weight-loss claims compared to results from randomized controlled trials. *Obesity (Silver Spring)*. 2017;25(11):1885-93.
911. Fatis M, Weiner A, Hawkins J, Van Dorsten B. Following up on a commercial weight loss program: do the pounds stay off after your picture has been in the newspaper? *J Am Diet Assoc*. 1989;89(4):547-8.
912. Fatis M, Weiner A, Hawkins J, Van Dorsten B. Following up on a commercial weight loss program: do the pounds stay off after your picture has been in the newspaper? *J Am Diet Assoc*. 1989;89(4):547-8.
913. United States. Congress. House. Committee on Small Business. Subcommittee on Regulation, Business Opportunities, and Energy. *Deception and Fraud in the Diet Industry*. Washington, D.C.: U.S. Government Printing Office; 1990.
914. Primack C. A review and critique of published real-world weight management program studies. *Postgrad Med*. 2018;130(6):548-60.
915. Gudzone KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med*. 2015;162(7):501-12.
916. McEvedy SM, Sullivan-Mort G, McLean SA, Pascoe MC, Paxton SJ. Ineffectiveness of commercial weight-loss programs for achieving modest but meaningful weight loss: systematic review and meta-analysis. *J Health Psychol*. 2017;22(12):1614-27.
917. Finkelstein EA, Kruger E. Meta-and cost-effectiveness analysis of commercial weight loss strategies. *Obesity (Silver Spring)*. 2014;22(9):1942-51.
918. Finley CE, Barlow CE, Greenway FL, Rock CL, Rolls BJ, Blair SN. Retention rates and weight loss in a commercial weight loss program. *Int J Obes (Lond)*. 2007;31(2):292-8.
919. Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann Intern Med*. 2005;142(1):56-66.
920. Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. *JAMA*. 2003;289(14):1792-8.
921. Paul-Ebhohimhen V, Avenell A. A systematic review of the effectiveness of group versus individual treatments for adult obesity. *Obes Facts*. 2009;2(1):17-24.
922. Madigan CD, Daley AJ, Lewis AL, Jolly K, Aveyard P. Which weight-loss programmes are as effective as Weight Watchers®?: non-inferiority analysis. *Br J Gen Pract*. 2014;64(620):e128-36.

923. Wagonfeld S, Wolowitz HM. Obesity and the self-help group: a look at TOPS. *Am J Psychiatry*. 1968;125(2):249-52.
924. Mitchell NS, Dickinson LM, Kempe A, Tsai AG. Determining the effectiveness of Take Off Pounds Sensibly (TOPS), a nationally available nonprofit weight loss program. *Obesity (Silver Spring)*. 2011;19(3):568-73.
925. Mitchell NS, Polsky S, Catenacci VA, Furniss AL, Prochazka AV. Up to 7 years of sustained weight loss for weight-loss program completers. *Am J Prev Med*. 2015;49(2):248-58.
926. Stunkard AJ. The management of obesity. *NY State J of Med*. 1958;58:79-87.
927. Calder RK, Mussap AJ. Factors influencing women's choice of weight-loss diet. *J Health Psychol*. 2015;20(5):612-24.
928. Slavich GM. Understanding inflammation, its regulation, and relevance for health: a top scientific and public priority. *Brain Behav Immun*. 2015;45:13-4.
929. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9(11):E95.
930. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9(11):E95.
931. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003;108(12):e81-5.
932. Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ*. 2016;115(6):317-21.
933. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003;108(12):e81-5.
934. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003;108(12):e81-5.
935. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9(11):E95.
936. Egger G, Dixon J. Non-nutrient causes of low-grade, systemic inflammation: support for a "canary in the mineshaft" view of obesity in chronic disease. *Obes Rev*. 2011;12(5):339-45.
937. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689-96.
938. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689-96.
939. Shivappa N, Godos J, Hébert JR, et al. Dietary Inflammatory Index and cardiovascular risk and mortality—a meta-analysis. *Nutrients*. 2018;10(2):200.
940. Xu H, Sjögren P, Årnlöv J, et al. A proinflammatory diet is associated with systemic inflammation and reduced kidney function in elderly adults. *J Nutr*. 2015;145(4):729-35.
941. Han YY, Forno E, Shivappa N, Wirth MD, Hébert JR, Celedón JC. The Dietary Inflammatory Index and current wheeze among children and adults in the United States. *J Allergy Clin Immunol Pract*. 2018;6(3):834-41.
942. Cantero I, Abete I, Babio N, et al. Dietary Inflammatory Index and liver status in subjects with different adiposity levels within the PREDIMED trial. *Clin Nutr*. 2018;37(5):1736-43.
943. Shivappa N, Wirth MD, Hurley TG, Hébert JR. Association between the dietary inflammatory index (DII) and telomere length and C-reactive protein from the National Health and Nutrition Examination Survey—1999-2002. *Mol Nutr Food Res*. 2017;61(4).
944. García-Calzón S, Zalba G, Ruiz-Canela M, et al. Dietary inflammatory index and telomere length in subjects with a high cardiovascular disease risk from the PREDIMED-NAVARRA study: cross-sectional and longitudinal analyses over 5 y. *Am J Clin Nutr*. 2015;102(4):897-904.
945. Frith E, Shivappa N, Mann JR, Hébert JR, Wirth MD, Loprinzi PD. Dietary inflammatory index and memory function: population-based national sample of elderly Americans. *Br J Nutr*. 2018;119(5):552-8.
946. Shivappa N, Stubbs B, Hébert JR, et al. The relationship between the Dietary Inflammatory Index and incident frailty: a longitudinal cohort study. *J Am Med Dir Assoc*. 2018;19(1):77-82.
947. Phillips CM, Shivappa N, Hébert JR, Perry JJ. Dietary inflammatory index and mental health: a cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. *Clin Nutr*. 2018;37(5):1485-91.
948. Shivappa N, Jackson MD, Bennett F, Hébert JR. Increased Dietary Inflammatory Index (DII) is associated with increased risk of prostate cancer in Jamaican men. *Nutr Cancer*. 2015;67(6):941-8.
949. Shivappa N, Hébert JR, Jalilpiran Y, Faghih S. Association between Dietary Inflammatory Index and prostate cancer in Shiraz province of Iran. *Asian Pac J Cancer Prev*. 2018;19(2):415-20.
950. Shivappa N, Miao Q, Walker M, Hébert JR, Aronson KJ. Association between a Dietary Inflammatory Index and prostate cancer risk in Ontario, Canada. *Nutr Cancer*. 2017;69(6):825-32.
951. Huang WQ, Mo XF, Ye YB, et al. A higher Dietary Inflammatory Index score is associated with a higher risk of breast cancer among Chinese women: a case-control study. *Br J Nutr*. 2017;117(10):1358-67.
952. Shivappa N, Sandin S, Löf M, Hébert JR, Adami HO, Weiderpass E. Prospective study of dietary inflammatory index and risk of breast cancer in Swedish women. *Br J Cancer*. 2015;113(7):1099-103.
953. Shivappa N, Hébert JR, Zucchetto A, et al. Dietary inflammatory index and endometrial cancer risk in an Italian case-control study. *Br J Nutr*. 2016;115(1):138-46.
954. Shivappa N, Hébert JR, Rosato V, et al. Dietary inflammatory index and ovarian cancer risk in a large Italian case-control study. *Cancer Causes Control*. 2016;27(7):897-906.
955. Shivappa N, Zucchetto A, Serraino D, Rossi M, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Italy. *Cancer Causes Control*. 2015;26(10):1439-47.
956. Shivappa N, Hébert JR, Ferraroni M, La Vecchia C, Rossi M. Association between dietary inflammatory index and gastric cancer risk in an Italian case-control study. *Nutr Cancer*. 2016;68(8):1262-8.
957. Shivappa N, Hébert JR, Polesel J, et al. Inflammatory potential of diet and risk for hepatocellular cancer in a case-control study from Italy. *Br J Nutr*. 2016;115(2):324-31.
958. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. *Br J Nutr*. 2015;113(2):292-8.
959. Shivappa N, Godos J, Hébert JR, et al. Dietary Inflammatory Index and colorectal cancer risk—a meta-analysis. *Nutrients*. 2017 Sep 20;9(9):1043.
960. Shivappa N, Hébert JR, Rosato V, et al. Dietary Inflammatory Index and renal cell carcinoma risk in an Italian case-control study. *Nutr Cancer*. 2017;69(6):833-9.

961. Shivappa N, Hébert JR, Rosato V, et al. Dietary Inflammatory Index and risk of bladder cancer in a large Italian case-control study. *Urology*. 2017;100:84-9.
962. Shivappa N, Hébert JR, Taborelli M, et al. Dietary inflammatory index and non-Hodgkin lymphoma risk in an Italian case-control study. *Cancer Causes Control*. 2017;28(7):791-9.
963. Fowler ME, Akinyemiju TF. Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. *Int J Cancer*. 2017;141(11):2215-27.
964. Shivappa N, Hebert JR, Kivimaki M, Akbaraly T. Alternate Healthy Eating Index 2010, Dietary Inflammatory Index and risk of mortality: results from the Whitehall II cohort study and meta-analysis of previous Dietary Inflammatory Index and mortality studies. *Br J Nutr*. 2017;118(3):210-21.
965. Edwards MK, Shivappa N, Mann JR, Hébert JR, Wirth MD, Loprinzi PD. The association between physical activity and dietary inflammatory index on mortality risk in U.S. adults. *Phys Sportsmed*. 2018;46(2):249-54.
966. Shivappa N, Harris H, Wolk A, Hebert JR. Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. *Eur J Nutr*. 2016;55(5):1891-900.
967. Shivappa N, Blair CK, Prizment AE, Jacobs DR, Steck SE, Hébert JR. Association between inflammatory potential of diet and mortality in the Iowa Women's Health study. *Eur J Nutr*. 2016;55(4):1491-502.
968. Ruiz-Canela M, Zazpe I, Shivappa N, et al. Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PREvención con Dieta MEDiterránea) trial. *Br J Nutr*. 2015;113(6):984-95.
969. Ramallal R, Toledo E, Martínez JA, et al. Inflammatory potential of diet, weight gain, and incidence of overweight/obesity: the SUN cohort. *Obesity (Silver Spring)*. 2017;25(6):997-1005.
970. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev*. 2013;14(3):232-44.
971. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13(4):851-63.
972. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13(4):851-63.
973. Pasarica M, Sereda OR, Redman LM, et al. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes*. 2009;58(3):718-25.
974. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796-808.
975. Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res*. 2005;46(11):2347-55.
976. Bays HE, González-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther*. 2008;6(3):343-68.
977. Welsh P, Polisecki E, Robertson M, et al. Unraveling the directional link between adiposity and inflammation: a bidirectional Mendelian randomization approach. *J Clin Endocrinol Metab*. 2010;95(1):93-9.
978. Timpson NJ, Nordestgaard BG, Harbord RM, et al. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. *Int J Obes (Lond)*. 2011;35(2):300-8.
979. Kreutzer C, Peters S, Schulte DM, et al. Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors. *Diabetes*. 2017;66(9):2407-15.
980. National Center for Health Statistics. FastStats: obesity and overweight. Centers for Disease Control and Prevention. Published June 13, 2016. Available at: <https://www.cdc.gov/nchs/fastats/obesity-overweight.htm>. Accessed on March 31, 2019.
981. Araújo EP, Torsoni MA, Velloso LA. Hypothalamic inflammation and obesity. *Vitam Horm*. 2010;82:129-43.
982. Friedman JM. Modern science versus the stigma of obesity. *Nat Med*. 2004;10(6):563-9.
983. Allison DB, Heshka S, Sepulveda D, Heymsfield SB. Counting calories—caveat emptor. *JAMA*. 1993;270(12):1454-6.
984. Timper K, Brüning JC. Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity. *Dis Model Mech*. 2017;10(6):679-89.
985. Sims EA. Experimental obesity, dietary-induced thermogenesis, and their clinical implications. *Clin Endocrinol Metab*. 1976;5(2):377-95.
986. Sims EA, Goldman RF, Gluck CM, Horton ES, Kelleher PC, Rowe DW. Experimental obesity in man. *Trans Assoc Am Physicians*. 1968;81:153-70.
987. Thaler JP, Guyenet SJ, Dorfman MD, Wisse BE, Schwartz MW. Hypothalamic inflammation: marker or mechanism of obesity pathogenesis? *Diabetes*. 2013;62(8):2629-34.
988. Mohr B. Neuropathology communication from Dr. Mohr, privat docent in Würzburg. 1840. *Obes Res*. 1993;1(4):334-5.
989. Hochberg I, Hochberg Z. Expanding the definition of hypothalamic obesity. *Obes Rev*. 2010;11(10):709-21.
990. Skorzevska A, Lal S, Wasserman J, Guyda H. Abnormal food-seeking behavior after surgery for craniopharyngioma. *Neuropsychobiology*. 1989;21(1):17-20.
991. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997;387(6636):903-8.
992. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med*. 1999;341(12):879-84.
993. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA*. 1999;282(16):1568-75.
994. Cunha DA, Igoillo-Esteve M, Gurzov EN, et al. Death protein 5 and p53-upregulated modulator of apoptosis mediate the endoplasmic reticulum stress-mitochondrial dialog triggering lipotoxic rodent and human β -cell apoptosis. *Diabetes*. 2012;61(11):2763-75.
995. Jais A, Brüning JC. Hypothalamic inflammation in obesity and metabolic disease. *J Clin Invest*. 2017;127(1):24-32.
996. Laposata M. Fatty acids: biochemistry to clinical significance. *Am J Clin Pathol*. 1995;104(2):172-9.

997. Sergi D, Kahn DE, Morris AC, Williams LM. Palmitic acid induces inflammation in hypothalamic neurons via ceramide synthesis. *Proc Nutr Soc.* 2016;75(OCE2):E46.
998. Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Rep.* 2014;9(6):2124-38.
999. Berkseth KE, Guyenet SJ, Melhorn SJ, et al. Hypothalamic gliosis associated with high-fat diet feeding is reversible in mice: a combined immunohistochemical and magnetic resonance imaging study. *Endocrinology.* 2014;155(8):2858-67.
1000. Ioannidis JP. Extrapolating from animals to humans. *Sci Transl Med.* 2012;4(151):151ps15.
1001. Lai M, Chandrasekera PC, Barnard ND. You are what you eat, or are you? The challenges of translating high-fat-fed rodents to human obesity and diabetes. *Nutr Diabetes.* 2014;4:e135.
1002. Borg ML, Omran SF, Weir J, Meikle PJ, Watt MJ. Consumption of a high-fat diet, but not regular endurance exercise training, regulates hypothalamic lipid accumulation in mice. *J Physiol (Lond).* 2012;590(17):4377-89.
1003. Agricultural Research Service, United States Department of Agriculture. Basic report: 10860, pork, cured, bacon, cooked, baked. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301584>. Accessed March 31, 2019.
1004. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 2012;122(1):153-62.
1005. Schur EA, Melhorn SJ, Oh SK, et al. Radiologic evidence that hypothalamic gliosis is associated with obesity and insulin resistance in humans. *Obesity (Silver Spring).* 2015;23(11):2142-8.
1006. Kreutzer C, Peters S, Schulte DM, et al. Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors. *Diabetes.* 2017;66(9):2407-15.
1007. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr.* 2013;97(4):689-97.
1008. Dumas JA, Bunn JY, Nickerson J, et al. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. *Metab Clin Exp.* 2016;65(10):1582-8.
1009. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr.* 2013;97(4):689-97.
1010. Gan L, England E, Yang JY, et al. A 72-hour high fat diet increases transcript levels of the neuropeptide galanin in the dorsal hippocampus of the rat. *BMC Neurosci.* 2015;16:51.
1011. Hargrave SL, Jones S, Davidson TL. The outward spiral: a vicious cycle model of obesity and cognitive dysfunction. *Curr Opin Behav Sci.* 2016;9:40-6.
1012. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. *BMC Med.* 2015;13:215.
1013. Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. *Neurology.* 2004;62(9):1573-9.
1014. Edwards LM, Murray AJ, Holloway CJ, et al. Short-term consumption of a high-fat diet impairs whole-body efficiency and cognitive function in sedentary men. *FASEB J.* 2011;25(3):1088-96.
1015. Holloway CJ, Cochlin LE, Emmanuel Y, et al. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. *Am J Clin Nutr.* 2011;93(4):748-55.
1016. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE.* 2017;12(2):e0172645.
1017. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE.* 2017;12(2):e0172645.
1018. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE.* 2017;12(2):e0172645.
1019. Hernández EÁ, Kahl S, Seelig A, et al. Acute dietary fat intake initiates alterations in energy metabolism and insulin resistance. *J Clin Invest.* 2017;127(2):695-708.
1020. Parks E, Yki-Järvinen H, Hawkins M. Out of the frying pan: dietary saturated fat influences nonalcoholic fatty liver disease. *J Clin Invest.* 2017;127(2):454-6.
1021. Shivappa N, Steck SE, Hurlley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2014;17(8):1689-96.
1022. United States Department of Health and Human Services, United States Department of Agriculture. Appendix 13. Food sources of dietary fiber. *2015-2020 Dietary Guidelines for Americans. 8th Edition.* DietaryGuidelines.gov. Published December 2015. Available at: <https://health.gov/dietaryguidelines/2015/guidelines/appendix-13>. Accessed March 31, 2019.
1023. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: food sources, bioavailability, metabolism, and bioactivity. *Adv Nutr.* 2017;8(3):423-35.
1024. Haytowitz DB, Bhagwat S, Harnly J, Holden JM, Gebhardt SE. Sources of flavonoids in the U.S. diet using USDA's updated database on the flavonoid content of selected foods. United States Department of Agriculture. 2006. Available at: https://www.ars.usda.gov/ARSUserFiles/80400525/Articles/AICR06_flav.pdf. Accessed on March 31, 2019.
1025. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: food sources, bioavailability, metabolism, and bioactivity. *Adv Nutr.* 2017;8(3):423-35.
1026. Epidemiology and Genomics Research Program. Top food sources of saturated fat among U.S. population, 2005-2006 NHANES. National Cancer Institute Division of Cancer Control and Population Sciences, National Institutes of Health.

- Health. Updated April 20, 2018. Available at: https://epi.grants.cancer.gov/diet/foodsources/sat_fat/sf.html. Accessed March 31, 2019.
1027. Exler J, Lemar L, Smith J. Fat and fatty acid content of selected foods containing trans-fatty acids. United States Department of Agriculture. Published January 1996. Available at: https://www.ars.usda.gov/arsuserfiles/80400525/data/classics/trans_fa.pdf. Accessed March 31, 2019.
 1028. Ricker MA, Haas WC. Anti-inflammatory diet in clinical practice: a review. *Nutr Clin Pract*. 2017;32(3):318-25.
 1029. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689-96.
 1030. Muldoon MF, Laderian B, Kuan DC, Sereika SM, Marsland AL, Manuck SB. Fish oil supplementation does not lower C-reactive protein or interleukin-6 levels in healthy adults. *J Intern Med*. 2016;279(1):98-109.
 1031. Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α : a meta-analysis. *PLoS ONE*. 2014;9(2):e88103.
 1032. Gopinath B, Buyken AE, Flood VM, Empson M, Rochtchina E, Mitchell P. Consumption of polyunsaturated fatty acids, fish, and nuts and risk of inflammatory disease mortality. *Am J Clin Nutr*. 2011;93(5):1073-9.
 1033. Raymond MR, Christensen KY, Thompson BA, Anderson HA. Associations between fish consumption and contaminant biomarkers with cardiovascular conditions among older male anglers in Wisconsin. *J Occup Environ Med*. 2016;58(7):676-82.
 1034. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med*. 2002;8(2):185-92.
 1035. Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environ Health Perspect*. 2012;120(6):779-89.
 1036. Lind L, Lind PM, Lejonklou MH, et al. Uppsala consensus statement on environmental contaminants and the global obesity epidemic. *Environ Health Perspect*. 2016;124(5):A81-3.
 1037. Davy BM, Estabrooks PA. The validity of self-reported dietary intake data: focus on the "What We Eat In America" component of the National Health and Nutrition Examination Survey research initiative. *Mayo Clin Proc*. 2015;90(7):845-7.
 1038. Chamorro-García R, Sahu M, Abbey RJ, Laude J, Pham N, Blumberg B. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice. *Environ Health Perspect*. 2013;121(3):359-66.
 1039. Baynes RE, Dedonder K, Kissell L, et al. Health concerns and management of select veterinary drug residues. *Food Chem Toxicol*. 2016;88:112-22.
 1040. Nachman KE, Raber G, Francesconi KA, Navas-Acien A, Love DC. Arsenic species in poultry feather meal. *Sci Total Environ*. 2012;417-8:183-8.
 1041. Love DC, Halden RU, Davis MF, Nachman KE. Feather meal: a previously unrecognized route for reentry into the food supply of multiple pharmaceuticals and personal care products (PPCPs). *Environ Sci Technol*. 2012;46(7):3795-802.
 1042. Love DC, Halden RU, Davis MF, Nachman KE. Feather meal: a previously unrecognized route for reentry into the food supply of multiple pharmaceuticals and personal care products (PPCPs). *Environ Sci Technol*. 2012;46(7):3795-802.
 1043. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med*. 2002;8(2):185-92.
 1044. Day MJ. One Health approach to preventing obesity in people and their pets. *J Comp Pathol*. 2017;156(4):293-5.
 1045. Klimentidis YC, Beasley TM, Lin HY, et al. Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics. *Proc Biol Sci*. 2011;278(1712):1626-32.
 1046. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559-65.
 1047. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. *Nat Rev Endocrinol*. 2015;11(11):653-61.
 1048. Gore AC, Crews D, Doan LL, La Merrill M, Patisaul H, Zota A. Introduction to endocrine disrupting chemicals (EDCs): a guide for public interest organizations and policy-makers. Endocrine Society, IPEN. Published December 2014. Available at: http://ipen.org/sites/default/files/documents/ipen-intro-edc-v1_9a-en-web.pdf. Accessed March 31, 2019.
 1049. Sousa ACA, Pastorinho MR, Takahashi S, et al. History on organotin compounds, from snails to humans. *Environ Chem Lett*. 2014;12(117):117-37.
 1050. Filipkowska A, Zloch I, Wawrzyniak-Wydrowska B, Kowalewska G. Organotins in fish muscle and liver from the Polish coast of the Baltic Sea: is the total ban successful? *Mar Pollut Bull*. 2016;111(1-2):493-9.
 1051. Holtcamp W. Obesogens: an environmental link to obesity. *Environ Health Perspect*. 2012;120(2):a62-8.
 1052. Holtcamp W. Obesogens: an environmental link to obesity. *Environ Health Perspect*. 2012;120(2):a62-8.
 1053. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559-65.
 1054. Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. *Birth Defects Res C Embryo Today*. 2011;93(1):34-50.
 1055. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559-65.
 1056. Darbre PD. Endocrine disruptors and obesity. *Curr Obes Rep*. 2017;6(1):18-27.
 1057. Pillai HK, Fang M, Beglov D, et al. Ligand binding and activation of PPAR γ by Firemaster® 550: effects on adipogenesis and osteogenesis in vitro. *Environ Health Perspect*. 2014;122(11):1225-32.
 1058. Rosen CJ, Bouxsein ML. Mechanisms of disease: is osteoporosis the obesity of bone? *Nat Clin Pract Rheumatol*. 2006;2(1):35-43.
 1059. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008;31(5):845-51.
 1060. Sousa ACA, Pastorinho MR, Takahashi S, et al. History on organotin compounds, from snails to humans. *Environ Chem Lett*. 2014;12(117):117-37.

1061. Filipkowska A, Zloch I, Wawrzyniak-Wydrowska B, Kowalewska G. Organotins in fish muscle and liver from the Polish coast of the Baltic Sea: is the total ban successful? *Mar Pollut Bull.* 2016;111(1-2):493-9.
1062. Guérin T, Sirost V, Volatier JL, Leblanc JC. Organotin levels in seafood and its implications for health risk in high-seafood consumers. *Sci Total Environ.* 2007;388(1-3):66-77.
1063. Cardwell RD, Keithly J, Simmonds J. Tributyltin in U.S. market-bought seafood and assessment of human health risks. *Hum Ecol Risk Assess.* 1999;5(2):317-35.
1064. Belfroid AC, Purperhart M, Ariese F. Organotin levels in seafood. *Mar Pollut Bull.* 2000;40(3):226-32.
1065. Zoeller RT. Regulation of endocrine-disrupting chemicals insufficient to safeguard public health. *J Clin Endocrinol Metab.* 2014;99(6):1993-4.
1066. Fromberg A, Granby K, Højgård A, Fagt S, Larsen JC. Estimation of dietary intake of PCB and organochlorine pesticides for children and adults. *Food Chem.* 2011;125:1179-87.
1067. Cano-Sancho G, Salmon AG, La Merrill MA. Association between exposure *p,p'*-DDT and its *p,p'*-DDE with obesity: integrated systematic review and meta-analysis. *Environ Health Perspect.* 2017;125(9):096002.
1068. Legler J, Fletcher T, Govarts E, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab.* 2015;100(4):1278-88.
1069. Howden LM, Meyer JA. Age and sex composition, 2010. United States Census Bureau. Published May 2011. Available at: <https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>. Accessed March 31, 2019.
1070. Child and Adolescent Health Measurement Initiative. 2016 National Survey of Children's Health (NSCH) data query. Data Resource Center for Child and Adolescent Health. Available at: <https://www.childhealthdata.org>. Accessed March 31, 2019.
1071. Legler J, Fletcher T, Govarts E, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab.* 2015;100(4):1278-88.
1072. Rochester JR. Bisphenol A and human health: a review of the literature. *Reprod Toxicol.* 2013;42:132-55.
1073. Dodds EC, Lawson W. Synthetic estrogenic agents without the phenanthrene nucleus. *Nature.* 1936;137:996.
1074. Eladak S, Grisin T, Moison D, et al. A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound. *Fertil Steril.* 2015;103(1):11-21.
1075. Rezg R, El-Fazaa S, Gharbi N, Mornagui B. Bisphenol A and human chronic diseases: current evidences, possible mechanisms, and future perspectives. *Environ Int.* 2014;64:83-90.
1076. Masuno H, Iwanami J, Kidani T, Sakayama K, Honda K. Bisphenol A accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci.* 2005;84(2):319-27.
1077. Boucher JG, Boudreau A, Atlas E. Bisphenol A induces differentiation of human preadipocytes in the absence of glucocorticoid and is inhibited by an estrogen-receptor antagonist. *Nutr Diabetes.* 2014;4:e102.
1078. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect.* 2008;116(1):39-44.
1079. Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Environ Health Perspect.* 2010;118(8):1055-70.
1080. Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. *Endocrinology.* 1993;132(6):2279-86.
1081. Wang J, Sun B, Hou M, Pan X, Li X. The environmental obesogen bisphenol A promotes adipogenesis by increasing the amount of 11 β -hydroxysteroid dehydrogenase type 1 in the adipose tissue of children. *Int J Obes (Lond).* 2013;37(7):999-1005.
1082. Ben-Jonathan N, Hуго ER, Brandebourg TD. Effects of bisphenol A on adipokine release from human adipose tissue: implications for the metabolic syndrome. *Mol Cell Endocrinol.* 2009;304(1-2):49-54.
1083. Ohlstein JF, Strong AL, McLachlan JA, Gimble JM, Burow ME, Bunnell BA. Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells. *J Mol Endocrinol.* 2014;53(3):345-53.
1084. Holtkamp W. Obesogens: an environmental link to obesity. *Environ Health Perspect.* 2012;120(2):a62-8.
1085. Boucher JG, Boudreau A, Ahmed S, Atlas E. In vitro effects of bisphenol A β -D-glucuronide (BPA-G) on adipogenesis in human and murine preadipocytes. *Environ Health Perspect.* 2015;123(12):1287-93.
1086. Legeay S, Faure S. Is bisphenol A an environmental obesogen? *Fundam Clin Pharmacol.* 2017;31(6):594-609.
1087. Do MT, Chang VC, Mendez MA, de Groh M. Urinary bisphenol A and obesity in adults: results from the Canadian Health Measures Survey. *Health Promot Chronic Dis Prev Can.* 2017;37(12):403-12.
1088. Rancière F, Lyons JG, Loh VH, et al. Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health.* 2015;14:46.
1089. Corbasson I, Hankinson SE, Stanek EJ III, Reeves KW. Urinary bisphenol-A, phthalate metabolites and body composition in US adults, NHANES 1999-2006. *Int J Environ Health Res.* 2016;26(5-6):606-17.
1090. Li DK, Zhou Z, Miao M, et al. Relationship between urine bisphenol-A level and declining male sexual function. *J Androl.* 2010;31(5):500-6.
1091. Geens T, Aerts D, Berthot C, et al. A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem Toxicol.* 2012;50(10):3725-40.
1092. Hormann AM, vom Saal FS, Nagel SC, et al. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). *PLoS ONE.* 2014;9(10):e110509.
1093. Geens T, Aerts D, Berthot C, et al. A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem Toxicol.* 2012;50(10):3725-40.
1094. Christensen KL, Lorber M, Koslitz S, Brüning T, Koch HM. The contribution of diet to total bisphenol A body burden in humans: results of a 48 hour fasting study. *Environ Int.* 2012;50:7-14.
1095. Trasande L. Further limiting bisphenol A in food uses could provide health and economic benefits. *Health Aff (Millwood).* 2014;33(2):316-23.
1096. Rudel RA, Gray JM, Engel CL, et al. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect.* 2011;119(7):914-20.
1097. Carwile JL, Ye X, Zhou X, Calafat AM, Michels KB. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. *JAMA.* 2011;306(20):2218-20.

1098. Bertoli S, Leone A, Battezzati A. Human bisphenol A exposure and the “diabesity phenotype.” *Dose Response*. 2015;13(3):1559325815599173.
1099. Schechter A, Malik N, Haffner D, et al. Bisphenol A (BPA) in U.S. food. *Environ Sci Technol*. 2010;44(24):9425-30.
1100. Song Y, Hauser R, Hu FB, Franke AA, Liu S, Sun Q. Urinary concentrations of bisphenol A and phthalate metabolites and weight change: a prospective investigation in US women. *Int J Obes (Lond)*. 2014;38(12):1532-7.
1101. Legler J, Fletcher T, Govarts E, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015;100(4):1278-88.
1102. Koch HM, Lorber M, Christensen KL, Pålme C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: results of a 48h fasting study with urine collection and personal activity patterns. *Int J Hyg Environ Health*. 2013;216(6):672-81.
1103. Ji K, Lim Kho Y, Park Y, Choi K. Influence of a five-day vegetarian diet on urinary levels of antibiotics and phthalate metabolites: a pilot study with “Temple Stay” participants. *Environ Res*. 2010;110(4):375-82.
1104. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43.
1105. Colacino JA, Harris TR, Schechter A. Dietary intake is associated with phthalate body burden in a nationally representative sample. *Environ Health Perspect*. 2010;118(7):998-1003.
1106. Castle L, Gilbert J, Eklund T. Migration of plasticizer from poly(vinyl chloride) milk tubing. *Food Addit Contam*. 1990;7(5):591-6.
1107. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43.
1108. Gore AC, Crews D, Doan LL, La Merrill M, Patisaul H, Zota A. Introduction to endocrine disrupting chemicals (EDCs): a guide for public interest organizations and policy-makers. Endocrine Society, IPEN. Published December 2014. Available at: http://ipen.org/sites/default/files/documents/ipen-intro-edc-v1_9a-en-web.pdf. Accessed March 31, 2019.
1109. Gore AC, Crews D, Doan LL, La Merrill M, Patisaul H, Zota A. Introduction to endocrine disrupting chemicals (EDCs): a guide for public interest organizations and policy-makers. Endocrine Society, IPEN. Published December 2014. Available at: http://ipen.org/sites/default/files/documents/ipen-intro-edc-v1_9a-en-web.pdf. Accessed March 31, 2019.
1110. Corbasson I, Hankinson SE, Stanek EJ, Reeves KW. Urinary bisphenol-A, phthalate metabolites and body composition in US adults, NHANES 1999-2006. *Int J Environ Health Res*. 2016;26(5-6):606-17.
1111. United States Food and Drug Administration. Bisphenol A (BPA): use in food contact application. Updated June 27, 2018. Available at: <https://www.fda.gov/newsevents/publichealthfocus/ucm064437.htm>. Accessed March 31, 2019.
1112. Dallio M, Masarone M, Errico S, et al. Role of bisphenol A as environmental factor in the promotion of non-alcoholic fatty liver disease: in vitro and clinical study. *Aliment Pharmacol Ther*. 2018;47(6):826-37.
1113. United States Consumer Product Safety Commission. CPSC prohibits certain phthalates in children’s toys and child care products. Published October 20, 2017. Available at: <https://www.cpsc.gov/content/cpsc-prohibits-certain-phthalates-in-children%E2%80%99s-toys-and-child-care-products>. Accessed March 31, 2019.
1114. Nilsson NH, Malmgren-Hansen B, Bernth N, Pedersen E, Pommer K. Survey and health assessment of chemicals substances in sex toys. Survey of Chemical Substances in Consumer Products. 2006;77:1-85. Available at: <https://www2.mst.dk/udgiv/publications/2006/87-7052-227-8/pdf/87-7052-228-6.pdf>. Accessed March 31, 2019.
1115. Barrett ES, Parlett LE, Wang C, Drobnis EZ, Redmon JB, Swan SH. Environmental exposure to di-2-ethylhexyl phthalate is associated with low interest in sexual activity in premenopausal women. *Horm Behav*. 2014;66(5):787-92.
1116. Domingo JL, Nadal M. Carcinogenicity of consumption of red and processed meat: what about environmental contaminants? *Environ Res*. 2016;145:109-15.
1117. Trafialek J, Kolanowski W. Dietary exposure to meat-related carcinogenic substances: is there a way to estimate the risk? *Int J Food Sci Nutr*. 2014;65(6):774-80.
1118. Wu CC, Bao LJ, Guo Y, Li SM, Zeng EY. Barbecue fumes: an overlooked source of health hazards in outdoor settings? *Environ Sci Technol*. 2015;49(17):10607-15.
1119. Scinicariello F, Buser MC. Urinary polycyclic aromatic hydrocarbons and childhood obesity: NHANES (2001-2006). *Environ Health Perspect*. 2014;122(3):299-303.
1120. Steck SE, Gaudet MM, Eng SM, et al. Cooked meat and risk of breast cancer—lifetime versus recent dietary intake. *Epidemiology*. 2007;18(3):373-82.
1121. Rundle A, Hoepner L, Hassoun A, et al. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol*. 2012;175(11):1163-72.
1122. Van Rooij JG, Veeger MM, Bodelier-Bade MM, Scheepers PT, Jongeneelen FJ. Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of interindividual variability in the baseline excretion of 1-hydroxypyrene in urine. *Int Arch Occup Environ Health*. 1994;66(1):55-65.
1123. Ramesh A, Walker SA, Hood DB, Guillén MD, Schneider K, Weyand EH. Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol*. 2004;23(5):301-33.
1124. Harris KL, Banks LD, Mantey JA, Huderson AC, Ramesh A. Bioaccessibility of polycyclic aromatic hydrocarbons: relevance to toxicity and carcinogenesis. *Expert Opin Drug Metab Toxicol*. 2013;9(11):1465-80.
1125. Crinnion WJ. The role of persistent organic pollutants in the worldwide epidemic of type 2 diabetes mellitus and the possible connection to farmed Atlantic salmon (*Salmo salar*). *Altern Med Rev*. 2011;16(4):301-13.
1126. Li Z, Romanoff L, Bartell S, et al. Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chem Res Toxicol*. 2012;25(7):1452-61.
1127. Li QQ, Loganath A, Chong YS, Tan J, Obbard JP. Persistent organic pollutants and adverse health effects in humans. *J Toxicol Environ Health Part A*. 2006;69(21):1987-2005.
1128. Schafer KS, Kegley SE. Persistent toxic chemicals in the US food supply. *J Epidemiol Community Health*. 2002;56(11):813-7.
1129. Dearfield KL, Edwards SR, O’Keefe MM, et al. Dietary estimates of dioxins consumed in U.S. Department of Agriculture-regulated meat and poultry products. *J Food Prot*. 2013;76(9):1597-607.

1130. Hernández ÁR, Boada LD, Almeida-González M, et al. An estimation of the carcinogenic risk associated with the intake of multiple relevant carcinogens found in meat and charcuterie products. *Sci Total Environ*. 2015;514:33–41.
1131. Hernández ÁR, Boada LD, Almeida-González M, et al. An estimation of the carcinogenic risk associated with the intake of multiple relevant carcinogens found in meat and charcuterie products. *Sci Total Environ*. 2015;514:33–41.
1132. Huwe JK, Larsen GL. Polychlorinated dioxins, furans, and biphenyls, and polybrominated diphenyl ethers in a U.S. meat market basket and estimates of dietary intake. *Environ Sci Technol*. 2005;39(15):5606–11.
1133. Fang M, Webster TF, Ferguson PL, Stapleton HM. Characterizing the peroxisome proliferator-activated receptor (PPAR γ) ligand binding potential of several major flame retardants, their metabolites, and chemical mixtures in house dust. *Environ Health Perspect*. 2015;123(2):166–72.
1134. Pillai HK, Fang M, Beglov D, et al. Ligand binding and activation of PPAR γ by Firemaster® 550: effects on adipogenesis and osteogenesis in vitro. *Environ Health Perspect*. 2014;122(11):1225–32.
1135. Fraser AJ, Webster TF, McClean MD. Diet contributes significantly to the body burden of PBDEs in the general U.S. population. *Environ Health Perspect*. 2009;117(10):1520–5.
1136. Hergenrath J, Hlady G, Wallace B, Savage E. Pollutants in breast milk of vegetarians. *N Engl J Med*. 1981;304(13):792.
1137. Lee YM, Kim KS, Jacobs DR, Lee DH. Persistent organic pollutants in adipose tissue should be considered in obesity research. *Obes Rev*. 2017;18(2):129–39.
1138. Srikumar TS, Källgård B, Ockerman PA, Akesson B. The effects of a 2-year switch from a mixed to a lactovegetarian diet on trace element status in hypertensive subjects. *Eur J Clin Nutr*. 1992;46(9):661–9.
1139. Hernández ÁR, Boada LD, Mendoza Z, et al. Consumption of organic meat does not diminish the carcinogenic potential associated with the intake of persistent organic pollutants (POPs). *Environ Sci Pollut Res Int*. 2017;24(5):4261–73.
1140. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care*. 2006;29(7):1638–44.
1141. Ax E, Lampa E, Lind L, et al. Circulating levels of environmental contaminants are associated with dietary patterns in older adults. *Environ Int*. 2015;75:93–102.
1142. Ax E, Lampa E, Lind L, et al. Circulating levels of environmental contaminants are associated with dietary patterns in older adults. *Environ Int*. 2015;75:93–102.
1143. Muscogiuri G, Barrea L, Laudisio D, Savastano S, Colao A. Obesogenic endocrine disruptors and obesity: myths and truths. *Arch Toxicol*. 2017;91(11):3469–75.
1144. Jansen A, Lyche JL, Polder A, Aaseth J, Skaug MA. Increased blood levels of persistent organic pollutants (POP) in obese individuals after weight loss—a review. *J Toxicol Environ Health B Crit Rev*. 2017;20(1):22–37.
1145. Hue O, Marcotte J, Berrigan F, et al. Increased plasma levels of toxic pollutants accompanying weight loss induced by hypocaloric diet or by bariatric surgery. *Obes Surg*. 2006;16(9):1145–54.
1146. Tremblay A, Pelletier C, Doucet E, Imbeault P. Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution. *Int J Obes Relat Metab Disord*. 2004;28(7):936–9.
1147. Lee YM, Kim KS, Jacobs DR, Lee DH. Persistent organic pollutants in adipose tissue should be considered in obesity research. *Obes Rev*. 2017;18(2):129–39.
1148. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559–65.
1149. Laverda NL, Goldsmith DF, Alavanja MC, Hunting KL. Pesticide exposures and body mass index (BMI) of pesticide applicators from the Agricultural Health Study. *J Toxicol Environ Health Part A*. 2015;78(20):1255–76.
1150. Hayes TB, Khoury V, Narayan A, et al. Atrazine induces complete feminization and chemical castration in male African clawed frogs (*Xenopus laevis*). *Proc Natl Acad Sci USA*. 2010;107(10):4612–7.
1151. Laverda NL, Goldsmith DF, Alavanja MC, Hunting KL. Pesticide exposures and body mass index (BMI) of pesticide applicators from the Agricultural Health Study. *J Toxicol Environ Health Part A*. 2015;78(20):1255–76.
1152. Kesse-Guyot E, Péneau S, Méjean C, et al. Profiles of organic food consumers in a large sample of French adults: results from the Nutrinet-Santé cohort study. *PLoS ONE*. 2013;8(10):e76998.
1153. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: systematic review and meta-analysis. *PLoS ONE*. 2017;12(5):e0177151.
1154. Kim TJ, Roesler NM, von dem Knesebeck O. Causation or selection—examining the relation between education and overweight/obesity in prospective observational studies: a meta-analysis. *Obes Rev*. 2017;18(6):660–72.
1155. Kesse-Guyot E, Péneau S, Méjean C, et al. Profiles of organic food consumers in a large sample of French adults: results from the Nutrinet-Santé cohort study. *PLoS ONE*. 2013;8(10):e76998.
1156. Kesse-Guyot E, Baudry J, Assmann KE, Galan P, Hercberg S, Lairon D. Prospective association between consumption frequency of organic food and body weight change, risk of overweight or obesity: results from the NutriNet-Santé Study. *Br J Nutr*. 2017;117(2):325–34.
1157. Hyatt JW Jr. Improved molding composition to imitate ivory and other substances. United States Patent 88,633. April 6, 1869.
1158. Erren TC, Gross JV, Steffany F, Meyer-Rochow VB. “Plastic ocean”: what about cancer? *Environ Pollut*. 2015;207:436–7.
1159. Seltnerich N. New link in the food chain? Marine plastic pollution and seafood safety. *Environ Health Perspect*. 2015;123(2):A34–41.
1160. Cheung PK, Fok L. Evidence of microbeads from personal care product contaminating the sea. *Mar Pollut Bull*. 2016;109(1):582–5.
1161. Seltnerich N. New link in the food chain? Marine plastic pollution and seafood safety. *Environ Health Perspect*. 2015;123(2):A34–41.
1162. Repposi A, Farabegoli F, Gazzotti T, Zironi E, Pagliuca G. Bisphenol A in edible part of seafood. *Ital J Food Saf*. 2016;5(2):5666.
1163. Santillo D, Miller K, Johnston P. Microplastics as contaminants in commercially important seafood species. *Integr Environ Assess Manag*. 2017;13(3):516–21.

1164. Karami A, Golieskardi A, Choo CK, Larat V, Karbalaei S, Salamatinia B. Microplastic and mesoplastic contamination in canned sardines and sprats. *Sci Total Environ*. 2018;612:1380-6.
1165. Vandermeersch G, Van Cauwenberghe L, Janssen CR, et al. A critical view on microplastic quantification in aquatic organisms. *Environ Res*. 2015;143(Pt B):46-55.
1166. Karami A, Golieskardi A, Ho YB, Larat V, Salamatinia B. Microplastics in eviscerated flesh and excised organs of dried fish. *Sci Rep*. 2017;7(1):5473.
1167. Akhbarizadeh R, Moore F, Keshavarzi B. Investigating a probable relationship between microplastics and potentially toxic elements in fish muscles from northeast of Persian Gulf. *Environ Pollut*. 2018;232:154-63.
1168. Akhbarizadeh R, Moore F, Keshavarzi B. Investigating a probable relationship between microplastics and potentially toxic elements in fish muscles from northeast of Persian Gulf. *Environ Pollut*. 2018;232:154-63.
1169. Sharma S, Chatterjee S. Microplastic pollution, a threat to marine ecosystem and human health: a short review. *Environ Sci Pollut Res Int*. 2017;24(27):21530-47.
1170. Akhbarizadeh R, Moore F, Keshavarzi B. Investigating a probable relationship between microplastics and potentially toxic elements in fish muscles from northeast of Persian Gulf. *Environ Pollut*. 2018;232:154-63.
1171. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559-65.
1172. Gore AC, Crews D, Doan LL, La Merrill M, Patisaul H, Zota A. Introduction to endocrine disrupting chemicals (EDCs): a guide for public interest organizations and policy-makers. Endocrine Society, IPEN. Published December 2014. Available at: http://ipen.org/sites/default/files/documents/ipen-intro-edc-v1_9a-en-web.pdf. Accessed March 31, 2019.
1173. Roberts R. BPA exposure and health effects: educating physicians and patients. *Am Fam Physician*. 2012;85(11):1040-4.
1174. Ryan KK, Seeley RJ. Physiology. Food as a hormone. *Science*. 2013;339(6122):918-9.
1175. Schmier JK, Miller PE, Levine JA, et al. Cost savings of reduced constipation rates attributed to increased dietary fiber intakes: a decision-analytic model. *BMC Public Health*. 2014;14:374.
1176. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. 2016;14(8):e1002533.
1177. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep*. 2009;11(4):307-13.
1178. O'Hara AM, Shanahan F. The gut flora as a forgotten organ. *EMBO Rep*. 2006;7(7):688-93.
1179. Kumari M, Kozyrskij AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18-31.
1180. Haines I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients*. 2017;9(1):57.
1181. Kim YK, Shin C. The microbiota-gut-brain axis in neuropsychiatric disorders: pathophysiological mechanisms and novel treatments. *Curr Neuropsychopharmacol*. 2018;16(5):559-73.
1182. Cani PD, Joly E, Horsmans Y, Delzenne NM. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr*. 2006;60(5):567-72.
1183. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. *Nutr Rev*. 2001;59(5):129-39.
1184. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102(11):1621-30.
1185. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. *Nutr Rev*. 2001;59(5):129-39.
1186. Agricultural Research Service, United States Department of Agriculture. Basic report: 09003, apples, raw, with skin (includes foods for USDA's Food Distribution Program). National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/2122>. Accessed March 31, 2019.
1187. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45138303, Evolution Fresh, cold-pressed juice, apple, UPC: 762357515155. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45138303>. Accessed March 31, 2019.
1188. Slavin JL. Dietary fiber and body weight. *Nutrition*. 2005;21(3):411-8.
1189. McCance RA, Prior KM, Widdowson EM. A radiological study of the rate of passage of brown and white bread through the digestive tract of man. *Br J Nutr*. 1953;7(1-2):98-104.
1190. Berthoud HR. The vagus nerve, food intake and obesity. *Regul Pept*. 2008;149(1-3):15-25.
1191. Lyon MR, Kacinik V. Is there a place for dietary fiber supplements in weight management? *Curr Obes Rep*. 2012;1(2):59-67.
1192. Benini L, Castellani G, Brighenti F, et al. Gastric emptying of a solid meal is accelerated by the removal of dietary fibre naturally present in food. *Gut*. 1995;36(6):825-30.
1193. Southgate DA, Durnin JV. Calorie conversion factors. An experimental reassessment of the factors used in the calculation of the energy value of human diets. *Br J Nutr*. 1970;24(2):517-35.
1194. Macrae TF, Hutchinson JC, Irwin JO, Bacon JS, McDougall EI. Comparative digestibility of wholemeal and white breads and the effect of the degree of fineness of grinding on the former. *J Hyg (Lond)*. 1942;42(4):423-35.
1195. Southgate DA, Durnin JV. Calorie conversion factors. An experimental reassessment of the factors used in the calculation of the energy value of human diets. *Br J Nutr*. 1970;24(2):517-35.
1196. Levine AS, Silvis SE. Absorption of whole peanuts, peanut oil, and peanut butter. *N Engl J Med*. 1980;303(16):917-8.
1197. Macrae TF, Hutchinson JC, Irwin JO, Bacon JS, McDougall EI. Comparative digestibility of wholemeal and white breads and the effect of the degree of fineness of grinding on the former. *J Hyg (Lond)*. 1942;42(4):423-35.
1198. Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr*. 2011;94(1):58-65.
1199. Beyer PL, Flynn MA. Effects of high-and low-fiber diets on human feces. *J Am Diet Assoc*. 1978;72(3):271-7.
1200. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet*. 2013;113(12):1610-9.

1201. Wisker E, Maltz A, Feldheim W. Metabolizable energy of diets low or high in dietary fiber from cereals when eaten by humans. *J Nutr*. 1988;118(8):945-52.
1202. Baer DJ, Rumppler WV, Miles CW, Fahey GC. Dietary fiber decreases the metabolizable energy content and nutrient digestibility of mixed diets fed to humans. *J Nutr*. 1997;127(4):579-86.
1203. Chambers ES, Morrison DJ, Frost G. Control of appetite and energy intake by SCFA: what are the potential underlying mechanisms? *Proc Nutr Soc*. 2015;74(3):328-36.
1204. Slavin JL. Dietary fiber and body weight. *Nutrition*. 2005;21(3):411-8.
1205. Heaton KW. Food fibre as an obstacle to energy intake. *Lancet*. 1973;2(7843):1418-21.
1206. van Avesaat M, Troost FJ, Ripken D, Hendriks HF, Masclee AA. Ileal brake activation: macronutrient-specific effects on eating behavior? *Int J Obes (Lond)*. 2015;39(2):235-43.
1207. Hocking MP, Davis GL, Franzini DA, Woodward ER. Long-term consequences after jejunioileal bypass for morbid obesity. *Dig Dis Sci*. 1998;43(11):2493-9.
1208. van Avesaat M, Troost FJ, Ripken D, Hendriks HF, Masclee AA. Ileal brake activation: macronutrient-specific effects on eating behavior? *Int J Obes (Lond)*. 2015;39(2):235-43.
1209. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. *Nutr Rev*. 2001;59(5):129-39.
1210. Castiglia-Delavaud C, Verdier E, Besle JM, et al. Net energy value of non-starch polysaccharide isolates (sugarbeet fibre and commercial inulin) and their impact on nutrient digestive utilization in healthy human subjects. *Br J Nutr*. 1998;80(4):343-52.
1211. Yen JT, Nienaber JA, Hill DA, Pond WG. Oxygen consumption by portal vein-drained organs and by whole animal in conscious growing swine. *Proc Soc Exp Biol Med*. 1989;190(4):393-8.
1212. Cherbut C, Bruley des Varannes S, Schnee M, Rival M, Galmiche JP, Delort-Laval J. Involvement of small intestinal motility in blood glucose response to dietary fibre in man. *Br J Nutr*. 1994;71(5):675-85.
1213. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003;278(13):11312-9.
1214. Bianconi E, Piovesan A, Facchin F, et al. An estimation of the number of cells in the human body. *Ann Hum Biol*. 2013;40(6):463-71.
1215. O'Connor CM, Adams JU. *Essentials of Cell Biology*. Cambridge, MA: NPG Education; 2010.
1216. Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. *Nat Rev Drug Discov*. 2017;16(12):829-42.
1217. Layden BT, Angueira AR, Brodsky M, Durai V, Lowe WL. Short chain fatty acids and their receptors: new metabolic targets. *Transl Res*. 2013;161(3):131-40.
1218. Kumari M, Kozyrskiy AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18-31.
1219. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003;278(13):11312-9.
1220. Ang Z, Ding JL. GPR41 and GPR43 in obesity and inflammation—protective or causative? *Front Immunol*. 2016;7:28.
1221. McKenzie CI, Mackay CR, Macia L. GPR43—a prototypic metabolite sensor linking metabolic and inflammatory diseases. *Trends Endocrinol Metab*. 2015;26(10):511-2.
1222. Jiao J, Xu JY, Zhang W, Han S, Qin LQ. Effect of dietary fiber on circulating C-reactive protein in overweight and obese adults: a meta-analysis of randomized controlled trials. *Int J Food Sci Nutr*. 2015;66(1):114-9.
1223. Haines I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients*. 2017;9(1):57.
1224. Al-Lahham SH, Roelofsens H, Priebe M, et al. Regulation of adipokine production in human adipose tissue by propionic acid. *Eur J Clin Invest*. 2010;40(5):401-7.
1225. Schwartz MW, Morton GJ. Obesity: keeping hunger at bay. *Nature*. 2002;418(6898):595-7.
1226. Helander HF, Fändriks L. The enteroendocrine “letter cells”—time for a new nomenclature? *Scand J Gastroenterol*. 2012;47(1):3-12.
1227. Kaji I, Karaki S, Kuwahara A. Short-chain fatty acid receptor and its contribution to glucagon-like peptide-1 release. *Digestion*. 2014;89(1):31-6.
1228. Kumari M, Kozyrskiy AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18-31.
1229. Freeland KR, Wolever TM. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin and tumour necrosis factor-alpha. *Br J Nutr*. 2010;103(3):460-6.
1230. Greenway F, O'Neil CE, Stewart L, Rood J, Keenan M, Martin R. Fourteen weeks of treatment with Viscofiber increased fasting levels of glucagon-like peptide-1 and peptide-YY. *J Med Food*. 2007;10(4):720-4.
1231. Sandberg JC, Björck IM, Nilsson AC. Rye-based evening meals favorably affected glucose regulation and appetite variables at the following breakfast; a randomized controlled study in healthy subjects. *PLoS ONE*. 2016;11(3):e0151985.
1232. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat Rev Endocrinol*. 2015;11(10):577-91.
1233. Schwartz MW, Morton GJ. Obesity: keeping hunger at bay. *Nature*. 2002;418(6898):595-7.
1234. Tarini J, Wolever TM. The fermentable fibre inulin increases postprandial serum short-chain fatty acids and reduces free-fatty acids and ghrelin in healthy subjects. *Appl Physiol Nutr Metab*. 2010;35(1):9-16.
1235. Hume MP, Nicolucci AC, Reimer RA. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. *Am J Clin Nutr*. 2017;105(4):790-9.
1236. Byrne CS, Chambers ES, Alhabeed H, et al. Increased colonic propionate reduces anticipatory reward responses in the human striatum to high-energy foods. *Am J Clin Nutr*. 2016;104(1):5-14.
1237. Sayer RD, Amankwaah AF, Tamer GG, et al. Effects of dietary protein and fiber at breakfast on appetite, ad libitum energy intake at lunch, and neural responses to visual food stimuli in overweight adults. *Nutrients*. 2016;8(1):21.
1238. McRorie JW. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 1: what to look for and how to recommend an effective fiber therapy. *Nutr Today*. 2015;50(2):82-9.
1239. Burkitt DP, Walker AR, Painter NS. Dietary fiber and disease. *JAMA*. 1974;229(8):1068-74.

1240. King DE, Mainous AG, Lambourne CA. Trends in dietary fiber intake in the United States, 1999–2008. *J Acad Nutr Diet*. 2012;112(5):642–8.
1241. Balthazar EA, de Oliveira MR. Differences in dietary pattern between obese and eutrophic children. *BMC Res Notes*. 2011;4:567.
1242. Davis JN, Alexander KE, Ventura EE, Toledo-Corral CM, Goran MI. Inverse relation between dietary fiber intake and visceral adiposity in overweight Latino youth. *Am J Clin Nutr*. 2009;90(5):1160–6.
1243. Tucker LA, Thomas KS. Increasing total fiber intake reduces risk of weight and fat gains in women. *J Nutr*. 2009;139(3):576–81.
1244. Drehmer M, Camey SA, Nunes MA, et al. Fibre intake and evolution of BMI: from pre-pregnancy to postpartum. *Public Health Nutr*. 2013;16(8):1403–13.
1245. Du H, van der A DL, Boshuizen HC, et al. Dietary fiber and subsequent changes in body weight and waist circumference in European men and women. *Am J Clin Nutr*. 2010;91(2):329–36.
1246. Slavin JL. Dietary fiber and body weight. *Nutrition*. 2005;21(3):411–8.
1247. Canfora EE, van der Beek CM, Jocken JWE, et al. Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Sci Rep*. 2017;7(1):2360.
1248. van der Beek CM, Canfora EE, Lenaerts K, et al. Distal, not proximal, colonic acetate infusions promote fat oxidation and improve metabolic markers in overweight/obese men. *Clin Sci*. 2016;130(22):2073–82.
1249. Canfora EE, van der Beek CM, Jocken JWE, et al. Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. *Sci Rep*. 2017;7(1):2360.
1250. Chambers ES, Byrne CS, Aspey K, et al. Acute oral sodium propionate supplementation raises resting energy expenditure and lipid oxidation in fasted humans. *Diabetes Obes Metab*. 2018;20(4):1034–9.
1251. Alhabeeb H, Chambers ES, Frost G, Morrison DJ, Preston T. Inulin propionate ester increases satiety and decreases appetite but does not affect gastric emptying in healthy humans. *Proc Nutr Soc*. 2014;73(OCE1):E21.
1252. Chambers ES, Viardot A, Psichas A, et al. Targeted delivery of propionate to the colon stimulates the release of anorectic gut hormones and suppresses appetite in humans. *Proc Nutr Soc*. 2014;73(OCE1):E15.
1253. Polyviou T, MacDougall K, Chambers ES, et al. Randomised clinical study: inulin short-chain fatty acid esters for targeted delivery of short-chain fatty acids to the human colon. *Aliment Pharmacol Ther*. 2016;44(7):662–72.
1254. Nilsson A, Johansson E, Ekström L, Björck I. Effects of a brown beans evening meal on metabolic risk markers and appetite regulating hormones at a subsequent standardized breakfast: a randomized cross-over study. *PLoS ONE*. 2013;8(4):e59985.
1255. Ibrügger S, Vignæs LK, Blennow A, et al. Second meal effect on appetite and fermentation of wholegrain rye foods. *Appetite*. 2014;80:248–56.
1256. Brownlee I, Chater P, Pearson J, Wilcox MD. Dietary fibre and weight loss: where are we now? *Food Hydrocoll*. 2017;68:186–91.
1257. Chambers ES, Viardot A, Psichas A, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut*. 2015;64(11):1744–54.
1258. Thompson SV, Hannon BA, An R, Holscher HD. Effects of isolated soluble fiber supplementation on body weight, glycemia, and insulinemia in adults with overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2017;106(6):1514–28.
1259. Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. *J Pediatr*. 2007;151(3):293–8.
1260. Rytting KR, Tellnes G, Haegh L, Bøe E, Fagerthun H. A dietary fibre supplement and weight maintenance after weight reduction: a randomized, double-blind, placebo-controlled long-term trial. *Int J Obes*. 1989;13(2):165–71.
1261. Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr*. 2014;111(7):1147–61.
1262. Clark MJ, Slavin JL. The effect of fiber on satiety and food intake: a systematic review. *J Am Coll Nutr*. 2013;32(3):200–11.
1263. Grube B, Chong PW, Lau KZ, Orzechowski HD. A natural fiber complex reduces body weight in the overweight and obese: a double-blind, randomized, placebo-controlled study. *Obesity (Silver Spring)*. 2013;21(1):58–64.
1264. Howarth NC, Saltzman E, McCrory MA, et al. Fermentable and nonfermentable fiber supplements did not alter hunger, satiety or body weight in a pilot study of men and women consuming self-selected diets. *J Nutr*. 2003;133(10):3141–4.
1265. Ma Y, Olendzki BC, Wang J, et al. Single-component versus multicomponent dietary goals for the metabolic syndrome: a randomized trial. *Ann Intern Med*. 2015;162(4):248–57.
1266. McCarthy M. High fibre diet may be good alternative to complex weight loss regimen, US study finds. *BMJ*. 2015;350:h965.
1267. Ma Y, Olendzki BC, Wang J, et al. Single-component versus multicomponent dietary goals for the metabolic syndrome: a randomized trial. *Ann Intern Med*. 2015;162(4):248–57.
1268. Ma Y, Olendzki BC, Wang J, et al. Single-component versus multicomponent dietary goals for the metabolic syndrome: a randomized trial. *Ann Intern Med*. 2015;162(4):248–57.
1269. King DE, Mainous AG, Lambourne CA. Trends in dietary fiber intake in the United States, 1999–2008. *J Acad Nutr Diet*. 2012;112(5):642–8.
1270. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*. Washington, D.C.: National Academies Press; 2005.
1271. Baron JA, Schori A, Crow B, Carter R, Mann JI. A randomized controlled trial of low carbohydrate and low fat/high fiber diets for weight loss. *Am J Public Health*. 1986;76(11):1293–6.
1272. Clemens R, Kranz S, Mobley AR, et al. Filling America's fiber intake gap: summary of a roundtable to probe realistic solutions with a focus on grain-based foods. *J Nutr*. 2012;142(7):1390S–401S.
1273. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*. Washington, D.C.: National Academies Press; 2005.
1274. Jew S, Abumweis SS, Jones PJ. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food*. 2009;12(5):925–34.

1275. Jew S, Abumweis SS, Jones PJ. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food*. 2009;12(5):925-34.
1276. Leach JD, Sobolik KD. High dietary intake of prebiotic inulin-type fructans in the prehistoric Chihuahuan Desert. *Br J Nutr*. 2010;103(11):1558-61.
1277. Spiller G. *Topics in Dietary Fiber Research*. New York: Plenum Press; 1978.
1278. Ungar PS, Sponheimer M. The diets of early hominins. *Science*. 2011;334(6053):190-3.
1279. McKenzie CI, Mackay CR, Macia L. GPR43—a prototypic metabolite sensor linking metabolic and inflammatory diseases. *Trends Endocrinol Metab*. 2015;26(10):511-2.
1280. Frost GS, Walton GE, Swann JR, et al. Impacts of plant-based foods in ancestral hominin diets on the metabolism and function of gut microbiota in vitro. *MBio*. 2014;5(3):e00853-14.
1281. Sleeth ML, Thompson EL, Ford HE, Zac-Varghese SE, Frost G. Free fatty acid receptor 2 and nutrient sensing: a proposed role for fibre, fermentable carbohydrates and short-chain fatty acids in appetite regulation. *Nutr Res Rev*. 2010;23(1):135-45.
1282. King DE, Mainous AG, Lambourne CA. Trends in dietary fiber intake in the United States, 1999-2008. *J Acad Nutr Diet*. 2012;112(5):642-8.
1283. Wick JY. Diverticular disease: eat your fiber! *Consult Pharm*. 2012;27(9):613-8.
1284. Institute of Medicine (U.S.). *Dietary Reference Intakes: Proposed Definition of Dietary Fiber*. Washington, D.C.: National Academies Press; 2001.
1285. Krebs-Smith SM, Guenther PM, Subar AF, Kirkpatrick SI, Dodd KW. Americans do not meet federal dietary recommendations. *J Nutr*. 2010;140(10):1832-8.
1286. Block G, Lanza E. Dietary fiber sources in the United States by demographic group. *J Natl Cancer Inst*. 1987;79(1):83-91.
1287. Chambers ES, Viardot A, Psichas A, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut*. 2015;64(11):1744-54.
1288. Polyviou T, MacDougall K, Chambers ES, et al. Randomised clinical study: inulin short-chain fatty acid esters for targeted delivery of short-chain fatty acids to the human colon. *Aliment Pharmacol Ther*. 2016;44(7):662-72.
1289. Chambers ES, Viardot A, Psichas A, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut*. 2015;64(11):1744-54.
1290. Kimura I, Inoue D, Hirano K, Tsujimoto G. The SCFA receptor GPR43 and energy metabolism. *Front Endocrinol (Lausanne)*. 2014;5:85.
1291. Sleeth ML, Thompson EL, Ford HE, Zac-Varghese SE, Frost G. Free fatty acid receptor 2 and nutrient sensing: a proposed role for fibre, fermentable carbohydrates and short-chain fatty acids in appetite regulation. *Nutr Res Rev*. 2010;23(1):135-45.
1292. Sugeran DT. JAMA patient page. Constipation. *JAMA*. 2013;310(13):1416.
1293. Burkitt DP, Meisner P. How to manage constipation with high-fiber diet. *Geriatrics*. 1979;34(2):33-5, 38-40.
1294. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr*. 1995;49(9):675-90.
1295. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr*. 1995;49(9):675-90.
1296. Agricultural Research Service. USDA Food Composition Databases. United States Department of Agriculture. 2018. Available at: <https://ndb.nal.usda.gov/ndb>. Accessed April 1, 2019.
1297. Welch RW. Satiety: have we neglected dietary non-nutrients? *Proc Nutr Soc*. 2011;70(2):145-54.
1298. Welch RW. Satiety: have we neglected dietary non-nutrients? *Proc Nutr Soc*. 2011;70(2):145-54.
1299. Spetter MS, Mars M, Viergever MA, de Graaf C, Smeets PA. Taste matters—effects of bypassing oral stimulation on hormone and appetite responses. *Physiol Behav*. 2014;137:9-17.
1300. Agricultural Research Service. USDA Food Composition Databases. United States Department of Agriculture. 2018. Available at: <https://ndb.nal.usda.gov/ndb>. Accessed April 1, 2019.
1301. Alexander JE, Colyer A, Morris PJ. The effect of reducing dietary energy density via the addition of water to a dry diet, on body weight, energy intake and physical activity in adult neutered cats. *J Nutr Sci*. 2014;3:e21.
1302. Alexander JE, Colyer A, Morris PJ. The effect of reducing energy density, via the addition of water to dry diet, on body weight and activity in dogs. *J Nutr Sci*. 2017;6:e42.
1303. Lappalainen R, Mennen L, van Weert L, Mykkänen H. Drinking water with a meal: a simple method of coping with feelings of hunger, satiety and desire to eat. *Eur J Clin Nutr*. 1993;47(11):815-9.
1304. Rolls BJ, Kim S, Fedoroff IC. Effects of drinks sweetened with sucrose or aspartame on hunger, thirst and food intake in men. *Physiol Behav*. 1990;48(1):19-26.
1305. DellaValle DM, Roe LS, Rolls BJ. Does the consumption of caloric and non-caloric beverages with a meal affect energy intake? *Appetite*. 2005;44(2):187-93.
1306. Camps G, Mars M, de Graaf C, Smeets PAM. A tale of gastric layering and sieving: gastric emptying of a liquid meal with water blended in or consumed separately. *Physiol Behav*. 2017;176:26-30.
1307. Westerterp-Plantenga MS. Analysis of energy density of food in relation to energy intake regulation in human subjects. *Br J Nutr*. 2001;85(3):351-61.
1308. Rolls BJ, Bell EA, Thorwart ML. Water incorporated into a food but not served with a food decreases energy intake in lean women. *Am J Clin Nutr*. 1999;70(4):448-55.
1309. Marciani L, Hall N, Pritchard SE, et al. Preventing gastric sieving by blending a solid/water meal enhances satiation in healthy humans. *J Nutr*. 2012;142(7):1253-8.
1310. Santangelo A, Peracchi M, Conte D, Fraquelli M, Porrini M. Physical state of meal affects gastric emptying, cholecystokinin release and satiety. *Br J Nutr*. 1998;80(6):521-7.
1311. Marciani L, Hall N, Pritchard SE, et al. Preventing gastric sieving by blending a solid/water meal enhances satiation in healthy humans. *J Nutr*. 2012;142(7):1253-8.
1312. Camps G, Mars M, de Graaf C, Smeets PAM. A tale of gastric layering and sieving: gastric emptying of a liquid meal with water blended in or consumed separately. *Physiol Behav*. 2017;176:26-30.
1313. Murakami K, Sasaki S, Takahashi Y, Uenishi K. Intake of water from foods, but not water from beverages, is related to lower body mass index and waist circumference in free-living humans [corrected]. *Nutrition*. 2008;24(10):925-32.

1314. Agricultural Research Service. USDA Food Composition Databases. United States Department of Agriculture. 2018. Available at: <https://ndb.nal.usda.gov/ndb>. Accessed April 1, 2019.
1315. Wilson T, Anderson JA, Andersen KF, et al. Glycemic response of type 2 diabetics to raisins. *FNS*. 2012;3(8):1162-6.
1316. Keast DR, O'Neil CE, Jones JM. Dried fruit consumption is associated with improved diet quality and reduced obesity in US adults: National Health and Nutrition Examination Survey, 1999-2004. *Nutr Res*. 2011;31(6):460-7.
1317. Patel BP, Bellissimo N, Luhovyy B, et al. An after-school snack of raisins lowers cumulative food intake in young children. *J Food Sci*. 2013;78 Suppl 1:A5-10.
1318. James LJ, Funnell MP, Milner S. An afternoon snack of berries reduces subsequent energy intake compared to an isoenergetic confectionary snack. *Appetite*. 2015;95:132-7.
1319. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-22.
1320. Conceição de Oliveira M, Sichieri R, Sanchez Moura A. Weight loss associated with a daily intake of three apples or three pears among overweight women. *Nutrition*. 2003;19(3):253-6.
1321. Patel BP, Bellissimo N, Luhovyy B, et al. An after-school snack of raisins lowers cumulative food intake in young children. *J Food Sci*. 2013;78 Suppl 1:A5-10.
1322. Patel BP, Luhovyy B, Mollard R, Painter JE, Anderson GH. A premeal snack of raisins decreases mealtime food intake more than grapes in young children. *Appl Physiol Nutr Metab*. 2013;38(4):382-9.
1323. Furchner-Evanson A, Petrisko Y, Howarth L, Nemoseck T, Kern M. Type of snack influences satiety responses in adult women. *Appetite*. 2010;54(3):564-9.
1324. Farajian P, Katsagani M, Zampelas A. Short-term effects of a snack including dried prunes on energy intake and satiety in normal-weight individuals. *Eat Behav*. 2010;11(3):201-3.
1325. Howarth L, Petrisko Y, Furchner-Evanson A, Nemoseck T, Kern M. Snack selection influences nutrient intake, triglycerides, and bowel habits of adult women: a pilot study. *J Am Diet Assoc*. 2010;110(9):1322-7.
1326. Puglisi MJ, Vaishnav U, Shrestha S, et al. Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. *Lipids Health Dis*. 2008;7:14.
1327. Chai SC, Hooshmand S, Saadat RL, Payton ME, Brummel-Smith K, Arjmandi BH. Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women. *J Acad Nutr Diet*. 2012;112(8):1158-68.
1328. Peterson JM, Montgomery S, Haddad E, Kearney L, Tonstad S. Effect of consumption of dried California mission figs on lipid concentrations. *Ann Nutr Metab*. 2011;58(3):232-8.
1329. Rock W, Rosenblat M, Borochoy-Neori H, et al. Effects of date (*Phoenix dactylifera* L., Medjool or Hallawi Variety) consumption by healthy subjects on serum glucose and lipid levels and on serum oxidative status: a pilot study. *J Agric Food Chem*. 2009;57(17):8010-7.
1330. Chai SC, Hooshmand S, Saadat RL, Payton ME, Brummel-Smith K, Arjmandi BH. Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women. *J Acad Nutr Diet*. 2012;112(8):1158-68.
1331. Patel BP, Luhovyy B, Mollard R, Painter JE, Anderson GH. A premeal snack of raisins decreases mealtime food intake more than grapes in young children. *Appl Physiol Nutr Metab*. 2013;38(4):382-9.
1332. Augustin LS, Kendall CW, Jenkins DJ, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis*. 2015;25(9):795-815.
1333. Granfeldt Y, Björck I, Hagander B. On the importance of processing conditions, product thickness and egg addition for the glycaemic and hormonal responses to pasta: a comparison with bread made from "pasta ingredients." *Eur J Clin Nutr*. 1991;45(10):489-99.
1334. Woolnough JW, Bird AR, Monro JA, Brennan CS. The effect of a brief salivary α -amylase exposure during chewing on subsequent in vitro starch digestion curve profiles. *Int J Mol Sci*. 2010;11(8):2780-90.
1335. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281-3.
1336. Lennerz BS, Alsop DC, Holsen LM, et al. Effects of dietary glycemic index on brain regions related to reward and craving in men. *Am J Clin Nutr*. 2013;98(3):641-7.
1337. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE*. 2015;10(2):e0117959.
1338. Warren JM, Henry CJ, Simonite V. Low glycemic index breakfasts and reduced food intake in preadolescent children. *Pediatrics*. 2003;112(5):e414.
1339. Bornet FRJ, Jardy-Gennetier AE, Jacquet N, Stowell J. Glycaemic response to foods: impact on satiety and long-term weight regulation. *Appetite*. 2007;49(3):535-53.
1340. Wu CL, Nicholas C, Williams C, Took A, Hardy L. The influence of high-carbohydrate meals with different glycaemic indices on substrate utilisation during subsequent exercise. *Br J Nutr*. 2003;90(6):1049-56.
1341. Sun FH, Wong SH, Huang YJ, Chen YJ, Tsang KF. Substrate utilization during brisk walking is affected by glycemic index and fructose content of a pre-exercise meal. *Eur J Appl Physiol*. 2012;112(7):2565-74.
1342. Wu CL, Nicholas C, Williams C, Took A, Hardy L. The influence of high-carbohydrate meals with different glycaemic indices on substrate utilisation during subsequent exercise. *Br J Nutr*. 2003;90(6):1049-56.
1343. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med*. 1995;332(10):621-8.
1344. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA*. 2004;292(20):2482-90.
1345. Kahlhöfer J, Lagerpusch M, Enderle J, et al. Carbohydrate intake and glycemic index affect substrate oxidation during a controlled weight cycle in healthy men. *Eur J Clin Nutr*. 2014;68(9):1060-6.
1346. Pereira EV, Costa Jde A, Alfenas Rde C. Effect of glycemic index on obesity control. *Arch Endocrinol Metab*. 2015;59(3):245-51.
1347. Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med*. 2003;157(8):773-9.
1348. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev*. 2007;(3):CD005105.

1349. Ludwig DS, Ebbeling CB. Weight-loss maintenance—mind over matter? *N Engl J Med*. 2010;363(22):2159-61.
1350. Larsen TM, Dalskov SM, van Baak M, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med*. 2010;363(22):2102-13.
1351. Aller EE, Larsen TM, Claus H, et al. Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. *Int J Obes (Lond)*. 2014;38(12):1511-7.
1352. Aller EE, Larsen TM, Claus H, et al. Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. *Int J Obes (Lond)*. 2014;38(12):1511-7.
1353. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA*. 2004;292(20):2482-90.
1354. Jenkins DJ, Taylor RH, Goff DV, et al. Scope and specificity of acarbose in slowing carbohydrate absorption in man. *Diabetes*. 1981;30(11):951-4.
1355. Augustin LS, Kendall CW, Jenkins DJ, et al. Glycemic index, glycemic load and glycemic response: an International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis*. 2015;25(9):795-815.
1356. Li Y, Tong Y, Zhang Y, Huang L, Wu T, Tong N. Acarbose monotherapy and weight loss in Eastern and Western populations with hyperglycaemia: an ethnicity-specific meta-analysis. *Int J Clin Pract*. 2014;68(11):1318-32.
1357. Schnell O, Weng J, Sheu WH, et al. Acarbose reduces body weight irrespective of glycemic control in patients with diabetes: results of a worldwide, non-interventional, observational study data pool. *J Diabetes Complicat*. 2016;30(4):628-37.
1358. Grussu D, Stewart D, McDougall GJ. Berry polyphenols inhibit α -amylase in vitro: identifying active components in rowanberry and raspberry. *J Agric Food Chem*. 2011;59(6):2324-31.
1359. Englyst H, Wiggins HS, Cummings JH. Determination of the non-starch polysaccharides in plant foods by gas-liquid chromatography of constituent sugars as alditol acetates. *Analyst*. 1982;107(1272):307-18.
1360. Goldring JM. Resistant starch: safe intakes and legal status. *J AOAC Int*. 2004;87(3):733-9.
1361. Yadav BS, Sharma A, Yadav RB. Studies on effect of multiple heating/cooling cycles on the resistant starch formation in cereals, legumes and tubers. *Int J Food Sci Nutr*. 2009;60 Suppl 4:258-72.
1362. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006. *Am J Clin Nutr*. 2011;93(4):836-43.
1363. Bentley J. U.S. trends in food availability and a dietary assessment of loss-adjusted food availability, 1970-2014. EIB-166. United States Department of Agriculture, Economic Research Service. Published January 2017. Available at: <https://www.ers.usda.gov/publications/pub-details/?pubid=82219>. Accessed April 1, 2019.
1364. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006. *Am J Clin Nutr*. 2011;93(4):836-43.
1365. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1366. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971-2006. *Am J Clin Nutr*. 2011;93(4):836-43.
1367. Select Committee on Nutrition and Human Needs, United States Senate. *Dietary Goals for the United States, Second Edition*. Washington, D.C.: U.S. Government Printing Office; 1977. Available at: <https://thescienceofnutrition.files.wordpress.com/2014/03/dietary-goals-for-the-united-states.pdf>. Accessed April 1, 2019.
1368. Ludwig DS. Lowering the bar on the low-fat diet. *JAMA*. 2016;316(20):2087-8.
1369. Schermerl A, Wong CL, L'Abbé MR. Are foods with fat-related claims useful for weight management? *Appetite*. 2016;96:154-9.
1370. Nguyen PK, Lin S, Heidenreich P. A systematic comparison of sugar content in low-fat vs regular versions of food. *Nutr Diabetes*. 2016;6:e193.
1371. McDevitt RM, Poppitt SD, Murgatroyd PR, Prentice AM. Macronutrient disposal during controlled overfeeding with glucose, fructose, sucrose, or fat in lean and obese women. *Am J Clin Nutr*. 2000;72(2):369-77.
1372. Raben A, MacDonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14 d ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord*. 1997;21(10):846-59.
1373. Davis LW. Durable goods and residential demand for energy and water: evidence from a field trial. *RAND J Econ*. 2008;39(2):530-46.
1374. Schermerl A, Wong CL, L'Abbé MR. Are foods with fat-related claims useful for weight management? *Appetite*. 2016;96:154-9.
1375. Wansink B, Chandon P. Can "low-fat" nutrition labels lead to obesity? *J Mark Res*. 2006;43(4):605-17. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
1376. Fernan C, Schuldt JP, Niederdeppe J. Health halo effects from product titles and nutrient content claims in the context of "protein" bars. *Health Commun*. 2018;33(12):1425-33.
1377. Scrinis G. On the ideology of nutritionism. *Gastronomica*. 2008;8(1):39-48.
1378. Schwartz MB, Vartanian LR, Wharton CM, Brownell KD. Examining the nutritional quality of breakfast cereals marketed to children. *J Am Diet Assoc*. 2008;108(4):702-5.
1379. Jacobs DR, Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. *Nutr Rev*. 2007;65(10):439-50.
1380. Schuldt JP, Pearson AR. Nutrient-centrism and perceived risk of chronic disease. *J Health Psychol*. 2015;20(6):899-906.
1381. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr*. 1997;66(2):239-46.
1382. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. *Am J Prev Med*. 2014;46(1):17-23.

1383. Catenacci VA, Ogden LG, Stuht J, et al. Physical activity patterns in the National Weight Control Registry. *Obesity (Silver Spring)*. 2008;16(1):153-61.
1384. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. *Am J Prev Med*. 2014;46(1):17-23.
1385. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr*. 1997;66(2):239-46.
1386. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. *Am J Prev Med*. 2014;46(1):17-23.
1387. Food Surveys Research Group. Nutrient intakes from food: mean amounts and percentages of calories from protein, carbohydrate, fat, and alcohol, one day, 2005-2006. 2008. Agricultural Research Service, United States Department of Agriculture. Available at: www.ars.usda.gov/ba/bhnrc/fsrg. Accessed April 1, 2019.
1388. McGuire MT, Wing RR, Klem ML, Lang W, Hill JO. What predicts weight regain in a group of successful weight losers? *J Consult Clin Psychol*. 1999;67(2):177-85.
1389. Hill JO, Wyatt H, Phelan S, Wing R. The National Weight Control Registry: is it useful in helping deal with our obesity epidemic? *J Nutr Educ Behav*. 2005;37(4):206-10.
1390. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(12):968-79.
1391. Willett WC. Dietary fat plays a major role in obesity: no. *Obes Rev*. 2002;3(2):59-68.
1392. Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. *Cochrane Database Syst Rev*. 2015;(8):CD011834.
1393. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr*. 1998;68(6):1157-73.
1394. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(12):968-79.
1395. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann NY Acad Sci*. 2007;1114:434-55.
1396. Draper HH. The Aboriginal Eskimo diet in modern perspective. *Am Anthropol*. 1977;79:309-16.
1397. Barnard RJ. Very-low-fat diets. *Circulation*. 1999;100(9):1011-5.
1398. Eaton SB. Humans, lipids and evolution. *Lipids*. 1992;27(10):814-20.
1399. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45212188, lean ground beef, UPC: 710178576015. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45212188>. Accessed March 31, 2019.
1400. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45346248, extra lean ground beef, UPC: 027182574211. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45346248>. Accessed March 31, 2019.
1401. Baschetti R. Genetically unknown foods or thrifty genes? *Am J Clin Nutr*. 1999;70(3):420-1.
1402. Baschetti R. Definition of low-fat diets. *Arch Intern Med*. 2006;166(13):1419-20.
1403. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med*. 2008;359(3):229-41.
1404. Bazzano LA, Hu T. Effects of low-carbohydrate and low-fat diets. *Ann Intern Med*. 2015;162(5):393.
1405. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA*. 2007;297(9):969-77.
1406. McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. *Int J Obes Relat Metab Disord*. 2001;25(10):1503-11.
1407. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Better dietary adherence and weight maintenance achieved by a long-term moderate-fat diet. *Br J Nutr*. 2007;97(2):399-404.
1408. Das SK, Gilhooly CH, Golden JK, et al. Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. *Am J Clin Nutr*. 2007;85(4):1023-30.
1409. Hall KD. Prescribing low-fat diets: useless for long-term weight loss? *Lancet Diabetes Endocrinol*. 2015;3(12):920-1.
1410. Hall KD. Prescribing low-fat diets: useless for long-term weight loss? *Lancet Diabetes Endocrinol*. 2015;3(12):920-1.
1411. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med*. 1995;155(18):1933-41.
1412. Chaiton M, Diemert L, Cohen JE, et al. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open*. 2016;6(6):e011045.
1413. Shintani TT, Hughes CK, Beckham S, O'Connor HK. Obesity and cardiovascular risk intervention through the ad libitum feeding of traditional Hawaiian diet. *Am J Clin Nutr*. 1991;53(6 Suppl):1647S-51S.
1414. Thuesen L, Henriksen LB, Engby B. One-year experience with a low-fat, low-cholesterol diet in patients with coronary heart disease. *Am J Clin Nutr*. 1986;44(2):212-9.
1415. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280(23):2001-7.
1416. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280(23):2001-7.
1417. Zhi J, Melia AT, Guerciolini R, et al. Retrospective population-based analysis of the dose-response (fecal fat excretion) relationship of orlistat in normal and obese volunteers. *Clin Pharmacol Ther*. 1994;56(1):82-5.
1418. Sahebkar A, Simental-Mendía LE, Reiner Ž, et al. Effect of orlistat on plasma lipids and body weight: a systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacol Res*. 2017;122:53-65.
1419. Sumithran P, Proietto J. Benefit-risk assessment of orlistat in the treatment of obesity. *Drug Saf*. 2014;37(8):597-608.

1420. Buyschaert B, Aydin S, Morelle J, Hermans MP, Jadoul M, Demoulin N. Weight loss at a high cost: orlistat-induced late-onset severe kidney disease. *Diabetes Metab.* 2016;42(1):62-4.
1421. Sall D, Wang J, Rashkin M, Welch M, Droegge C, Schauer D. Orlistat-induced fulminant hepatic failure. *Clin Obes.* 2014;4(6):342-7.
1422. Hollywood A, Ogden J. Taking orlistat: predicting weight loss over 6 months. *J Obes.* 2011;2011:806896.
1423. Fox M, Thumshirn M, Menne D, Stutz B, Fried M, Schwizer W. The pathophysiology of faecal spotting in obese subjects during treatment with orlistat. *Aliment Pharmacol Ther.* 2004;19(3):311-21.
1424. Before you begin with alli. myalli.com. 2008. Available at: <https://web.archive.org/web/20080821141135/http://www.myalli.com:80/howdoesitwork/treatmenteffects.aspx>. Accessed March 31, 2019.
1425. Schroll JB, Penninga EI, Gøtzsche PC. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of orlistat: a document analysis. *PLoS Med.* 2016;13(8):e1002101.
1426. Hollywood A, Ogden J. Taking orlistat: predicting weight loss over 6 months. *J Obes.* 2011;2011:806896.
1427. Padwal R, Kezouh A, Levine M, Etminan M. Long-term persistence with orlistat and sibutramine in a population-based cohort. *Int J Obes (Lond).* 2007;31(10):1567-70.
1428. Shintani TT, Hughes CK, Beckham S, O'Connor HK. Obesity and cardiovascular risk intervention through the ad libitum feeding of traditional Hawaiian diet. *Am J Clin Nutr.* 1991;53(6 Suppl):1647S-51S.
1429. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, et al. Body weight and low-density lipoprotein cholesterol changes after consumption of a low-fat ad libitum diet. *JAMA.* 1995;274(18):1450-5.
1430. Toubro S, Astrup A. Randomised comparison of diets for maintaining obese subjects' weight after major weight loss: ad lib, low fat, high carbohydrate diet v fixed energy intake. *BMJ.* 1997;314(7073):29-34.
1431. Donahoo W, Wyatt HR, Kriehn J, et al. Dietary fat increases energy intake across the range of typical consumption in the United States. *Obesity (Silver Spring).* 2008;16(1):64-9.
1432. Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA. Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr.* 1987;46(6):886-92.
1433. Astrup A. The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *Int J Obes Relat Metab Disord.* 2001;25 Suppl 1:S46-50.
1434. Saltzman E, Dallal GE, Roberts SB. Effect of high-fat and low-fat diets on voluntary energy intake and substrate oxidation: studies in identical twins consuming diets matched for energy density, fiber, and palatability. *Am J Clin Nutr.* 1997;66(6):1332-9.
1435. Gil KM, Skeie B, Kvetan V, Askanazi J, Friedman MI. Parenteral nutrition and oral intake: effect of glucose and fat infusions. *JPEN J Parenter Enteral Nutr.* 1991;15(4):426-32.
1436. Gil KM, Skeie B, Kvetan V, Askanazi J, Friedman MI. Parenteral nutrition and oral intake: effect of glucose and fat infusions. *JPEN J Parenter Enteral Nutr.* 1991;15(4):426-32.
1437. Blundell JE, Burley VJ, Cotton JR, Lawton CL. Dietary fat and the control of energy intake: evaluating the effects of fat on meal size and postmeal satiety. *Am J Clin Nutr.* 1993;57(5 Suppl):772S-7S.
1438. van Avesaat M, Troost FJ, Ripken D, Hendriks HF, Masclee AA. Ileal brake activation: macronutrient-specific effects on eating behavior? *Int J Obes (Lond).* 2015;39(2):235-43.
1439. Westerterp KR. Physical activity and physical activity induced energy expenditure in humans: measurement, determinants, and effects. *Front Physiol.* 2013;4:90.
1440. Astrup A. The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *Int J Obes Relat Metab Disord.* 2001;25 Suppl 1:S46-50.
1441. Bray GA, Smith SR, Dejonge L, et al. Effect of diet composition on energy expenditure during weight loss: the POUNDS LOST Study. *Int J Obes (Lond).* 2012;36(3):448-55.
1442. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc.* 2011;43(8):1575-81.
1443. Bray GA, Smith SR, Dejonge L, et al. Effect of diet composition on energy expenditure during weight loss: the POUNDS LOST Study. *Int J Obes (Lond).* 2012;36(3):448-55.
1444. Flatt JP. Misconceptions in body weight regulation: implications for the obesity pandemic. *Crit Rev Clin Lab Sci.* 2012;49(4):150-65.
1445. Astrup A. The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *Int J Obes Relat Metab Disord.* 2001;25 Suppl 1:S46-50.
1446. Lean ME, James WP. Metabolic effects of isoenergetic nutrient exchange over 24 hours in relation to obesity in women. *Int J Obes.* 1988;12(1):15-27.
1447. Lammert O, Grunnet N, Faber P, et al. Effects of isoenergetic overfeeding of either carbohydrate or fat in young men. *Br J Nutr.* 2000;84(2):233-45.
1448. Danforth E. Diet and obesity. *Am J Clin Nutr.* 1985;41(5 Suppl):1132-45.
1449. Danforth E. Diet and obesity. *Am J Clin Nutr.* 1985;41(5 Suppl):1132-45.
1450. Danforth E. Diet and obesity. *Am J Clin Nutr.* 1985;41(5 Suppl):1132-45.
1451. Ruge T, Hodson L, Cheeseman J, et al. Fasted to fed trafficking of fatty acids in human adipose tissue reveals a novel regulatory step for enhanced fat storage. *J Clin Endocrinol Metab.* 2009;94(5):1781-8.
1452. Maffei C, Schutz Y, Grezzani A, Provera S, Piacentini G, Tatò L. Meal-induced thermogenesis and obesity: is a fat meal a risk factor for fat gain in children? *J Clin Endocrinol Metab.* 2001;86(1):214-9.
1453. Votruba SB, Mattison RS, Dumesic DA, Koutsari C, Jensen MD. Meal fatty acid uptake in visceral fat in women. *Diabetes.* 2007;56(10):2589-97.
1454. Björntorp P, Sjöström L. Carbohydrate storage in man: speculations and some quantitative considerations. *Metab Clin Exp.* 1978;27(12 Suppl 2):1853-65.
1455. Acheson KJ, Schutz Y, Bessard T, Anantharaman K, Flatt JP, Jéquier E. Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. *Am J Clin Nutr.* 1988;48(2):240-7.
1456. Sevastianova K, Santos A, Kotronen A, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

1457. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45157114, cotton candy, UPC: 043427007795. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45157114>. Accessed March 31, 2019.
1458. Sevastianova K, Santos A, Kotronen A, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr*. 2012;96(4):727-34.
1459. Aarsland A, Chinkes D, Wolfe RR. Hepatic and whole-body fat synthesis in humans during carbohydrate overfeeding. *Am J Clin Nutr*. 1997;65(6):1774-82.
1460. Schutz Y, Flatt JP, Jéquier E. Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity. *Am J Clin Nutr*. 1989;50(2):307-14.
1461. Flatt JP. Misconceptions in body weight regulation: implications for the obesity pandemic. *Crit Rev Clin Lab Sci*. 2012;49(4):150-65.
1462. Flatt JP. Misconceptions in body weight regulation: implications for the obesity pandemic. *Crit Rev Clin Lab Sci*. 2012;49(4):150-65.
1463. Lin PH, Wang Y, Grambow SC, Goggins W, Almirall D. Dietary saturated fat intake is negatively associated with weight maintenance among the PREMIER participants. *Obesity (Silver Spring)*. 2012;20(3):571-5.
1464. Epidemiology and Genomics Research Program. Top food sources of saturated fat among U.S. population, 2005-2006 NHANES. National Cancer Institute Division of Cancer Control and Population Sciences, National Institutes of Health. Updated April 20, 2018. Available at: https://epi.grants.cancer.gov/diet/foodsources/sat_fat/sf.html. Accessed March 31, 2019.
1465. Fernández de la Puebla RA, Fuentes F, Pérez-Martínez P, et al. A reduction in dietary saturated fat decreases body fat content in overweight, hypercholesterolemic males. *Nutr Metab Cardiovasc Dis*. 2003;13(5):273-7.
1466. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *Br J Nutr*. 2003;90(3):717-27.
1467. Bjeremo H, Iggman D, Kullberg J, et al. Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial. *Am J Clin Nutr*. 2012;95(5):1003-12.
1468. Enjoji M, Nakamura M. Is the control of dietary cholesterol intake sufficiently effective to ameliorate nonalcoholic fatty liver disease? *World J Gastroenterol*. 2010;16(7):800-3.
1469. Mokhtari Z, Poustchi H, Eslamparast T, Hekmatdoost A. Egg consumption and risk of non-alcoholic fatty liver disease. *World J Hepatol*. 2017;9(10):503-9.
1470. Rosqvist F, Iggman D, Kullberg J, et al. Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. *Diabetes*. 2014;63(7):2356-68.
1471. Bray GA, Krauss RM. Overfeeding of polyunsaturated versus saturated fatty acids reduces ectopic fat. *Diabetes*. 2014;63(7):2222-4.
1472. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1-23.
1473. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. The influence of the type of dietary fat on postprandial fat oxidation rates: monounsaturated (olive oil) vs saturated fat (cream). *Int J Obes Relat Metab Disord*. 2002;26(6):814-21.
1474. Jones PJ, Schoeller DA. Polyunsaturated:saturated ratio of diet fat influences energy substrate utilization in the human. *Metab Clin Exp*. 1988;37(2):145-51.
1475. Krishnan S, Cooper JA. Effect of dietary fatty acid composition on substrate utilization and body weight maintenance in humans. *Eur J Nutr*. 2014;53(3):691-710.
1476. Jonnalagadda SS, Egan SK, Heimbach JT, et al. Fatty acid consumption pattern of Americans: 1987-1988 USDA Nationwide Food Consumption Survey. *Nutr Res*. 1995;15(12):1767-81.
1477. Pimenta AS, Gaidhu MP, Habib S, et al. Prolonged exposure to palmitate impairs fatty acid oxidation despite activation of AMP-activated protein kinase in skeletal muscle cells. *J Cell Physiol*. 2008;217(2):478-85.
1478. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. The influence of the type of dietary fat on postprandial fat oxidation rates: monounsaturated (olive oil) vs saturated fat (cream). *Int J Obes Relat Metab Disord*. 2002;26(6):814-21.
1479. Fernández de la Puebla RA, Fuentes F, Pérez-Martínez P, et al. A reduction in dietary saturated fat decreases body fat content in overweight, hypercholesterolemic males. *Nutr Metab Cardiovasc Dis*. 2003;13(5):273-7.
1480. Casas-Agustench P, López-Uriarte P, Bulló M, et al. Acute effects of three high-fat meals with different fat saturations on energy expenditure, substrate oxidation and satiety. *Clin Nutr*. 2009;28(1):39-45.
1481. Clevenger HC, Kozimor AL, Paton CM, Cooper JA. Acute effect of dietary fatty acid composition on postprandial metabolism in women. *Exp Physiol*. 2014;99(9):1182-90.
1482. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689-97.
1483. Turner C. Coconut oil for weight loss. Nana's Nest. Published November 25, 2015. Available at: <http://1g83.com/9-reasons-to-use-coconut-oil-daily>. Accessed March 31, 2019.
1484. Maggio CA, Koopmans HS. Food intake after intragastric meals of short-, medium-, or long-chain triglyceride. *Physiol Behav*. 1982;28(5):921-6.
1485. Liao KM, Lee YY, Chen CK, Rasool AH. An open-label pilot study to assess the efficacy and safety of virgin coconut oil in reducing visceral adiposity. *ISRN Pharmacol*. 2011;2011:949686.
1486. Robinson E, Hardman CA, Halford JC, Jones A. Eating under observation: a systematic review and meta-analysis of the effect that heightened awareness of observation has on laboratory measured energy intake. *Am J Clin Nutr*. 2015;102(2):324-37.
1487. Valente FX, Cândido FG, Lopes LL, et al. Effects of coconut oil consumption on energy metabolism, cardiometabolic risk markers, and appetitive responses in women with excess body fat. *Eur J Nutr*. 2018;57(4):1627-37.
1488. Harris M, Hutchins A, Fryda L. The impact of virgin coconut oil and high-oleic safflower oil on body composition, lipids, and inflammatory markers in postmenopausal women. *J Med Food*. 2017;20(4):345-51.

1489. George BJ, Beasley TM, Brown AW, et al. Common scientific and statistical errors in obesity research. *Obesity (Silver Spring)*. 2016;24(4):781-90.
1490. Assunção ML, Ferreira HS, Dos Santos AF, Cabral CR, Florêncio TM. Effects of dietary coconut oil on the biochemical and anthropometric profiles of women presenting abdominal obesity. *Lipids*. 2009;44(7):593-601.
1491. Eyres L, Eyres MF, Chisholm A, Brown RC. Coconut oil consumption and cardiovascular risk factors in humans. *Nutr Rev*. 2016;74(4):267-80.
1492. Freeman AM, Morris PB, Barnard N, et al. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol*. 2017;69(9):1172-87.
1493. Wang D, Hawley NL, Thompson AA, et al. Dietary patterns are associated with metabolic outcomes among adult Samoans in a cross-sectional study. *J Nutr*. 2017;147(4):628-35.
1494. DiBello JR, McGarvey ST, Kraft P, et al. Dietary patterns are associated with metabolic syndrome in adult Samoans. *J Nutr*. 2009;139(10):1933-43.
1495. Cabré E, Hernández-Pérez JM, Fluvà L, Pastor C, Corominas A, Gassull MA. Absorption and transport of dietary long-chain fatty acids in cirrhosis: a stable-isotope-tracing study. *Am J Clin Nutr*. 2005;81(3):692-701.
1496. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *Br J Nutr*. 2003;90(3):717-27.
1497. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689-97.
1498. Hegsted M. Washington—dietary guidelines. FoodPolitics.com. Available at: <https://www.foodpolitics.com/wp-content/uploads/Hegsted.pdf>. Accessed March 31, 2019.
1499. United States Congress Senate Select Committee on Nutrition and Human Needs. Diet related to killer diseases, III: hearings before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-fifth Congress, first session, March 24, 1977. Response to Dietary Goals of the United States: re meat. Washington, D.C.: U.S. Government Printing Office; 1977. Available at: <https://catalog.hathitrust.org/Record/012480120/Home>. Accessed February 28, 2019.
1500. United States Congress Senate Select Committee on Nutrition and Human Needs. Dietary goals for the United States—supplemental view. Ninety-fifth Congress, first session. Washington, D.C.: U.S. Government Printing Office; 1977. Available at: <https://catalog.hathitrust.org/Record/002942190>. Accessed February 28, 2019.
1501. United States Congress Senate Select Committee on Nutrition and Human Needs. Dietary goals for the United States—supplemental view. Ninety-fifth Congress, first session. Washington, D.C.: U.S. Government Printing Office; 1977. Available at: <https://catalog.hathitrust.org/Record/002942190>. Accessed February 28, 2019.
1502. Brownell KD, Warner KE. The perils of ignoring history: Big Tobacco played dirty and millions died. How similar is Big Food? *Milbank Q*. 2009;87(1):259-94.
1503. Boseley S. Political context of the World Health Organization: sugar industry threatens to scupper the WHO. *Int J Health Serv*. 2003;33(4):831-3.
1504. Cannon G. Why the Bush administration and the global sugar industry are determined to demolish the 2004 WHO global strategy on diet, physical activity and health. *Public Health Nutr*. 2004;7(3):369-80.
1505. Stuckler D, Basu S, McKee M. Commentary: UN high level meeting on non-communicable diseases: an opportunity for whom? *BMJ*. 2011;343:d5336.
1506. Stanhope KL. Sugar consumption, metabolic disease and obesity: the state of the controversy. *Crit Rev Clin Lab Sci*. 2016;53(1):52-67.
1507. Cottrell RC. Sugar: an excess of anything can harm. *Nature*. 2012;483(7388):158.
1508. Brownell KD. Does a “toxic” environment make obesity inevitable? *Obesity Management*. 2005;1(2):52-5.
1509. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
1510. Roth Y. Do brands serve as reliable signals of nutritional quality? The case of breakfast cereals. *J Food Prod Market*. 2017;1:1-23.
1511. Poti JM, Braga B, Qin B. Ultra-processed food intake and obesity: what really matters for health-processing or nutrient content? *Curr Obes Rep*. 2017;6(4):420-31.
1512. Brownell KD. Does a “toxic” environment make obesity inevitable? *Obesity Management*. 2005;1(2):52-5.
1513. Connor JM. Breakfast cereals: the extreme food industry. *Agribusiness*. 1999;15(2):247-59.
1514. Sheiham A, James WP. Diet and dental caries: the pivotal role of free sugars reemphasized. *J Dent Res*. 2015;94(10):1341-7.
1515. Kearns CE, Glantz SA, Schmidt LA. Sugar industry influence on the scientific agenda of the National Institute of Dental Research's 1971 National Caries Program: a historical analysis of internal documents. *PLoS Med*. 2015;12(3):e1001798.
1516. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev*. 2009;22(1):93-108.
1517. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju SN, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388(10046):776-86.
1518. Maffetone PB, Rivera-Dominguez I, Laursen PB. Overfat and underfat: new terms and definitions long overdue. *Front Public Health*. 2016;4:279.
1519. Maffetone PB, Laursen PB. The prevalence of overfat adults and children in the US. *Front Public Health*. 2017;5:290.
1520. JAMA Editorial Board. Sugar as food. *JAMA*. 1913;61(7):492-3.
1521. Stare F. Sugar is a cheap safe food. *Trends Biochem Sci*. 1976;1(6):126-8.
1522. Tappy L, Lê KA. Health effects of fructose and fructose-containing caloric sweeteners: where do we stand 10 years after the initial whistle blowings? *Curr Diab Rep*. 2015;15(8):54.
1523. Bowman SA, Clemens JC, Martin CL, Anand J, Steinfeldt LC, Moshfegh AJ. Added sugars intake of Americans: what we eat in America, NHANES 2013-2014. United States Department of Agriculture. Published May 2017. Available at:

https://www.ars.usda.gov/arsuserfiles/80400530/pdf/dbrief/18_added_sugars_intake_of_americans_2013-2014.pdf. Accessed March 31, 2019.

1524. Rippe JM, Tappy L. Sweeteners and health: findings from recent research and their impact on obesity and related metabolic conditions. *Int J Obes (Lond)*. 2016;40 Suppl 1:S1-5.
1525. Lipton E. Rival industries sweet-talk the public. *New York Times*. Published February 11, 2014. Available at: <https://www.nytimes.com/2014/02/12/business/rival-industries-sweet-talk-the-public.html>. Accessed March 31, 2019.
1526. Kahn R, Sievenpiper JL. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes? We have, but the pox on sugar is overweight and overworked. *Diabetes Care*. 2014;37(4):957-62.
1527. Scientific Advisory Committee on Nutrition. *Carbohydrates and Health*. United Kingdom: Stationery Office Ltd; 2015. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/sacn_carbohydrates_and_health.pdf. Accessed March 31, 2019.
1528. Rippe JM, Tappy L. Sweeteners and health: findings from recent research and their impact on obesity and related metabolic conditions. *Int J Obes (Lond)*. 2016;40 Suppl 1:S1-5.
1529. Sørensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr*. 2005;82(2):421-7.
1530. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ*. 2012;346:e7492.
1531. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific opinion on Dietary Reference Values for carbohydrates and dietary fibre. *EFSA Journal*. 2010;8(3):1-77.
1532. Kuhnle GG, Tasevska N, Lentjes MA, et al. Association between sucrose intake and risk of overweight and obesity in a prospective sub-cohort of the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk). *Public Health Nutr*. 2015;18(15):2815-24.
1533. Kuhnle GG, Tasevska N, Lentjes MA, et al. Association between sucrose intake and risk of overweight and obesity in a prospective sub-cohort of the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk). *Public Health Nutr*. 2015;18(15):2815-24.
1534. FDA approves new high-intensity sweetener sucralose. United States Food and Drug Administration. Published April 1, 1998. Available at: <https://web.archive.org/web/20000818094111/http://www.fda.gov/80/bbs/topics/ANSWERS/ANS00859.html>. Accessed April 1, 2019.
1535. National Center for Biotechnology Information. Sucralose. PubChem, U.S. National Library of Medicine. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/71485>. Accessed April 1, 2019.
1536. Patel RM, Sarma R, Grimsley E. Popular sweetener sucralose as a migraine trigger. *Headache*. 2006;46(8):1303-4.
1537. Grotz V. Sucralose and migraine. *J Headache Pain*. 2007;48(1):164-5.
1538. Fowler SP. Low-calorie sweetener use and energy balance: results from experimental studies in animals, and large-scale prospective studies in humans. *Physiol Behav*. 2016;164(Pt B):517-23.
1539. Shearer J, Swithers SE. Artificial sweeteners and metabolic dysregulation: lessons learned from agriculture and the laboratory. *Rev Endocr Metab Disord*. 2016;17(2):179-86.
1540. Mandrioli D, Kearns CE, Bero LA. Relationship between research outcomes and risk of bias, study sponsorship, and author financial conflicts of interest in reviews of the effects of artificially sweetened beverages on weight outcomes: a systematic review of reviews. *PLoS ONE*. 2016;11(9):e0162198.
1541. Bes-Rastrollo M, Schulze M, Ruiz-Canela M, Martinez-Gonzalez M. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. *PLoS Med*. 2013;10(12):e1001578.
1542. Shearer J, Swithers SE. Artificial sweeteners and metabolic dysregulation: lessons learned from agriculture and the laboratory. *Rev Endocr Metab Disord*. 2016;17(2):179-86.
1543. Pearlman M, Obert J, Casey L. The association between artificial sweeteners and obesity. *Curr Gastroenterol Rep*. 2017;19(12):64.
1544. Shearer J, Swithers SE. Artificial sweeteners and metabolic dysregulation: lessons learned from agriculture and the laboratory. *Rev Endocr Metab Disord*. 2016;17(2):179-86.
1545. Pepino MY, Tiemann CD, Patterson BW, Wice BM, Klein S. Sucralose affects glycemic and hormonal responses to an oral glucose load. *Diabetes Care*. 2013;36(9):2530-5.
1546. Grotz V. Sucralose and migraine. *J Headache Pain*. 2007;48(1):164-5.
1547. Greenhill C. Gut microbiota: not so sweet—artificial sweeteners can cause glucose intolerance by affecting the gut microbiota. *Nat Rev Endocrinol*. 2014;10(11):637.
1548. Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E. Non-caloric artificial sweeteners and the microbiome: findings and challenges. *Gut Microbes*. 2015;6(2):149-55.
1549. Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E. Non-caloric artificial sweeteners and the microbiome: findings and challenges. *Gut Microbes*. 2015;6(2):149-55.
1550. Sylvestry AC, Walter PJ, Garraffo HM, Robien K, Rother KI. Widespread sucralose exposure in a randomized clinical trial in healthy young adults. *Am J Clin Nutr*. 2017;105(4):820-3.
1551. Cantley LC. Cancer, metabolism, fructose, artificial sweeteners, and going cold turkey on sugar. *BMC Biol*. 2013;12:8.
1552. Hill SE, Prokosch ML, Morin A, Rodeheffer CD. The effect of non-caloric sweeteners on cognition, choice, and post-consumption satisfaction. *Appetite*. 2014;83:82-8.
1553. Van Opstal AM, Kaal I, Van den Berg-Huysmans AA, et al. Dietary sugars and non-caloric sweeteners elicit different homeostatic and hedonic responses in the brain. *Nutrition*. 2019;60:80-6.
1554. Tey SL, Salleh NB, Henry CJ, Forde CG. Effects of non-nutritive (artificial vs natural) sweeteners on 24-h glucose profiles. *Eur J Clin Nutr*. 2017;71(9):1129-32.
1555. Tey SL, Salleh NB, Henry J, Forde CG. Effects of aspartame-, monk fruit-, stevia-and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *Int J Obes (Lond)*. 2017;41(3):450-7.

1556. Tey SL, Salleh NB, Henry J, Forde CG. Effects of aspartame-, monk fruit-, stevia-and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *Int J Obes (Lond)*. 2017;41(3):450-7.
1557. Madjd A, Taylor MA, Delavari A, Malekzadeh R, MacDonald IA, Farshchi HR. Beneficial effects of replacing diet beverages with water on type 2 diabetic obese women following a hypo-energetic diet: a randomized, 24-week clinical trial. *Diabetes Obes Metab*. 2017;19(1):125-32.
1558. Madjd A, Taylor MA, Delavari A, Malekzadeh R, MacDonald IA, Farshchi HR. Effects on weight loss in adults of replacing diet beverages with water during a hypoenergetic diet: a randomized, 24-wk clinical trial. *Am J Clin Nutr*. 2015;102(6):1305-12.
1559. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. 2014;514(7521):181-6.
1560. Malik VS, Willett WC, Hu FB. The Revised Nutrition Facts Label: a step forward and more room for improvement. *JAMA*. 2016;316(6):583-4.
1561. Ha V, Cozma AI, Choo VL, Mejia SB, de Souza RJ, Sievenpiper JL. Do fructose-containing sugars lead to adverse health consequences? Results of recent systematic reviews and meta-analyses. *Adv Nutr*. 2015;6(4):504S-11S.
1562. Purnell JQ, Fair DA. Fructose ingestion and cerebral, metabolic, and satiety responses. *JAMA*. 2013;309(1):85-6.
1563. Agricultural Research Service, United States Department of Agriculture. Basic report: 08013, cereals ready-to-eat, General Mills, Cheerios. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/08013>. Accessed March 31, 2019.
1564. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45260354, Froot Loops, sweetened multi-grain cereal, UPC: 038000391255. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45260354>. Accessed April 1, 2019.
1565. Harris JL, Schwartz MB, Ustjanauskas A, Ohri-Vachaspati P, Brownell KD. Effects of serving high-sugar cereals on children's breakfast-eating behavior. *Pediatrics*. 2011;127(1):71-6.
1566. Harington K, Smeele R, Van Loon F, et al. Desire for sweet taste unchanged after eating: evidence of a dessert mentality? *J Am Coll Nutr*. 2016;35(6):581-6.
1567. Purnell JQ, Fair DA. Fructose ingestion and cerebral, metabolic, and satiety responses. *JAMA*. 2013;309(1):85-6.
1568. Harington K, Smeele R, Van Loon F, et al. Desire for sweet taste unchanged after eating: evidence of a dessert mentality? *J Am Coll Nutr*. 2016;35(6):581-6.
1569. Tappy L. What nutritional physiology tells us about diet, sugar and obesity. *Int J Obes (Lond)*. 2016;40 Suppl 1:S28-9.
1570. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
1571. Thow AM, Hawkes C. Global sugar guidelines: an opportunity to strengthen nutrition policy. *Public Health Nutr*. 2014;17(10):2151-5.
1572. Kessler DA. Toward more comprehensive food labeling. *N Engl J Med*. 2014;371:193-5.
1573. Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. *Physiol Behav*. 2012;106(3):317-24.
1574. Tryon MS, Stanhope KL, Epel ES, et al. Excessive sugar consumption may be a difficult habit to break: a view from the brain and body. *J Clin Endocrinol Metab*. 2015;100(6):2239-47.
1575. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes? Health be damned! Pour on the sugar. *Diabetes Care*. 2014;37(4):950-6.
1576. Bowman SA, Clemens JC, Martin CL, et al. Added sugars intake of Americans: what we eat in America, NHANES 2013-2014. Food Surveys Research Group. Dietary Data Brief No. 18. Published May 2017. Available at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/DBrief/18_Added_Sugars_Intake_of_Americans_2013-2014.pdf. Accessed April 1, 2019.
1577. Linos N, Bassett MT. Added sugar intake and public health. *JAMA*. 2015;314(2):187.
1578. United States Department of Health and Human Services and United States Department of Agriculture. *2015-2020 Dietary Guidelines for Americans. 8th Edition*. Published December 2015. Available at: <http://health.gov/dietaryguidelines/2015/guidelines>. Accessed March 31, 2019.
1579. Zhang Z, Gillespie C, Welsh JA, Hu FB, Yang Q. Usual intake of added sugars and lipid profiles among the U.S. adolescents: National Health and Nutrition Examination Survey, 2005-2010. *J Adolesc Health*. 2015;56(3):352-9.
1580. Sugar Association. RE: Docket No. FDA-2012-N-1210, March 3, 2014, proposed rule, food labeling: revision of the Nutrition and Supplement Facts Label. Published July 31, 2014. Available at: <https://web.archive.org/web/20170504162332/http://www.sugar.org/wp-content/uploads/2014/07/7-31-14-NFP-Comments-re-Sugar-Association-Docket-No-FDA-2012-N-12102.pdf>. Accessed April 1, 2019.
1581. Anderson AS. Sugars and health—risk assessment to risk management. *Public Health Nutr*. 2014;17(10):2148-50.
1582. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009;120(11):1011-20.
1583. Centers for Disease Control and Prevention. Intake of calories and selected nutrients for the United States population, 1999-2000. United States Department of Health and Human Services. Available at: <https://www.cdc.gov/nchs/data/nhanes/databriefs/calories.pdf>. Accessed April 1, 2019.
1584. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009;120(11):1011-20.
1585. Rippe JM, Sievenpiper JL, Lê KA, White JS, Clemens R, Angelopoulos TJ. What is the appropriate upper limit for added sugars consumption? *Nutr Rev*. 2017;75(1):18-36.
1586. Vos MB, Kaar JL, Welsh JA, et al. Added sugars and cardiovascular disease risk in children: a scientific statement from the American Heart Association. *Circulation*. 2017;135(19):e1017-34.
1587. Siega-Riz AM, Deming DM, Reidy KC, Fox MK, Condon E, Briefel RR. Food consumption patterns of infants and toddlers: where are we now? *J Am Diet Assoc*. 2010;110(12 Suppl):S38-51.
1588. Albertson AM, Thompson DR, Franko DL, Holschuh NM. Weight indicators and nutrient intake in children and adolescents do not vary by sugar content in ready-to-eat cereal: results from National Health and Nutrition Examination Survey 2001-2006. *Nutr Res*. 2011;31(3):229-36.

1589. United States Department of Agriculture. SuperTracker. 2018. Available at: <https://web.archive.org/web/20180329114134/https://www.supertracker.usda.gov/foodapedia.aspx>. Accessed April 1, 2019.
1590. Harris JL, Schwartz MB, Brownell KD, et al. Cereal FACTS 2012: limited progress in the nutrition quality and marketing of children's cereals. Rudd Center for Food Policy & Obesity. Published June 2012. Available at: http://www.cerealfacts.org/media/cereal_facts_report_2012_7.12.pdf. Accessed April 1, 2019.
1591. Undurraga D, Naidenko O, Sharp R. Children's cereals: sugar by the pound. Washington, D.C.: Environmental Working Group; 2014. Available at: <https://static.ewg.org/reports/2014/cereals/pdf/2014-EWG-Cereals-Report.pdf>. Accessed April 1, 2019.
1592. Rippe JM, Sievenpiper JL, Lê KA, White JS, Clemens R, Angelopoulos TJ. What is the appropriate upper limit for added sugars consumption? *Nutr Rev*. 2017;75(1):18-36.
1593. Evans CEL. Sugars and health: a review of current evidence and future policy. *Proc Nutr Soc*. 2017;76(3):400-7.
1594. Guideline: sugars intake for adults and children. Geneva: World Health Organization. 2015;1-49. Available at: https://apps.who.int/iris/bitstream/handle/10665/149782/9789241549028_eng.pdf. Accessed April 1, 2019.
1595. Thow AM, Hawkes C. Global sugar guidelines: an opportunity to strengthen nutrition policy. *Public Health Nutr*. 2014;17(10):2151-5.
1596. Agricultural Research Service, United States Department of Agriculture. Basic report: 14148, beverages, carbonated, cola, regular. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/14148>. Accessed March 31, 2019.
1597. Madero M, Arriaga JC, Jalal D, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. *Metab Clin Exp*. 2011;60(11):1551-9.
1598. Bartolotto C. Does consuming sugar and artificial sweeteners change taste preferences? *Perm J*. 2015;19(3):81-4.
1599. Ott V, Finlayson G, Lehnert H, et al. Oxytocin reduces reward-driven food intake in humans. *Diabetes*. 2013;62(10):3418-25.
1600. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci (Regul Ed)*. 2011;15(1):37-46.
1601. Szczypka MS, Kwok K, Brot MD, et al. Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron*. 2001;30(3):819-28.
1602. Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage*. 2003;19(4):1709-15.
1603. Janssen HG, Davies IG, Richardson LD, Stevenson L. Determinants of takeaway and fast food consumption: a narrative review. *Nutr Res Rev*. 2018;31(1):16-34.
1604. Erlanson-Albertsson C. How palatable food disrupts appetite regulation. *Basic Clin Pharmacol Toxicol*. 2005;97(2):61-73.
1605. Bragulat V, Dziedzic M, Bruno C, et al. Food-related odor probes of brain reward circuits during hunger: a pilot fMRI study. *Obesity (Silver Spring)*. 2010;18(8):1566-71.
1606. Nesse RM, Berridge KC. Psychoactive drug use in evolutionary perspective. *Science*. 1997;278(5335):63-6.
1607. Meule A. Back by popular demand: a narrative review on the history of food addiction research. *Yale J Biol Med*. 2015;88(3):295-302.
1608. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS ONE*. 2007;2(8):e698.
1609. Dillehay TD, Rossen J, Ugent D, Karathanasis A, Vásquez V, Netherly P. Early Holocene coca chewing in northern Peru. *Antiquity*. 2010;84(326):939-53.
1610. Weil AT. Coca leaf as a therapeutic agent. *Am J Drug Alcohol Abuse*. 1978;5(1):75-86.
1611. Ifland JR, Preuss HG, Marcus MT, et al. Refined food addiction: a classic substance use disorder. *Med Hypotheses*. 2009;72(5):518-26.
1612. Belkova J, Rozkot M, Danek P, Klein P, Matonohova J, Podhorna I. Sugar and nutritional extremism. *Crit Rev Food Sci Nutr*. 2017;57(5):933-6.
1613. DiNicolantonio JJ, O'Keefe JH, Wilson WL. Sugar addiction: is it real? A narrative review. *Br J Sports Med*. 2018;52(14):910-3.
1614. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. *PLoS ONE*. 2007;2(8):e698.
1615. Gearhardt AN, Davis C, Kuschner R, Brownell KD. The addiction potential of hyperpalatable foods. *Curr Drug Abuse Rev*. 2011;4(3):140-5.
1616. Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. *Neurosci Biobehav Rev*. 2013;37(9 Pt A):2047-58.
1617. Ifland J, Preuss HG, Marcus MT, Rourke KM, Taylor W, Wright HT. Clearing the confusion around processed food addiction. *J Am Coll Nutr*. 2015;34(3):240-3.
1618. Yeomans MR, Gray RW. Selective effects of naltrexone on food pleasantness and intake. *Physiol Behav*. 1996;60(2):439-46.
1619. Bertino M, Beauchamp GK, Engelman K. Naltrexone, an opioid blocker, alters taste perception and nutrient intake in humans. *Am J Physiol*. 1991;261(1 Pt 2):R59-63.
1620. Eikemo M, Løseth GE, Johnstone T, Gjerstad J, Willoch F, Leknes S. Sweet taste pleasantness is modulated by morphine and naltrexone. *Psychopharmacology (Berl)*. 2016;233(21-22):3711-23.
1621. Trenchard E, Silverstone T. Naloxone reduces the food intake of normal human volunteers. *Appetite*. 1983;4(1):43-50.
1622. Spiegel TA, Stunkard AJ, Shrager EE, O'Brien CP, Morrison MF, Stellar E. Effect of naltrexone on food intake, hunger, and satiety in obese men. *Physiol Behav*. 1987;40(2):135-41.
1623. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci (Regul Ed)*. 2011;15(1):37-46.
1624. Harrison D, Bueno M, Yamada J, Adams-Webber T, Stevens B. Analgesic effects of sweet-tasting solutions for infants: current state of equipoise. *Pediatrics*. 2010;126(5):894-902.

1625. Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2013;(1):CD001069.
1626. Frank S, Linder K, Kullmann S, et al. Fat intake modulates cerebral blood flow in homeostatic and gustatory brain areas in humans. *Am J Clin Nutr*. 2012;95(6):1342-9.
1627. Smeets PA, de Graaf C, Stafleu A, van Osch MJ, van der Grond J. Functional MRI of human hypothalamic responses following glucose ingestion. *Neuroimage*. 2005;24(2):363-8.
1628. Lemeshow AR, Rimm EB, Hasin DS, et al. Food and beverage consumption and food addiction among women in the Nurses' Health Studies. *Appetite*. 2018;121:186-97.
1629. Yanovski S. Sugar and fat: cravings and aversions. *J Nutr*. 2003;133(3):835S-7S.
1630. Ambrosini GL, Johns DJ, Northstone K, Emmett PM, Jebb SA. Free sugars and total fat are important characteristics of a dietary pattern associated with adiposity across childhood and adolescence. *J Nutr*. 2016;146(4):778-84.
1631. Drewnowski A. Why do we like fat? *J Am Diet Assoc*. 1997;97(7 Suppl):S58-62.
1632. Drewnowski A. Why do we like fat? *J Am Diet Assoc*. 1997;97(7 Suppl):S58-62.
1633. Ambrosini GL, Johns DJ, Northstone K, Emmett PM, Jebb SA. Free sugars and total fat are important characteristics of a dietary pattern associated with adiposity across childhood and adolescence. *J Nutr*. 2016;146(4):778-84.
1634. Stinson EJ, Piaggi P, Ibrahim M, Venti C, Krakoff J, Votruba SB. High fat and sugar consumption during ad libitum intake predicts weight gain. *Obesity (Silver Spring)*. 2018;26(4):689-95.
1635. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE*. 2015;10(2):e0117959.
1636. Katona SJ. The Baby Food Hypothesis: an explanation why high fat high sugar (HFHS) mixtures are so addictive, providing novel treatment strategies to control appetite in obesity and anorexia. *Med Hypotheses*. 2016;88:33.
1637. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE*. 2015;10(2):e0117959.
1638. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE*. 2015;10(2):e0117959.
1639. Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS ONE*. 2015;10(2):e0117959.
1640. Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metab*. 2019;30(1):67-77.
1641. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
1642. Roberto CA, Swinburn B, Hawkes C, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. *Lancet*. 2015;385(9985):2400-9.
1643. Tri-County Cessation Center. Cigarette ingredients. New York State Department of Health Tobacco Control Program. Available at: <https://web.archive.org/web/20160121165220/http://www.tricountycessation.org/tobaccofacts/Cigarette-Ingredients.html>. Accessed April 1, 2019.
1644. Cocores JA, Gold MS. The Salted Food Addiction Hypothesis may explain overeating and the obesity epidemic. *Med Hypotheses*. 2009;73(6):892-9.
1645. Harnack LJ, Cogswell ME, Shikany JM, et al. Sources of sodium in US adults from 3 geographic regions. *Circulation*. 2017;135(19):1775-83.
1646. Beck M. Dinner preparation in the modern United States. *Br Food J*. 2007;109(7):531-47.
1647. Kant AK, Whitley MI, Graubard BI. Away from home meals: associations with biomarkers of chronic disease and dietary intake in American adults, NHANES 2005-2010. *Int J Obes (Lond)*. 2015;39(5):820-7.
1648. An R. Fast-food and full-service restaurant consumption and daily energy and nutrient intakes in US adults. *Eur J Clin Nutr*. 2016;70(1):97-103.
1649. Kant AK, Whitley MI, Graubard BI. Away from home meals: associations with biomarkers of chronic disease and dietary intake in American adults, NHANES 2005-2010. *Int J Obes (Lond)*. 2015;39(5):820-7.
1650. Shaath T, Fischer R, Goeser M, Rajpara A, Aires D. Scurvy in the present times: vitamin C allergy leading to strict fast food diet. *Dermatol Online J*. 2016;22(1).
1651. Urban LE, Roberts SB, Fierstein JL, Gary CE, Lichtenstein AH. Sodium, saturated fat, and trans fat content per 1,000 kilocalories: temporal trends in fast-food restaurants, United States, 2000-2013. *Prev Chronic Dis*. 2014;11:E228.
1652. Nago ES, Lachat CK, Dossa RA, Kolsteren PW. Association of out-of-home eating with anthropometric changes: a systematic review of prospective studies. *Crit Rev Food Sci Nutr*. 2014;54(9):1103-16.
1653. Close MA, Lytle LA, Viera AJ. Is frequency of fast food and sit-down restaurant eating occasions differentially associated with less healthful eating habits? *Prev Med Rep*. 2016;4:574-7.
1654. Ebbeling CB, Garcia-Lago E, Leidig MM, Seger-Shippe LG, Feldman HA, Ludwig DS. Altering portion sizes and eating rate to attenuate gorging during a fast food meal: effects on energy intake. *Pediatrics*. 2007;119(5):869-75.
1655. Ebbeling CB, Sinclair KB, Pereira MA, Garcia-Lago E, Feldman HA, Ludwig DS. Compensation for energy intake from fast food among overweight and lean adolescents. *JAMA*. 2004;291(23):2828-33.
1656. Ebbeling CB, Garcia-Lago E, Leidig MM, Seger-Shippe LG, Feldman HA, Ludwig DS. Altering portion sizes and eating rate to attenuate gorging during a fast food meal: effects on energy intake. *Pediatrics*. 2007;119(5):869-75.
1657. Grow HM, Schwartz MB. Food marketing to youth: serious business. *JAMA*. 2014;312(18):1918-9.
1658. Flint SW. Infecting academic conferences: brands linked to ill health. *Lancet Glob Health*. 2015;3(5):e259.
1659. Keast RS, Sayonpark D, Sacks G, Swinburn BA, Riddell LJ. The influence of caffeine on energy content of sugar-sweetened beverages: "the caffeine-calorie effect." *Eur J Clin Nutr*. 2011;65(12):1338-44.
1660. Keast RS, Riddell LJ. Caffeine as a flavor additive in soft-drinks. *Appetite*. 2007;49(1):255-9.
1661. James JE. Dietary caffeine: "unnatural" exposure requiring precaution? *J Subst Use*. 2014;19(5):394-7.
1662. Griffiths RR, Woodson PP. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Ther*. 1988;246(1):21-9.
1663. Yeomans MR, Jackson A, Lee MD, et al. Acquisition and extinction of flavour preferences conditioned by caffeine in humans. *Appetite*. 2000;35(2):131-41.
1664. James JE. Dietary caffeine: "unnatural" exposure requiring precaution? *J Subst Use*. 2014;19(5):394-7.

1665. Temple JL. Caffeine use in children: what we know, what we have left to learn, and why we should worry. *Neurosci Biobehav Rev*. 2009;33(6):793-806.
1666. Morin JP, Rodríguez-Durán LF, Guzmán-Ramos K, et al. Palatable hyper-caloric foods impact on neuronal plasticity. *Front Behav Neurosci*. 2017;11:19.
1667. Abe S, Nishino S, Kanaya T, Inoue T. Yummy food is made from fat and sugar. *Circ J*. 2017;81(8):1100-1.
1668. Erlanson-Albertsson C. How palatable food disrupts appetite regulation. *Basic Clin Pharmacol Toxicol*. 2005;97(2):61-73.
1669. Anguah KO, Lovejoy JC, Craig BA, et al. Can the palatability of healthy, satiety-promoting foods increase with repeated exposure during weight loss? *Foods*. 2017;6(2):16.
1670. Blais CA, Pangborn RM, Borhani NO, et al. Effect of dietary sodium restriction on taste responses to sodium chloride: a longitudinal study. *Am J Clin Nutr*. 1986;44(2):232-43.
1671. DiPatrizio NV. Is fat taste ready for primetime? *Physiol Behav*. 2014;136:145-54.
1672. Grieve FG, Vander Weg MW. Desire to eat high-and low-fat foods following a low-fat dietary intervention. *J Nutr Educ Behav*. 2003;35(2):98-102.
1673. Stewart JE, Newman LP, Keast RS. Oral sensitivity to oleic acid is associated with fat intake and body mass index. *Clin Nutr*. 2011;30(6):838-44.
1674. Bolhuis DP, Newman LP, Keast RS. Effects of salt and fat combinations on taste preference and perception. *Chem Senses*. 2016;41(3):189-95.
1675. Beidler LM, Smallman RL. Renewal of cells within taste buds. *J Cell Biol*. 1965;27(2):263-72.
1676. Barlow P, Serôdio P, Ruskin G, McKee M, Stuckler D. Science organisations and Coca-Cola's "war" with the public health community: insights from an internal industry document. *J Epidemiol Community Health*. 2018;72(9):761-3.
1677. Westerterp KR, Speakman JR. Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. *Int J Obes (Lond)*. 2008;32(8):1256-63.
1678. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1679. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1680. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1681. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1682. Hall KD, Guo J, Dore M, Chow CC. The progressive increase of food waste in America and its environmental impact. *PLoS ONE*. 2009;4(11):e7940.
1683. Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr*. 2009;90(6):1453-6.
1684. Nielsen SJ, Popkin BM. Patterns and trends in food portion sizes, 1977-1998. *JAMA*. 2003;289(4):450-3.
1685. Wansink B, Park SB. At the movies: how external cues and perceived taste impact consumption volume. *Food Quality and Preference*. 2001;12:69-74. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
1686. Lieberman LS. Evolutionary and anthropological perspectives on optimal foraging in obesogenic environments. *Appetite*. 2006;47(1):3-9.
1687. Duffey KJ, Popkin BM. Energy density, portion size, and eating occasions: contributions to increased energy intake in the United States, 1977-2006. *PLoS Med*. 2011;8(6):e1001050.
1688. Rolls BJ, Roe LS, Meengs JS. Reductions in portion size and energy density of foods are additive and lead to sustained decreases in energy intake. *Am J Clin Nutr*. 2006;83(1):11-7.
1689. Williams RA, Roe LS, Rolls BJ. Assessment of satiety depends on the energy density and portion size of the test meal. *Obesity (Silver Spring)*. 2014;22(2):318-24.
1690. Westerterp-Plantenga MS, Pasman WJ, Yedema MJ, Wijckmans-Duijsens NE. Energy intake adaptation of food intake to extreme energy densities of food by obese and non-obese women. *Eur J Clin Nutr*. 1996;50(6):401-7.
1691. Agricultural Research Service, United States Department of Agriculture. Basic report: 04053, oil, olive, salad or cooking. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/04053>. Accessed April 1, 2019.
1692. Agricultural Research Service, United States Department of Agriculture. Basic report: 09042, blackberries, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301063>. Accessed April 1, 2019.
1693. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45059273, cherry tomatoes, UPC: 854693000447. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45059273>. Accessed April 1, 2019.
1694. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45156418, Jelly Belly, jelly beans, UPC: 071567997157. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45156418>. Accessed April 1, 2019.
1695. Agricultural Research Service, United States Department of Agriculture. Basic report: 11674, potatoes, baked, flesh and skin, without salt. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/11674>. Accessed April 1, 2019.
1696. Agricultural Research Service, United States Department of Agriculture. Basic report: 21238, McDonald's, french fries. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/305473>. Accessed April 1, 2019.
1697. Ebbeling CB, Garcia-Lago E, Leidig MM, Seger-Shippe LG, Feldman HA, Ludwig DS. Altering portion sizes and eating rate to attenuate gorging during a fast food meal: effects on energy intake. *Pediatrics*. 2007;119(5):869-75.
1698. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45184791, ice cream strawberries & cream, UPC: 079893092959. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45184791>. Accessed April 1, 2019.

1699. Agricultural Research Service, United States Department of Agriculture. Basic report: 09316, strawberries, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301283>. Accessed April 1, 2019.
1700. Agricultural Research Service, United States Department of Agriculture. Basic report: 11477, squash, summer, zucchini, includes skin, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/302072>. Accessed April 1, 2019.
1701. Agricultural Research Service, United States Department of Agriculture. Basic report: 11206, cucumber, peeled, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/11206>. Accessed April 1, 2019.
1702. Agricultural Research Service, United States Department of Agriculture. Basic report: 11233, kale, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301876>. Accessed April 1, 2019.
1703. Welch RW. Satiety: have we neglected dietary non-nutrients? *Proc Nutr Soc.* 2011;70(2):145-54.
1704. Ledikwe JH, Blanck HM, Kettel Khan L, et al. Dietary energy density is associated with energy intake and weight status in US adults. *Am J Clin Nutr.* 2006;83(6):1362-8.
1705. Ledikwe JH, Blanck HM, Kettel Khan L, et al. Dietary energy density is associated with energy intake and weight status in US adults. *Am J Clin Nutr.* 2006;83(6):1362-8.
1706. Rolls BJ. Plenary lecture 1: dietary strategies for the prevention and treatment of obesity. *Proc Nutr Soc.* 2010;69(1):70-9.
1707. Prentice AM, Jebb SA. Fast foods, energy density and obesity: a possible mechanistic link. *Obes Rev.* 2003;4(4):187-94.
1708. Ebbeling CB, Sinclair KB, Pereira MA, Garcia-Lago E, Feldman HA, Ludwig DS. Compensation for energy intake from fast food among overweight and lean adolescents. *JAMA.* 2004;291(23):2828-33.
1709. Stender S, Dyerberg J, Astrup A. Fast food: unfriendly and unhealthy. *Int J Obes (Lond).* 2007;31(6):887-90.
1710. Prentice AM, Jebb SA. Fast foods, energy density and obesity: a possible mechanistic link. *Obes Rev.* 2003;4(4):187-94.
1711. English LK, Fearnbach SN, Wilson SJ, et al. Food portion size and energy density evoke different patterns of brain activation in children. *Am J Clin Nutr.* 2017;105(2):295-305.
1712. Bailey RL. Modern foraging: presence of food and energy density influence motivational processing of food advertisements. *Appetite.* 2016;107:568-74.
1713. Hendry CJK. How much food does man require? New insights. *Nutr Bull.* 2012;37(3):241-6.
1714. Jenkins DJ, Kendall CW. The garden of Eden: plant-based diets, the genetic drive to store fat and conserve cholesterol, and implications for epidemiology in the 21st century. *Epidemiology.* 2006;17(2):128-30.
1715. Pérez-Escamilla R, Obbagy JE, Altman JM, et al. Dietary energy density and body weight in adults and children: a systematic review. *J Acad Nutr Diet.* 2012;112(5):671-84.
1716. Rolls BJ, Roe LS. Effect of the volume of liquid food infused intragastrically on satiety in women. *Physiol Behav.* 2002;76(4-5):623-31.
1717. Duncan KH, Bacon JA, Weinsier RL. The effects of high and low energy density diets on satiety, energy intake, and eating time of obese and nonobese subjects. *Am J Clin Nutr.* 1983;37(5):763-7.
1718. Pérez-Escamilla R, Obbagy JE, Altman JM, et al. Dietary energy density and body weight in adults and children: a systematic review. *J Acad Nutr Diet.* 2012;112(5):671-84.
1719. Ledikwe JH, Blanck HM, Kettel Khan LK, et al. Low-energy-density diets are associated with high diet quality in adults in the United States. *J Am Diet Assoc.* 2006;106(8):1172-80.
1720. Heymsfield SB. Meal replacements and energy balance. *Physiol Behav.* 2010;100(1):90-4.
1721. Wadden TA, Foster GD, Sarwer DB, et al. Dieting and the development of eating disorders in obese women: results of a randomized controlled trial. *Am J Clin Nutr.* 2004;80(3):560-8.
1722. Lowe MR, Butryn ML, Thomas JG, Coletta M. Meal replacements, reduced energy density eating, and weight loss maintenance in primary care patients: a randomized controlled trial. *Obesity (Silver Spring).* 2014;22(1):94-100.
1723. Shintani TT, Hughes CK, Beckham S, O'Connor HK. Obesity and cardiovascular risk intervention through the ad libitum feeding of traditional Hawaiian diet. *Am J Clin Nutr.* 1991;53(6 Suppl):1647S-51.
1724. Grunwald GK, Seagle HM, Peters JC, Hill JO. Quantifying and separating the effects of macronutrient composition and non-macronutrients on energy density. *Br J Nutr.* 2001;86(2):265-76.
1725. Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM. Covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating ad libitum. *Am J Clin Nutr.* 1995;62(2):316-29.
1726. Agricultural Research Service, United States Department of Agriculture. Food composition databases show nutrients list. Available at: <https://ndb.nal.usda.gov/ndb/nutrients/report/nutrientsfrm?max=25&offset=0&totCount=0&nutrient1=208&nutrient2=&fg=4&subset=0&sort=f&measureby=g>. Accessed April 1, 2019.
1727. Agricultural Research Service, United States Department of Agriculture. Basic report: 01001, butter, salted. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/299278>. Accessed April 1, 2019.
1728. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. *Metab Syndr Relat Disord.* 2011;9(1):1-12.
1729. Bes-Rastrollo M, Sánchez-Villegas A, de la Fuente C, de Irala J, Martínez JA, Martínez-González MA. Olive oil consumption and weight change: the SUN prospective cohort study. *Lipids.* 2006;41(3):249-56.
1730. Benítez-Arciniega AD, Gómez-Ulloa D, Vila A, et al. Olive oil consumption, BMI, and risk of obesity in Spanish adults. *Obes Facts.* 2012;5(1):52-9.
1731. Bautista-Castaño I, Sánchez-Villegas A, Estruch R, et al. Changes in bread consumption and 4-year changes in adiposity in Spanish subjects at high cardiovascular risk. *Br J Nutr.* 2013;110(2):337-46.
1732. Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM. Covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating ad libitum. *Am J Clin Nutr.* 1995;62(2):316-29.

1733. Prentice AM. Manipulation of dietary fat and energy density and subsequent effects on substrate flux and food intake. *Am J Clin Nutr.* 1998;67(3 Suppl):535S-41S.
1734. La Fontaine HA, Crowe TC, Swinburn BA, Gibbons CJ. Two important exceptions to the relationship between energy density and fat content: foods with reduced-fat claims and high-fat vegetable-based dishes. *Public Health Nutr.* 2004;7(4):563-8.
1735. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45317499, Devil's Food Cookie Cakes, UPC: 819898019342. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45317499>. Accessed April 1, 2019.
1736. Agricultural Research Service, United States Department of Agriculture. Basic report: 18245, danish pastry, cheese. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/304541>. Accessed April 1, 2019.
1737. La Fontaine HA, Crowe TC, Swinburn BA, Gibbons CJ. Two important exceptions to the relationship between energy density and fat content: foods with reduced-fat claims and high-fat vegetable-based dishes. *Public Health Nutr.* 2004;7(4):563-8.
1738. Zhu Y, Hollis JH. Soup consumption is associated with a lower dietary energy density and a better diet quality in US adults. *Br J Nutr.* 2014;111(8):1474-80.
1739. Rolls BJ, Roe LS, Beach AM, Kris-Etherton PM. Provision of foods differing in energy density affects long-term weight loss. *Obes Res.* 2005;13(6):1052-60.
1740. Campbell's® low sodium soups. Ready to serve low sodium chicken broth. Campbells.com. Available at: <https://www.campbells.com/campbell-soup/campbells-low-sodium-soups/ready-to-serve-low-sodium-chicken-broth>. Accessed March 31, 2019.
1741. Smethers AD, Rolls BJ. Dietary management of obesity: cornerstones of healthy eating patterns. *Med Clin North Am.* 2018;102(1):107-24.
1742. Drewnowski A, Almiron-Roig E, Marmonier C, Lluch A. Dietary energy density and body weight: is there a relationship? *Nutr Rev.* 2004;62(11):403-13.
1743. Agricultural Research Service, United States Department of Agriculture. Food composition databases show nutrients list. Available at: <https://ndb.nal.usda.gov/ndb/nutrients/report/nutrientsfrm?max=25&offset=0&totalCount=0&nutrient1=208&nutrient2=&fg=4&subset=0&sort=f&measureby=g>. Accessed April 1, 2019.
1744. Robson AA. Food nanotechnology: water is the key to lowering the energy density of processed foods. *Nutr Health.* 2011;20(3-4):231-6.
1745. Spill MK, Birch LL, Roe LS, Rolls BJ. Hiding vegetables to reduce energy density: an effective strategy to increase children's vegetable intake and reduce energy intake. *Am J Clin Nutr.* 2011;94(3):735-41.
1746. Spill MK, Birch LL, Roe LS, Rolls BJ. Hiding vegetables to reduce energy density: an effective strategy to increase children's vegetable intake and reduce energy intake. *Am J Clin Nutr.* 2011;94(3):735-41.
1747. Cooke L. The importance of exposure for healthy eating in childhood: a review. *J Hum Nutr Diet.* 2007;20(4):294-301.
1748. Pescud M, Pettigrew S. Parents' experiences with hiding vegetables as a strategy for improving children's diets. *BFJ.* 2014;116(12):1853-63.
1749. Blatt AD, Roe LS, Rolls BJ. Hidden vegetables: an effective strategy to reduce energy intake and increase vegetable intake in adults. *Am J Clin Nutr.* 2011;93(4):756-63.
1750. Katan MB, Ludwig DS. Extra calories cause weight gain—but how much? *JAMA.* 2010;303(1):65-6.
1751. Ello-Martin JA, Roe LS, Ledikwe JH, Beach AM, Rolls BJ. Dietary energy density in the treatment of obesity: a year-long trial comparing 2 weight-loss diets. *Am J Clin Nutr.* 2007;85(6):1465-77.
1752. Chang UJ, Hong YH, Suh HJ, Jung EY. Lowering the energy density of parboiled rice by adding water-rich vegetables can decrease total energy intake in a parboiled rice-based diet without reducing satiety on healthy women. *Appetite.* 2010;55(2):338-42.
1753. Leahy KE, Birch LL, Fisher JO, Rolls BJ. Reductions in entrée energy density increase children's vegetable intake and reduce energy intake. *Obesity (Silver Spring).* 2008;16(7):1559-65.
1754. Agricultural Research Service, United States Department of Agriculture. Basic report: 11260, mushrooms, white, raw. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301902>. Accessed April 1, 2019.
1755. Cheskin LJ, Davis LM, Lipsky LM, et al. Lack of energy compensation over 4 days when white button mushrooms are substituted for beef. *Appetite.* 2008;51(1):50-7.
1756. Poddar KH, Ames M, Hsin-Jen C, Feeney MJ, Wang Y, Cheskin LJ. Positive effect of mushrooms substituted for meat on body weight, body composition, and health parameters. A 1-year randomized clinical trial. *Appetite.* 2013;71:379-87.
1757. Agricultural Research Service, United States Department of Agriculture. Basic report: 11179, corn, sweet, yellow, frozen, kernels cut off cob, boiled, drained, without salt. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/301833>. Accessed April 1, 2019.
1758. Agricultural Research Service, United States Department of Agriculture. Basic report: 19034, snacks, popcorn, air-popped. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/304810>. Accessed April 1, 2019.
1759. Nguyen V, Cooper L, Lowndes J, et al. Popcorn is more satiating than potato chips in normal-weight adults. *Nutr J.* 2012;11:71.
1760. Osterholt KM, Roe LS, Rolls BJ. Incorporation of air into a snack food reduces energy intake. *Appetite.* 2007;48(3):351-8.
1761. Cheetos® Crunchy cheese flavored snacks. Nutrition facts. FritoLay.com. Available at: <https://www.fritolay.com/snacks/product-page/cheetos>. Accessed March 31, 2019.
1762. Cheetos® Puffs cheese flavored snacks. Nutrition facts. FritoLay.com. Available at: <https://www.fritolay.com/snacks/product-page/cheetos>. Accessed March 31, 2019.

1763. Rolls BJ, Meengs JS, Roe LS. Variations in cereal volume affect the amount selected and eaten for breakfast. *J Acad Nutr Diet*. 2014;114(9):1411-6.
1764. Bell EA, Rolls BJ. Energy density of foods affects energy intake across multiple levels of fat content in lean and obese women. *Am J Clin Nutr*. 2001;73(6):1010-8.
1765. Welch RW. Satiety: have we neglected dietary non-nutrients? *Proc Nutr Soc*. 2011;70(2):145-54.
1766. de Oliveira MC, Sichier R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite*. 2008;51(2):291-5.
1767. Williams RA, Roe LS, Rolls BJ. Comparison of three methods to reduce energy density. Effects on daily energy intake. *Appetite*. 2013;66:75-83.
1768. Obbagy JE, Condrasky MD, Roe LS, Sharp JL, Rolls BJ. Chefs' opinions about reducing the calorie content of menu items in restaurants. *Obesity (Silver Spring)*. 2011;19(2):332-7.
1769. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645-52.
1770. Tucker LA. Consumption of nuts and seeds and telomere length in 5,582 men and women of the National Health and Nutrition Examination Survey (NHANES). *J Nutr Health Aging*. 2017;21(3):233-40.
1771. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
1772. Ros E. Eat nuts, live longer. *J Am Coll Cardiol*. 2017;70(20):2533-5.
1773. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
1774. Fernández-Montero A, Bes-Rastrollo M, Barrio-López MT, et al. Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: the SUN project. *Nutrition*. 2014;30(9):1022-7.
1775. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
1776. Fernández-Montero A, Martínez-González MA, Moreno-Galarraga L. Re. "Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: the SUN project": authors' response. *Nutrition*. 2015;31(10):1299-300.
1777. Hull S, Re R, Chambers L, Echaniz A, Wickham MS. A mid-morning snack of almonds generates satiety and appropriate adjustment of subsequent food intake in healthy women. *Eur J Nutr*. 2015;54(5):803-10.
1778. Fraser GE, Bennett HW, Jaceldo KB, Sabaté J. Effect on body weight of a free 76 kilojoule (320 calorie) daily supplement of almonds for six months. *J Am Coll Nutr*. 2002;21(3):275-83.
1779. Wang X, Li Z, Liu Y, Lv X, Yang W. Effects of pistachios on body weight in Chinese subjects with metabolic syndrome. *Nutr J*. 2012;11:20.
1780. Tey SL, Gray AR, Chisholm AW, Delahunty CM, Brown RC. The dose of hazelnuts influences acceptance and diet quality but not inflammatory markers and body composition in overweight and obese individuals. *J Nutr*. 2013;143(8):1254-62.
1781. Sabaté J, Cordero-MacIntyre Z, Siapco G, Torabian S, Haddad E. Does regular walnut consumption lead to weight gain? *Br J Nutr*. 2005;94(5):859-64.
1782. Farr OM, Tuccinardi D, Upadhyay J, Oussaada SM, Mantzoros CS. Walnut consumption increases activation of the insula to highly desirable food cues: a randomized, double-blind, placebo-controlled, cross-over fMRI study. *Diabetes Obes Metab*. 2018;20(1):173-7.
1783. Baer DJ, Gebauer SK, Novotny JA. Walnuts consumed by healthy adults provide less available energy than predicted by the Atwater factors. *J Nutr*. 2016;146(1):9-13.
1784. Grundy MM, Carrière F, Mackie AR, Gray DA, Butterworth PJ, Ellis PR. The role of plant cell wall encapsulation and porosity in regulating lipolysis during the digestion of almond seeds. *Food Funct*. 2016;7(1):69-78.
1785. Fogelholm M, Anderssen S, Gunnarsdottir I, Lahti-Koski M. Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. *Food Nutr Res*. 2012;56.
1786. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, D.C.: American Institute for Cancer Research; 2007. Available at: <https://www.wcrf.org/sites/default/files/english.pdf>. Accessed March 31, 2019.
1787. Hunt JN, Cash R, Newland P. Energy density of food, gastric emptying, and obesity. *Lancet*. 1975;2(7941):905-6.
1788. Milne I. 18th and 19th century dietary advice. *J R Coll Physicians Edinb*. 2014;44(4):347.
1789. Lobstein T. Child obesity: what can be done and who will do it? *Proc Nutr Soc*. 2008;67(3):301-6.
1790. American Egg Board. 2016 annual report. Chicago, IL; 2017. Available at: <https://www.aeb.org/about-aeb/annual-report>. Accessed March 31, 2019.
1791. Cattlemen's Beef Board. 2017 annual report. Centennial, CO; 2018. Available at: <https://www.beefboard.org/library/annual-reports.asp>. Accessed March 31, 2019.
1792. United States Department of Agriculture. U.S. Department of Agriculture report to Congress on the Dairy Promotion and Research Program and the Fluid Milk Processor Promotion Program: 2015 program activities. 2016. Available at: <https://www.ams.usda.gov/reports/report-congress-dairy-fluid-milk-promotion-research-programs>. Accessed March 31, 2019.
1793. National Pork Board. Audited financial statements and compliance report: years ended December 31, 2016 and 2015. 2017. Available at: <https://www.pork.org/about/annual-financial-reports>. Accessed March 31, 2019.
1794. Le LT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. *Nutrients*. 2014;6(6):2131-47.
1795. Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21,966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond)*. 2006;30(9):1389-96.
1796. Sabaté J, Lindsted KD, Harris RD, Johnston PK. Anthropometric parameters of schoolchildren with different lifestyles. *Am J Dis Child*. 1990;144(10):1159-63.

1797. Grant R, Bilgin A, Zeuschner C, et al. The relative impact of a vegetable-rich diet on key markers of health in a cohort of Australian adolescents. *Asia Pac J Clin Nutr*. 2008;17(1):107-15.
1798. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr*. 2010;91(5):1525S-9S.
1799. Fogelholm M, Anderssen S, Gunnarsdottir I, Lahti-Koski M. Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. *Food Nutr Res*. 2012;56:19103.
1800. Fogelholm M, Kanerva N, Männistö S. Association between red and processed meat consumption and chronic diseases: the confounding role of other dietary factors. *Eur J Clin Nutr*. 2015;69(9):1060-5.
1801. Fogelholm M, Anderssen S, Gunnarsdottir I, Lahti-Koski M. Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. *Food Nutr Res*. 2012;56:19103.
1802. Grosso G, Micek A, Godos J, et al. Health risk factors associated with meat, fruit and vegetable consumption in cohort studies: a comprehensive meta-analysis. *PLoS ONE*. 2017;12(8):e0183787.
1803. Le IT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. *Nutrients*. 2014;6(6):2131-47.
1804. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364(25):2392-404.
1805. Tucker LA, Tucker JM, Bailey B, Lecheminant JD. Meat intake increases risk of weight gain in women: a prospective cohort investigation. *Am J Health Promot*. 2014;29(1):e43-52.
1806. Babio N, Sorlí M, Bulló M, et al. Association between red meat consumption and metabolic syndrome in a Mediterranean population at high cardiovascular risk: cross-sectional and 1-year follow-up assessment. *Nutr Metab Cardiovasc Dis*. 2012;22(3):200-7.
1807. Kahn HS, Tatham LM, Heath CW. Contrasting factors associated with abdominal and peripheral weight gain among adult women. *Int J Obes Relat Metab Disord*. 1997;21(10):903-11.
1808. Kahn HS, Tatham LM, Rodriguez C, Calle EE, Thun MJ, Heath CW. Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. *Am J Public Health*. 1997;87(5):747-54.
1809. Wang Y, Beydoun MA. Meat consumption is associated with obesity and central obesity among US adults. *Int J Obes (Lond)*. 2009;33(6):621-8.
1810. Vergnaud AC, Norat T, Romaguera D, et al. Meat consumption and prospective weight change in participants of the EPIC-PANACEA study. *Am J Clin Nutr*. 2010;92(2):398-407.
1811. Gilsing AM, Weijenberg MP, Hughes LA, et al. Longitudinal changes in BMI in older adults are associated with meat consumption differentially, by type of meat consumed. *J Nutr*. 2012;142(2):340-9.
1812. Astrup A, Clifton P, Layman DK, Mattes RD, Westterp-Plantenga MS. Meat intake's influence on body fatness cannot be assessed without measurement of body fat. *Am J Clin Nutr*. 2010;92(5):1274-5.
1813. Vergnaud AC, Teresa N, Romaguera D, et al. Reply to A Astrup et al. *Am J Clin Nutr*. 2010;92(5):1275-6.
1814. Agricultural Research Service, United States Department of Agriculture. Basic report: 05061, chicken, broilers or fryers, breast, meat and skin, cooked, stewed. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/300147>. Accessed April 1, 2019.
1815. Gilsing AM, Weijenberg MP, Hughes LA, et al. Longitudinal changes in BMI in older adults are associated with meat consumption differentially, by type of meat consumed. *J Nutr*. 2012;142(2):340-9.
1816. Gilsing AM, Weijenberg MP, Hughes LA, et al. Longitudinal changes in BMI in older adults are associated with meat consumption differentially, by type of meat consumed. *J Nutr*. 2012;142(2):340-9.
1817. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45123781, chicken nuggets, UPC: 011110819659. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45123781>. Accessed April 1, 2019.
1818. Agricultural Research Service, United States Department of Agriculture. Basic report: 05057, chicken, broilers or fryers, breast, meat and skin, raw. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/05057>. Accessed April 1, 2019.
1819. Alkerwi A, Sauvageot N, Buckley JD, et al. The potential impact of animal protein intake on global and abdominal obesity: evidence from the Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study. *Public Health Nutr*. 2015;18(10):1831-8.
1820. Alkerwi A, Sauvageot N, Buckley JD, et al. The potential impact of animal protein intake on global and abdominal obesity: evidence from the Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study. *Public Health Nutr*. 2015;18(10):1831-8.
1821. Charlton KE, Tapsell LC, Batterham MJ, et al. Pork, beef and chicken have similar effects on acute satiety and hormonal markers of appetite. *Appetite*. 2011;56(1):1-8.
1822. Murphy KJ, Parker B, Dyer KA, et al. A comparison of regular consumption of fresh lean pork, beef and chicken on body composition: a randomized cross-over trial. *Nutrients*. 2014;6(2):682-96.
1823. Davidson MH, Hunninghake D, Maki KC, Kwiterovich PO, Kafonek S. Comparison of the effects of lean red meat vs lean white meat on serum lipid levels among free-living persons with hypercholesterolemia: a long-term, randomized clinical trial. *Arch Intern Med*. 1999;159(12):1331-8.
1824. Mahon AK, Flynn MG, Stewart LK, et al. Protein intake during energy restriction: effects on body composition and markers of metabolic and cardiovascular health in postmenopausal women. *J Am Coll Nutr*. 2007;26(2):182-9.
1825. Mann H, Djulbegovic B. Comparator bias: why comparisons must address genuine uncertainties. *J R Soc Med*. 2013;106(1):30-3.
1826. Burley VJ, Paul AW, Blundell JE. Influence of a high-fibre food (myco-protein) on appetite: effects on satiety (within meals) and satiety (following meals). *Eur J Clin Nutr*. 1993;47(6):409-18.
1827. Bottin JH, Swann JR, Cropp E, et al. Mycoprotein reduces energy intake and postprandial insulin release without altering glucagon-like peptide-1 and peptide tyrosine-tyrosine concentrations in healthy overweight and obese adults: a randomised-controlled trial. *Br J Nutr*. 2016;116(2):360-74.
1828. Williamson DA, Geiselman PJ, Lovejoy J, et al. Effects of consuming mycoprotein, tofu or chicken upon subsequent eating behaviour, hunger and safety. *Appetite*. 2006;46(1):41-8.

1829. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr*. 2010;91(5):1525S-9S.
1830. Shah NJ, Sureshkumar S, Shewade DG. Metabolomics: a tool ahead for understanding molecular mechanisms of drugs and diseases. *Indian J Clin Biochem*. 2015;30(3):247-54.
1831. Miekisch W, Schubert JK, Noeldge-Schomburg GF. Diagnostic potential of breath analysis—focus on volatile organic compounds. *Clin Chim Acta*. 2004;347(1-2):25-39.
1832. Rak K, Rader DJ. Cardiovascular disease: the diet-microbe morbid union. *Nature*. 2011;472(7341):40-1.
1833. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575-84.
1834. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575-84.
1835. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576-85.
1836. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576-85.
1837. Cho CE, Taesuwan S, Malysheva OV, et al. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: a randomized controlled trial. *Mol Nutr Food Res*. 2017;61(1).
1838. Hernández-Alonso P, Cañueto D, Giardina S, et al. Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in prediabetic subjects. *J Nutr Biochem*. 2017;45:48-53.
1839. McCarty MF. L-carnitine consumption, its metabolism by intestinal microbiota, and cardiovascular health. *Mayo Clin Proc*. 2013;88(8):786-9.
1840. Miao J, Ling AV, Manthena PV, et al. Flavin-containing monooxygenase 3 as a potential player in diabetes-associated atherosclerosis. *Nat Commun*. 2015;6:6498.
1841. Schugar RC, Shih DM, Warriar M, et al. The TMAO-producing enzyme flavin-containing monooxygenase 3 regulates obesity and the beiging of white adipose tissue. *Cell Rep*. 2017;19(12):2451-61.
1842. Heianza Y, Sun D, Smith SR, Bray GA, Sacks FM, Qi L. Changes in gut microbiota-related metabolites and long-term successful weight loss in response to weight-loss diets: the POUNDS Lost Trial. *Diabetes Care*. 2018;41(3):413-9.
1843. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576-85.
1844. Boutagy NE, Neilson AP, Osterberg KL, et al. Short-term high-fat diet increases postprandial trimethylamine-N-oxide in humans. *Nutr Res*. 2015;35(10):858-64.
1845. Storm JJ, Lima SL. Mothers forewarn offspring about predators: a transgenerational maternal effect on behavior. *Am Nat*. 2010;175(3):382-90.
1846. Galloway LF, Etterson JR. Transgenerational plasticity is adaptive in the wild. *Science*. 2007;318(5853):1134-6.
1847. Lee TM, Zucker I. Vole infant development is influenced perinatally by maternal photoperiodic history. *Am J Physiol*. 1988;255(5 Pt 2):R831-8.
1848. Kawahata A, Sakamoto H. Some observations on sweating of the Aino. *Jpn J Physiol*. 1951;2(2):166-9.
1849. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr*. 1999;70(5):811-6.
1850. Maslova E, Rytter D, Bech BH, et al. Maternal protein intake during pregnancy and offspring overweight 20 y later. *Am J Clin Nutr*. 2014;100(4):1139-48.
1851. Yin J, Quinn S, Dwyer T, Ponsonby AL, Jones G. Maternal diet, breastfeeding and adolescent body composition: a 16-year prospective study. *Eur J Clin Nutr*. 2012;66(12):1329-34.
1852. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *BJOG*. 2008;115(10):1243-9.
1853. Arya F, Egger S, Colquhoun D, Sullivan D, Pal S, Egger G. Differences in postprandial inflammatory responses to a "modern" v. traditional meat meal: a preliminary study. *Br J Nutr*. 2010;104(5):724-8.
1854. Buenz EJ. Lead exposure through eating wild game. *Am J Med*. 2016;129(5):457-8.
1855. Eaton SB. Humans, lipids and evolution. *Lipids*. 1992;27(10):814-20.
1856. Rehkamp S. A look at calorie sources in the American diet. Economic Research Service, United States Department of Agriculture. Published December 5, 2016. Available at: <https://www.ers.usda.gov/amber-waves/2016/december/a-look-at-calorie-sources-in-the-american-diet>. Accessed March 31, 2019.
1857. Wang Y, Lehane C, Ghebremeskel K, Crawford MA. Modern organic and broiler chickens sold for human consumption provide more energy from fat than protein. *Public Health Nutr*. 2010;13(3):400-8.
1858. Eaton SB. Humans, lipids and evolution. *Lipids*. 1992;27(10):814-20.
1859. Agricultural Research Service, United States Department of Agriculture. Basic report: 05123, chicken, stewing, meat and skin, raw. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/05123>. Accessed April 1, 2019.
1860. Wang Y, Lehane C, Ghebremeskel K, Crawford MA. Modern organic and broiler chickens sold for human consumption provide more energy from fat than protein. *Public Health Nutr*. 2010;13(3):400-8.
1861. Martínez Steele E, Baraldi LG, Louzada ML, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open*. 2016;6(3):e009892.
1862. Rehkamp S. A look at calorie sources in the American diet. Economic Research Service, United States Department of Agriculture. Published December 5, 2016. Available at: <https://www.ers.usda.gov/amber-waves/2016/december/a-look-at-calorie-sources-in-the-american-diet>. Accessed March 31, 2019.
1863. Huth PJ, Fulgoni VL, Keast DR, Park K, Auestad N. Major food sources of calories, added sugars, and saturated fat and their contribution to essential nutrient intakes in the U.S. diet: data from the National Health and Nutrition Examination Survey (2003-2006). *Nutr J*. 2013;12:116.
1864. Reedy J, Krebs-Smith SM. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. *J Am Diet Assoc*. 2010;110(10):1477-84.

1865. Katz D. *Disease-Proof: Slash Your Risk of Heart Disease, Cancer, Diabetes, and More—By 80 Percent*. New York: Penguin Group; 2013.
1866. Rehkamp S. A look at calorie sources in the American diet. Economic Research Service, United States Department of Agriculture. Published December 5, 2016. Available at: <https://www.ers.usda.gov/amber-waves/2016/december/a-look-at-calorie-sources-in-the-american-diet>. Accessed March 31, 2019.
1867. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364(25):2392–404.
1868. United States Department of Agriculture. Grains. ChooseMyPlate.gov. Updated November 3, 2017. Available at: <https://www.choosemyplate.gov/grains>. Accessed on March 31, 2019.
1869. Giacco R, Della Pepa G, Luongo D, Riccardi G. Whole grain intake in relation to body weight: from epidemiological evidence to clinical trials. *Nutr Metab Cardiovasc Dis*. 2011;21(12):901–8.
1870. Choumenkovitch SF, McKeown NM, Tovar A, et al. Whole grain consumption is inversely associated with BMI Z-score in rural school-aged children. *Public Health Nutr*. 2013;16(2):212–8.
1871. Koh-Banerjee P, Franz M, Sampson L, et al. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-y weight gain among men. *Am J Clin Nutr*. 2004;80(5):1237–45.
1872. Williams PG. Evaluation of the evidence between consumption of refined grains and health outcomes. *Nutr Rev*. 2012;70(2):80–99.
1873. Karl JP, Saltzman E. The role of whole grains in body weight regulation. *Adv Nutr*. 2012;3(5):697–707.
1874. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364(25):2392–404.
1875. Karl JP, Saltzman E. The role of whole grains in body weight regulation. *Adv Nutr*. 2012;3(5):697–707.
1876. Isaksson H, Sundberg B, Aman P, Fredriksson H, Olsson J. Whole grain rye porridge breakfast improves satiety compared to refined wheat bread breakfast. *Food Nutr Res*. 2008;52.
1877. Bodinham CL, Hitchen KL, Youngman PJ, Frost GS, Robertson MD. Short-term effects of whole-grain wheat on appetite and food intake in healthy adults: a pilot study. *Br J Nutr*. 2011;106(3):327–30.
1878. Isaksson H, Sundberg B, Aman P, Fredriksson H, Olsson J. Whole grain rye porridge breakfast improves satiety compared to refined wheat bread breakfast. *Food Nutr Res*. 2008;52.
1879. Isaksson H, Tillander I, Andersson R, et al. Whole grain rye breakfast—sustained satiety during three weeks of regular consumption. *Physiol Behav*. 2012;105(3):877–84.
1880. Hajihashemi P, Azadbakht L, Hashemipor M, Kelishadi R, Esmailzadeh A. Whole-grain intake favorably affects markers of systemic inflammation in obese children: a randomized controlled crossover clinical trial. *Mol Nutr Food Res*. 2014;58(6):1301–8.
1881. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr*. 2012;142(7):1304–13.
1882. Shimabukuro M, Higa M, Kinjo R, et al. Effects of the brown rice diet on visceral obesity and endothelial function: the BRAVO study. *Br J Nutr*. 2014;111(2):310–20.
1883. Hajihashemi P, Azadbakht L, Hashemipor M, Kelishadi R, Esmailzadeh A. Whole-grain intake favorably affects markers of systemic inflammation in obese children: a randomized controlled crossover clinical trial. *Mol Nutr Food Res*. 2014;58(6):1301–8.
1884. Tighe P, Duthie G, Vaughan N, et al. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. *Am J Clin Nutr*. 2010;92(4):733–40.
1885. Brownlee IA, Moore C, Chatfield M, et al. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr*. 2010;104(1):125–34.
1886. McKeown NM, Jacobs DR. In defence of phytochemical-rich dietary patterns. *Br J Nutr*. 2010;104(1):1–3.
1887. Brownlee IA, Moore C, Chatfield M, et al. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr*. 2010;104(1):125–34.
1888. McKeown NM, Troy LM, Jacques PF, Hoffmann U, O'Donnell CJ, Fox CS. Whole-and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: the Framingham Heart Study. *Am J Clin Nutr*. 2010;92(5):1165–71.
1889. Kristensen M, Pelletier X, Ross AB, Thielecke F. A high rate of non-compliance confounds the study of whole grains and weight maintenance in a randomised intervention trial—the case for greater use of dietary biomarkers in nutrition intervention studies. *Nutrients*. 2017;9(1):55.
1890. Jones JM, Engleson J. Whole grains: benefits and challenges. *Annu Rev Food Sci Technol*. 2010;1:19–40.
1891. Vanegas SM, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. *Am J Clin Nutr*. 2017;105(3):635–50.
1892. Schroeder N, Gallaher DD, Arndt EA, Marquart L. Influence of whole grain barley, whole grain wheat, and refined rice-based foods on short-term satiety and energy intake. *Appetite*. 2009;53(3):363–9.
1893. Karl JP, Saltzman E. The role of whole grains in body weight regulation. *Adv Nutr*. 2012;3(5):697–707.
1894. Shimabukuro M, Higa M, Kinjo R, et al. Effects of the brown rice diet on visceral obesity and endothelial function: the BRAVO study. *Br J Nutr*. 2014;111(2):310–20.
1895. Chang HC, Huang CN, Yeh DM, Wang SJ, Peng CH, Wang CJ. Oat prevents obesity and abdominal fat distribution, and improves liver function in humans. *Plant Foods Hum Nutr*. 2013;68(1):18–23.
1896. Kikuchi Y, Nozaki S, Makita M, et al. Effects of whole grain wheat bread on visceral fat obesity in Japanese subjects: a randomized double-blind study. *Plant Foods Hum Nutr*. 2018;73(3):161–5.
1897. Pol K, Christensen R, Bartels EM, Raben A, Tetens I, Kristensen M. Whole grain and body weight changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. *Am J Clin Nutr*. 2013;98(4):872–84.
1898. Karl JP, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr*. 2017;105(3):589–99.

1899. Livesey G. Thermogenesis associated with fermentable carbohydrate in humans, validity of indirect calorimetry, and implications of dietary thermogenesis for energy requirements, food energy and body weight. *Int J Obes Relat Metab Disord*. 2002;26(12):1553-69.
1900. Zou ML, Moughan PJ, Awati A, Livesey G. Accuracy of the Atwater factors and related food energy conversion factors with low-fat, high-fiber diets when energy intake is reduced spontaneously. *Am J Clin Nutr*. 2007;86(6):1649-56.
1901. Karl JP, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr*. 2017;105(3):589-99.
1902. Larsen SC, Ångquist L, Sørensen TI, Heitmann BL. 24h urinary sodium excretion and subsequent change in weight, waist circumference and body composition. *PLoS ONE*. 2013;8(7):e69689.
1903. Roberts WC. High salt intake, its origins, its economic impact, and its effect on blood pressure. *Am J Cardiol*. 2001;88(11):1338-46.
1904. Ellison RC, Soslenko JM, Harper GP, Gibbons L, Pratter FE, Miettinen OS. Obesity, sodium intake, and blood pressure in adolescents. *Hypertension*. 1980;2(4 Pt 2):78-82.
1905. Moosavian SP, Haghghatdoost F, Surkan PJ, Azadbakht L. Salt and obesity: a systematic review and meta-analysis of observational studies. *Int J Food Sci Nutr*. 2017;68(3):265-77.
1906. Elfassy T, Mossavar-Rahmani Y, Van Horn L, et al. Associations of sodium and potassium with obesity measures among diverse US Hispanic/Latino adults: results from the Hispanic Community Health Study/Study of Latinos. *Obesity (Silver Spring)*. 2018;26(2):442-50.
1907. Yoon YS, Oh SW. Sodium density and obesity; the Korea National Health and Nutrition Examination Survey 2007-2010. *Eur J Clin Nutr*. 2013;67(2):141-6.
1908. Centers for Disease Control and Prevention. Sodium intake among adults—United States, 2005–2006. *MMWR Morb Mortal Wkly Rep*. 2010;59(24):746-9.
1909. Ritz E. Salt appetite and addiction—unholy twins? *Nephrol Dial Transplant*. 2012;27(6):2146-8.
1910. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371(7):624-34.
1911. D'Elia L, Galletti F, Strazzullo P. Dietary salt intake and risk of gastric cancer. *Cancer Treat Res*. 2014;159:83-95.
1912. Rosinger A, Herrick K, Gahche J, Park S. Sugar-sweetened beverage consumption among U.S. adults, 2011-2014. *NCHS Data Brief*. 2017;(270):1-8.
1913. Rosinger A, Herrick K, Gahche J, Park S. Sugar-sweetened beverage consumption among U.S. youth, 2011-2014. *NCHS Data Brief*. 2017;(271):1-8.
1914. He FJ, Markandu ND, Sagnella GA, MacGregor GA. Effect of salt intake on renal excretion of water in humans. *Hypertension*. 2001;38(3):317-20.
1915. Ma Y, He FJ, MacGregor GA. High salt intake: independent risk factor for obesity? *Hypertension*. 2015;66(4):843-9.
1916. Libuda L, Kersting M, Alexy U. Consumption of dietary salt measured by urinary sodium excretion and its association with body weight status in healthy children and adolescents. *Public Health Nutr*. 2012;15(3):433-41.
1917. Lee SK, Kim MK. Relationship of sodium intake with obesity among Korean children and adolescents: Korea National Health and Nutrition Examination Survey. *Br J Nutr*. 2016;115(5):834-41.
1918. Yoon YS, Oh SW. Sodium density and obesity; the Korea National Health and Nutrition Examination Survey 2007-2010. *Eur J Clin Nutr*. 2013;67(2):141-6.
1919. Zhu H, Pollock NK, Kotak I, et al. Dietary sodium, adiposity, and inflammation in healthy adolescents. *Pediatrics*. 2014;133(3):e635-42.
1920. Larsen SC, Ångquist L, Sørensen TI, Heitmann BL. 24h urinary sodium excretion and subsequent change in weight, waist circumference and body composition. *PLoS ONE*. 2013;8(7):e69689.
1921. Zhu H, Pollock NK, Kotak I, et al. Dietary sodium, adiposity, and inflammation in healthy adolescents. *Pediatrics*. 2014;133(3):e635-42.
1922. Ma Y, He FJ, MacGregor GA. High salt intake: independent risk factor for obesity? *Hypertension*. 2015;66(4):843-9.
1923. Larsen SC, Ångquist L, Sørensen TI, Heitmann BL. 24h urinary sodium excretion and subsequent change in weight, waist circumference and body composition. *PLoS ONE*. 2013;8(7):e69689.
1924. Lee SK, Kim MK. Relationship of sodium intake with obesity among Korean children and adolescents: Korea National Health and Nutrition Examination Survey. *Br J Nutr*. 2016;115(5):834-41.
1925. Fonseca-Alaniz MH, Brito LC, Borges-Silva CN, Takada J, Andreotti S, Lima FB. High dietary sodium intake increases white adipose tissue mass and plasma leptin in rats. *Obesity (Silver Spring)*. 2007;15(9):2200-8.
1926. Cui H, Yang S, Zheng M, Liu R, Zhao G, Wen J. High-salt intake negatively regulates fat deposition in mouse. *Sci Rep*. 2017;7(1):2053.
1927. Zhang Y, Li F, Liu FQ, et al. Elevation of fasting ghrelin in healthy human subjects consuming a high-salt diet: a novel mechanism of obesity? *Nutrients*. 2016;8(6):323.
1928. Azegami T, Yuki Y, Sawada S, et al. Nanogel-based nasal ghrelin vaccine prevents obesity. *Mucosal Immunol*. 2017;10(5):1351-60.
1929. Cocores JA, Gold MS. The Salted Food Addiction Hypothesis may explain overeating and the obesity epidemic. *Med Hypotheses*. 2009;73(6):892-9.
1930. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393(10184):1958-72.
1931. Appel LJ, Anderson CA. Compelling evidence for public health action to reduce salt intake. *N Engl J Med*. 2010;362(7):650-2.
1932. Drewnowski A, Rehm CD. Sodium intakes of US children and adults from foods and beverages by location of origin and by specific food source. *Nutrients*. 2013;5(6):1840-55.
1933. Verma AK, Banerjee R. Low-sodium meat products: retaining salty taste for sweet health. *Crit Rev Food Sci Nutr*. 2012;52(1):72-84.
1934. Appel LJ, Anderson CA. Compelling evidence for public health action to reduce salt intake. *N Engl J Med*. 2010;362(7):650-2.

1935. Roberts WC. High salt intake, its origins, its economic impact, and its effect on blood pressure. *Am J Cardiol*. 2001;88(11):1338-46.
1936. Williams KJ, Wu X. Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward. *Atherosclerosis*. 2016;247:225-82.
1937. Brown A, Guess N, Dornhorst A, Taheri S, Frost G. Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done? *Diabetes Obes Metab*. 2017;19(12):1655-68.
1938. Roden M. How free fatty acids inhibit glucose utilization in human skeletal muscle. *News Physiol Sci*. 2004;19:92-6.
1939. Bachmann OP, Dahl DB, Brechtel K, et al. Effects of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. *Diabetes*. 2001;50(11):2579-84.
1940. Nowotny B, Zahiragic L, Krog D, et al. Mechanisms underlying the onset of oral lipid-induced skeletal muscle insulin resistance in humans. *Diabetes*. 2013;62(7):2240-8.
1941. Koska J, Ozias MK, Deer J, et al. A human model of dietary saturated fatty acid induced insulin resistance. *Metab Clin Exp*. 2016;65(11):1621-8.
1942. Le Stunff C, Fallin D, Schork NJ, Bougnères P. The insulin gene VNTR is associated with fasting insulin levels and development of juvenile obesity. *Nat Genet*. 2000;26(4):444-6.
1943. Page MM, Skovsø S, Cen H, et al. Reducing insulin via conditional partial gene ablation in adults reverses diet-induced weight gain. *FASEB J*. 2018;32(3):1196-206.
1944. Mehran AE, Templeman NM, Brigidi GS, et al. Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metab*. 2012;16(6):723-37.
1945. Lustig RH, Greenway F, Velasquez-Mieyer P, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-finding trial of a long-acting formulation of octreotide in promoting weight loss in obese adults with insulin hypersecretion. *Int J Obes (Lond)*. 2006;30(2):331-41.
1946. Alemzadeh R, Langley G, Upchurch L, Smith P, Slonim AE. Beneficial effect of diazoxide in obese hyperinsulinemic adults. *J Clin Endocrinol Metab*. 1998;83(6):1911-5.
1947. Page MM, Johnson JD. Mild suppression of hyperinsulinemia to treat obesity and insulin resistance. *Trends Endocrinol Metab*. 2018;29(6):389-99.
1948. Templeman NM, Skovsø S, Page MM, Lim GE, Johnson JD. A causal role for hyperinsulinemia in obesity. *J Endocrinol*. 2017;232(3):R173-83.
1949. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4(7):e002014.
1950. Nolan CJ, Larter CZ. Lipotoxicity: why do saturated fatty acids cause and monounsaturates protect against it? *J Gastroenterol Hepatol*. 2009;24(5):703-6.
1951. Vessby B, Uusitupa M, Hermansen K, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia*. 2001;44(3):312-9.
1952. Goff LM, Bell JD, So PW, Dornhorst A, Frost GS. Veganism and its relationship with insulin resistance and intramyocellular lipid. *Eur J Clin Nutr*. 2005;59(2):291-8.
1953. Gojda J, Patková J, Jaček M, et al. Higher insulin sensitivity in vegans is not associated with higher mitochondrial density. *Eur J Clin Nutr*. 2013;67(12):1310-5.
1954. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *Br J Nutr*. 2003;90(3):717-27.
1955. Vessby B, Uusitupa M, Hermansen K, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia*. 2001;44(3):312-9.
1956. Nowotny B, Zahiragic L, Krog D, et al. Mechanisms underlying the onset of oral lipid-induced skeletal muscle insulin resistance in humans. *Diabetes*. 2013;62(7):2240-8.
1957. Astley CM, Todd JN, Salem RM, et al. Genetic evidence that carbohydrate-stimulated insulin secretion leads to obesity. *Clin Chem*. 2018;64(1):192-200.
1958. Chaput JP, Tremblay A, Rimm EB, Bouchard C, Ludwig DS. A novel interaction between dietary composition and insulin secretion: effects on weight gain in the Quebec Family Study. *Am J Clin Nutr*. 2008;87(2):303-9.
1959. Sigal RJ, El-Hashimy M, Martin BC, Soeldner JS, Krolewski AS, Warram JH. Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. *Diabetes*. 1997;46(6):1025-9.
1960. Marventano S, Vetrani C, Vitale M, Godos J, Riccardi G, Grosso G. Whole grain intake and glycaemic control in healthy subjects: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2017;9(7):769.
1961. Weickert MO, Möhlig M, Schöfl C, et al. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. *Diabetes Care*. 2006;29(4):775-80.
1962. Rabinowitz D, Merimee TJ, Maffezzoli R, Burgess JA. Patterns of hormonal release after glucose, protein, and glucose plus protein. *Lancet*. 1966;2(7461):454-6.
1963. Pal S, Ellis V. The acute effects of four protein meals on insulin, glucose, appetite and energy intake in lean men. *Br J Nutr*. 2010;104(8):1241-8.
1964. Collier GR, Greenberg GR, Wolever TM, Jenkins DJ. The acute effect of fat on insulin secretion. *J Clin Endocrinol Metab*. 1988;66(2):323-6.
1965. Holt SH, Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. *Am J Clin Nutr*. 1997;66(5):1264-76.
1966. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. *Am J Clin Nutr*. 2011;93(5):984-96.
1967. Charlton KE, Tapsell LC, Batterham MJ, et al. Pork, beef and chicken have similar effects on acute satiety and hormonal markers of appetite. *Appetite*. 2011;56(1):1-8.
1968. Nuttall FQ, Mooradian AD, Gannon MC, Billington C, Krezowski P. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. *Diabetes Care*. 1984;7(5):465-70.
1969. Valachovicová M, Krajcovicová-Kudláčková M, Blazíček P, Babinská K. No evidence of insulin resistance in normal weight vegetarians. A case control study. *Eur J Nutr*. 2006;45(1):52-4.

1970. Kuo CS, Lai NS, Ho LT, Lin CL. Insulin sensitivity in Chinese ovo-lactovegetarians compared with omnivores. *Eur J Clin Nutr.* 2004;58(2):312-6.
1971. Toth MJ, Poehlman ET. Sympathetic nervous system activity and resting metabolic rate in vegetarians. *Metab Clin Exp.* 1994;43(5):621-5.
1972. Hung CJ, Huang PC, Li YH, Lu SC, Ho LT, Chou HF. Taiwanese vegetarians have higher insulin sensitivity than omnivores. *Br J Nutr.* 2006;95(1):129-35.
1973. Bloomer RJ, Kabir MM, Canale RE, et al. Effect of a 21 day Daniel Fast on metabolic and cardiovascular disease risk factors in men and women. *Lipids Health Dis.* 2010;9:94.
1974. McCarty MF. The origins of western obesity: a role for animal protein? *Med Hypotheses.* 2000;54(3):488-94.
1975. Remer T, Pietrzik K, Manz F. A moderate increase in daily protein intake causing an enhanced endogenous insulin secretion does not alter circulating levels or urinary excretion of dehydroepiandrosterone sulfate. *Metab Clin Exp.* 1996;45(12):1483-6.
1976. Pal S, Ellis V. The acute effects of four protein meals on insulin, glucose, appetite and energy intake in lean men. *Br J Nutr.* 2010;104(8):1241-8.
1977. Gulliford MC, Bicknell EJ, Scarpello JH. Differential effect of protein and fat ingestion on blood glucose responses to high-and low-glycemic-index carbohydrates in noninsulin-dependent diabetic subjects. *Am J Clin Nutr.* 1989;50(4):773-7.
1978. Sun L, Ranawana DV, Leow MK, Henry CJ. Effect of chicken, fat and vegetable on glycaemia and insulinaemia to a white rice-based meal in healthy adults. *Eur J Nutr.* 2014;53(8):1719-26.
1979. Bottin JH, Swann JR, Cropp E, et al. Mycoprotein reduces energy intake and postprandial insulin release without altering glucagon-like peptide-1 and peptide tyrosine-tyrosine concentrations in healthy overweight and obese adults: a randomised-controlled trial. *Br J Nutr.* 2016;116(2):360-74.
1980. Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr.* 1990;52(3):524-8.
1981. Westman EC, Feinman RD, Mavropoulos JC, et al. Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr.* 2007;86(2):276-84.
1982. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr.* 2013;110(7):1178-87.
1983. Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br J Nutr.* 2013;110(5):969-70.
1984. Zhou J, Xu H. Low carbohydrate and high protein diets and all-cause, cancer, and cardiovascular diseases mortalities: a systematic review and meta-analysis from 7 cohort studies. *Acta Endocrinologica (BUC).* 2014;(2):259-66.
1985. Smith MM, Trexler ET, Sommer AJ, et al. Unrestricted paleolithic diet is associated with unfavorable changes to blood lipids in healthy subjects. *Int J Exerc Sci.* 2014;7(2):128-39. *Note:* This study has been retracted, but evidently for a technicality, not data integrity reasons. Han A. Researcher who tangled with CrossFit loses two more papers. Retraction Watch. Published June 30, 2017. Available at: <https://retractionwatch.com/2017/06/30/researcher-tangled-crossfit-loses-two-papers>. Accessed April 1, 2019.
1986. Barnard RJ, Ugianskis EJ, Martin DA, Inkeles SB. Role of diet and exercise in the management of hyperinsulinemia and associated atherosclerotic risk factors. *Am J Cardiol.* 1992;69(5):440-4.
1987. Smith MM, Trexler ET, Sommer AJ, et al. Unrestricted paleolithic diet is associated with unfavorable changes to blood lipids in healthy subjects. *Int J Exerc Sci.* 2014;7(2):128-39. *Note:* This study has been retracted, but evidently for a technicality, not data integrity reasons. Han A. Researcher who tangled with CrossFit loses two more papers. Retraction Watch. Published June 30, 2017. Available at: <https://retractionwatch.com/2017/06/30/researcher-tangled-crossfit-loses-two-papers>. Accessed April 1, 2019.
1988. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metab Clin Exp.* 1988;37(11):1081-8.
1989. Quek R, Bi X, Henry CJ. Impact of protein-rich meals on glycaemic response of rice. *Br J Nutr.* 2016;115(7):1194-201.
1990. Azadbakht L, Kimiagar M, Mehrabi Y, et al. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007;85(3):735-41.
1991. Gulliford MC, Bicknell EJ, Scarpello JH. Differential effect of protein and fat ingestion on blood glucose responses to high-and low-glycemic-index carbohydrates in noninsulin-dependent diabetic subjects. *Am J Clin Nutr.* 1989;50(4):773-7.
1992. Ballance S, Knutsen SH, Fosvold ØW, Wickham M, Trenado CD, Monro J. Glycaemic and insulinaemic response to mashed potato alone, or with broccoli, broccoli fibre or cellulose in healthy adults. *Eur J Nutr.* 2018;57(1):199-207.
1993. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metab Clin Exp.* 1988;37(11):1081-8.
1994. Tian S, Xu Q, Jiang R, Han T, Sun C, Na L. Dietary protein consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *Nutrients.* 2017;9(9):982.
1995. Cavuoto P, Fenech MF. A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. *Cancer Treat Rev.* 2012;38(6):726-36.
1996. Yin J, Ren W, Chen S, et al. Metabolic regulation of methionine restriction in diabetes. *Mol Nutr Food Res.* 2018;62(10):e1700951.
1997. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr.* 2016;70(3):306-12.
1998. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses.* 2009;72(2):125-8.
1999. Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am J Clin Nutr.* 1990;52(3):524-8.

2000. Orgeron ML, Stone KP, Wanders D, Cortez CC, Van NT, Gettys TW. The impact of dietary methionine restriction on biomarkers of metabolic health. *Prog Mol Biol Transl Sci.* 2014;121:351-76.
2001. Cole JT. Metabolism of BCAAs. In: Rajendram R, et al, eds. *Branched Chain Amino Acids in Clinical Nutrition: Volume 1.* New York: Springer Science+Business Media; 2015:13-24.
2002. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. *Cell Metab.* 2012;15(5):606-14.
2003. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab.* 2009;9(4):311-26.
2004. Haufe S, Engeli S, Kaminski J, et al. Branched-chain amino acid catabolism rather than amino acids plasma concentrations is associated with diet-induced changes in insulin resistance in overweight to obese individuals. *Nutr Metab Cardiovasc Dis.* 2017;27(10):858-64.
2005. Langenberg C, Savage DB. An amino acid profile to predict diabetes? *Nat Med.* 2011;17(4):418-20.
2006. Nie C, He T, Zhang W, Zhang G, Ma X. Branched chain amino acids: beyond nutrition metabolism. *Int J Mol Sci.* 2018;19(4):954.
2007. Rhee EP, Ho JE, Chen MH, et al. A genome-wide association study of the human metabolome in a community-based cohort. *Cell Metab.* 2013;18(1):130-43.
2008. Cavallaro NL, Garry J, Shi X, Gerszten RE, Anderson EJ, Walford GA. A pilot, short-term dietary manipulation of branched chain amino acids has modest influence on fasting levels of branched chain amino acids. *Food Nutr Res.* 2016;60:28592.
2009. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr.* 2016;70(3):306-12.
2010. Fretts AM, Follis JL, Nettleton JA, et al. Consumption of meat is associated with higher fasting glucose and insulin concentrations regardless of glucose and insulin genetic risk scores: a meta-analysis of 50,345 Caucasians. *Am J Clin Nutr.* 2015;102(5):1266-78.
2011. Rouhani MH, Salehi-Abarougouei A, Surkan PJ, Azadbakht L. Is there a relationship between red or processed meat intake and obesity? A systematic review and meta-analysis of observational studies. *Obes Rev.* 2014;15(9):740-8.
2012. Aune D, Ursin G, Veierød MB. Meat consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *Diabetologia.* 2009;52(11):2277-87.
2013. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary protein intake and risk of type 2 diabetes in US men and women. *Am J Epidemiol.* 2016;183(8):715-28.
2014. Tucker LA, Tucker JM, Bailey B, LeCheminant JD. Meat intake increases risk of weight gain in women: a prospective cohort investigation. *Am J Health Promot.* 2014;29(1):e43-52.
2015. Krebs M, Krssak M, Bernroider E, et al. Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. *Diabetes.* 2002;51(3):599-605.
2016. Smith GI, Yoshino J, Stromsdorfer KL, et al. Protein ingestion induces muscle insulin resistance independent of leucine-mediated mTOR activation. *Diabetes.* 2015;64(5):1555-63.
2017. Gojda J, Rossmeislová L, Straková R, et al. Chronic dietary exposure to branched chain amino acids impairs glucose disposal in vegans but not in omnivores. *Eur J Clin Nutr.* 2017;71(5):594-601.
2018. Draper CF, Vassallo I, Di Cara A, et al. A 48-hour vegan diet challenge in healthy women and men induces a BRANCH-chain amino acid related, health associated, metabolic signature. *Mol Nutr Food Res.* 2018;62(3).
2019. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc.* 2002;102(11):1621-30.
2020. Agricultural Research Service. Nutrient intakes from food: mean amounts and percentages of calories from protein, carbohydrate, fat, and alcohol, one day, 2005-2006. 2008. United States Department of Agriculture. Available at: www.ars.usda.gov/ba/bhnrc/fsrg. Accessed April 1, 2019.
2021. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep.* 2016;16(2):520-30.
2022. Kahleova H, Klementova M, Herynek V, et al. The effect of a vegetarian vs conventional hypocaloric diabetic diet on thigh adipose tissue distribution in subjects with type 2 diabetes: a randomized study. *J Am Coll Nutr.* 2017;36(5):364-9.
2023. Cummings NE, Williams EM, Kasza I, et al. Restoration of metabolic health by decreased consumption of branched-chain amino acids. *J Physiol (Lond).* 2018;596(4):623-45.
2024. Isanejad M, Lacroix AZ, Thomson CA, et al. Branched-chain amino acid, meat intake and risk of type 2 diabetes in the Women's Health Initiative. *Br J Nutr.* 2017;117(11):1523-30.
2025. Isanejad M, Lacroix AZ, Thomson CA, et al. Branched-chain amino acid, meat intake and risk of type 2 diabetes in the Women's Health Initiative. *Br J Nutr.* 2017;117(11):1523-30.
2026. Melnik BC. Leucine signaling in the pathogenesis of type 2 diabetes and obesity. *World J Diabetes.* 2012;3(3):38-53.
2027. Prodhon UK, Milan AM, Thorstensen EB, et al. Altered dairy protein intake does not alter circulatory branched chain amino acids in healthy adults: a randomized controlled trial. *Nutrients.* 2018;10(10):1510.
2028. Draper CF, Vassallo I, Di Cara A, et al. A 48-hour vegan diet challenge in healthy women and men induces a BRANCH-chain amino acid related, health associated, metabolic signature. *Mol Nutr Food Res.* 2018;62(3).
2029. McCarty MF. The origins of western obesity: a role for animal protein? *Med Hypotheses.* 2000;54(3):488-94.
2030. McCarty MF. The origins of western obesity: a role for animal protein? *Med Hypotheses.* 2000;54(3):488-94.
2031. Slabber M, Barnard HC, Kuyl JM, Dannhauser A, Schall R. Effects of a low-insulin-response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. *Am J Clin Nutr.* 1994;60(1):48-53.
2032. McCarty MF. The origins of western obesity: a role for animal protein? *Med Hypotheses.* 2000;54(3):488-94.
2033. Lifshitz F, Lifshitz JZ. Globesity: the root causes of the obesity epidemic in the USA and now worldwide. *Pediatr Endocrinol Rev.* 2014;12(1):17-34.
2034. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010;42(11):937-48.

2035. Sanmiguél C, Gupta A, Mayer EA. Gut microbiome and obesity: a plausible explanation for obesity. *Curr Obes Rep.* 2015;4(2):250–61.
2036. Triggler DJ. Nous sommes tous des bactéries: implications for medicine, pharmacology and public health. *Biochem Pharmacol.* 2012;84(12):1543–50.
2037. Tuohy KM, Gougoulias C, Shen Q, Walton G, Fava F, Ramnani P. Studying the human gut microbiota in the trans-omics era—focus on metagenomics and metabonomics. *Curr Pharm Des.* 2009;15(13):1415–27.
2038. Shabana, Shahid SU, Irfan U. The gut microbiota and its potential role in obesity. *Future Microbiol.* 2018;13:589–603.
2039. Sleator RD. The human superorganism—of microbes and men. *Med Hypotheses.* 2010;74(2):214–5.
2040. Fleischmann RD, Adams MD, White O, et al. Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. *Science.* 1995;269(5223):496–512.
2041. Land M, Hauser L, Jun SR, et al. Insights from 20 years of bacterial genome sequencing. *Funct Integr Genomics.* 2015;15(2):141–61.
2042. Goodacre R. Metabolomics of a superorganism. *J Nutr.* 2007;137(1 Suppl):259S–66S.
2043. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep.* 2009;11(4):307–13.
2044. Stephen AM, Cummings JH. The microbial contribution to human faecal mass. *J Med Microbiol.* 1980;13(1):45–56.
2045. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* 2017;15(1):73.
2046. Kim A. Dysbiosis: a review highlighting obesity and inflammatory bowel disease. *J Clin Gastroenterol.* 2015;49 Suppl 1:S20–4.
2047. Patterson E, Ryan PM, Cryan JF, et al. Gut microbiota, obesity and diabetes. *Postgrad Med J.* 2016;92(1087):286–300.
2048. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep.* 2009;11(4):307–13.
2049. Wikoff W, Anfora A, Liu J, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A.* 2009;106(10):3698–703.
2050. Sanmiguél C, Gupta A, Mayer EA. Gut microbiome and obesity: a plausible explanation for obesity. *Curr Obes Rep.* 2015;4(2):250–61.
2051. Aydin S. Can peptides and gut microbiota be involved in the etiopathology of obesity? *Obes Surg.* 2017;27(1):202–4.
2052. Moore PR, Evenson A, Luckey TD, McCoy E, Elvehjem CA, Hart EB. Use of sulfasuxidine, streptothricin, and streptomycin in nutritional studies with the chick. *J Biol Chem.* 1946;165:437–41.
2053. Coates ME, Fuller R, Harrison GF, Lev M, Suffolk SF. A comparison of the growth of chicks in the Gustafsson germ-free apparatus and in a conventional environment, with and without dietary supplements of penicillin. *Br J Nutr.* 1963;17:141–50.
2054. United States Food and Drug Administration Center for Veterinary Medicine. 2016 summary report on antimicrobials sold or distributed for use in food-producing animals. FDA.gov. Published December 2017. Available at: <https://www.fda.gov/downloads/forindustry/userfees/animaldruguserfeeactadufa/ucm588085.pdf>. Accessed April 1, 2019.
2055. Pew Charitable Trusts. Record-high antibiotic sales for meat and poultry production. Published February 6, 2013. Available at: <http://www.pewtrusts.org/en/research-and-analysis/analysis/2013/02/06/recordhigh-antibiotic-sales-for-meat-and-poultry-production>. Accessed April 1, 2019.
2056. Tang KL, Caffrey NP, Nóbrega DB, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health.* 2017;1(8):e316–27.
2057. Riley LW, Raphael E, Faerstein E. Obesity in the United States—dysbiosis from exposure to low-dose antibiotics? *Front Public Health.* 2013;1:69.
2058. Done HY, Venkatesan AK, Halden RU. Does the recent growth of aquaculture create antibiotic resistance threats different from those associated with land animal production in agriculture? *AAPS J.* 2015;17(3):513–24.
2059. Buschmann A, Cabello F, Young K, Carvajal J, Varela DA, Henríquez L. Salmon aquaculture and coastal ecosystem health in Chile: analysis of regulations, environmental impacts and bioremediation systems. *Ocean Coast Manag.* 2009;52(5):243–9.
2060. Done HY, Halden RU. Reconnaissance of 47 antibiotics and associated microbial risks in seafood sold in the United States. *J Hazard Mater.* 2015;282:10–7.
2061. Cox LM, Blaser MJ. Antibiotics in early life and obesity. *Nat Rev Endocrinol.* 2015;11(3):182–90.
2062. Hersh AL, Jackson MA, Hicks LA. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics.* 2013;132(6):1146–54.
2063. Jakobsson HE, Jernberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS ONE.* 2010;5(3):e9836.
2064. Rasmussen SH, Shrestha S, Bjerregaard LG, et al. Antibiotic exposure in early life and childhood overweight and obesity: a systematic review and meta-analysis. *Diabetes Obes Metab.* 2018;20(6):1508–14.
2065. Shao X, Ding X, Wang B, et al. Antibiotic exposure in early life increases risk of childhood obesity: a systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2017;8:170.
2066. Shao X, Ding X, Wang B, et al. Antibiotic exposure in early life increases risk of childhood obesity: a systematic review and meta-analysis. *Front Endocrinol (Lausanne).* 2017;8:170.
2067. Do antibiotics cause obesity? *Arch Dis Child.* 2015;100(7):622.
2068. Thuny F, Richet H, Casalta JP, Angelakis E, Habib G, Raoult D. Vancomycin treatment of infective endocarditis is linked with recently acquired obesity. *PLoS ONE.* 2010;5(2):e9074.
2069. Li D, Chen H, Ferber J, Odouli R. Infection and antibiotic use in infancy and risk of childhood obesity: a longitudinal birth cohort study. *Lancet Diabetes Endocrinol.* 2017;5(1):18–25.

2070. Lane JA, Murray LJ, Harvey IM, Donovan JL, Nair P, Harvey RF. Randomised clinical trial: *Helicobacter pylori* eradication is associated with a significantly increased body mass index in a placebo-controlled study. *Aliment Pharmacol Ther.* 2011;33(8):922-9.
2071. Haight TH, Pierce WE. Effect of prolonged antibiotic administration of the weight of healthy young males. *J Nutr.* 1955;56(1):151-61.
2072. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science.* 2016;352(6285):544-5.
2073. ACOG Committee on Obstetric Practice. Vaginal seeding. American College of Obstetricians and Gynecologists. Published November 2017. Available at: <https://www.acog.org/clinical-guidance-and-publications/committee-opinions/committee-on-obstetric-practice/vaginal-seeding>. Accessed April 1, 2019.
2074. Pihl AF, Fonvig CE, Stjernholm T, Hansen T, Pedersen O, Holm JC. The role of the gut microbiota in childhood obesity. *Child Obes.* 2016;12(4):292-9.
2075. ACOG Committee on Obstetric Practice. Vaginal seeding. American College of Obstetricians and Gynecologists. Published November 2017. Available at: <https://www.acog.org/clinical-guidance-and-publications/committee-opinions/committee-on-obstetric-practice/vaginal-seeding>. Accessed April 1, 2019.
2076. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med.* 2016;22(3):250-3.
2077. Yan J, Liu L, Zhu Y, Huang G, Wang PP. The association between breastfeeding and childhood obesity: a meta-analysis. *BMC Public Health.* 2014;14:1267.
2078. Korpela K, Salonen A, Virta LJ, Kekkonen RA, de Vos WM. Association of early-life antibiotic use and protective effects of breastfeeding: role of the intestinal microbiota. *JAMA Pediatr.* 2016;170(8):750-7.
2079. Freeland KR, Wilson C, Wolever TM. Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased wheat fibre intake for 1 year in hyperinsulinaemic human subjects. *Br J Nutr.* 2010;103(1):82-90.
2080. Davis HC. Can the gastrointestinal microbiota be modulated by dietary fibre to treat obesity? *Ir J Med Sci.* 2018;187(2):393-402.
2081. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature.* 2013;500(7464):541-6.
2082. Grootaert C, Van de Wiele T, Van Roosbroeck I, et al. Bacterial monocultures, propionate, butyrate and H2O2 modulate the expression, secretion and structure of the fasting-induced adipose factor in gut epithelial cell lines. *Environ Microbiol.* 2011;13(7):1778-89.
2083. Hippe B, Zwielehner J, Liszt K, Lassi C, Unger F, Haslberger AG. Quantification of butyryl CoA:acetate CoA-transferase genes reveals different butyrate production capacity in individuals according to diet and age. *FEMS Microbiol Lett.* 2011;316(2):130-5.
2084. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lopley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol.* 2007;73(4):1073-8.
2085. Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr.* 2011;94(1):58-65.
2086. Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr.* 2011;94(1):58-65.
2087. Liszt K, Zwielehner J, Handschur M, Hippe B, Thaler R, Haslberger AG. Characterization of bacteria, clostridia and *Bacteroides* in faeces of vegetarians using qPCR and PCR-DGGE fingerprinting. *Ann Nutr Metab.* 2009;54(4):253-7.
2088. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J.* 2017;474(11):1823-36.
2089. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-8.
2090. Knights D, Ward TL, McKinlay CE, et al. Rethinking "enterotypes." *Cell Host Microbe.* 2014;16(4):433-7.
2091. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature.* 2011;473(7346):174-80.
2092. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-8.
2093. Chen T, Long W, Zhang C, Liu S, Zhao L, Hamaker BR. Fiber-utilizing capacity varies in *Prevotella*-versus *Bacteroides*-dominated gut microbiota. *Sci Rep.* 2017;7(1):2594.
2094. O'Keefe SJ, Chung D, Mahmoud N, et al. Why do African Americans get more colon cancer than Native Africans? *J Nutr.* 2007;137(1 Suppl):175S-82S.
2095. O'Keefe SJ, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun.* 2015;6:6342.
2096. O'Keefe SJ, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun.* 2015;6:6342.
2097. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484):559-63.
2098. Attene-Ramos MS, Wagner ED, Gaskins HR, Plewa MJ. Hydrogen sulfide induces direct radical-associated DNA damage. *Mol Cancer Res.* 2007;5(5):455-9.
2099. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484):559-63.
2100. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut.* 2016;65(11):1812-21.
2101. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature.* 2013;500(7464):541-6.
2102. Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. *Int J Obes (Lond).* 2017;41(7):1099-105.
2103. Requena T, Martínez-Cuesta MC, Peláez C. Diet and microbiota linked in health and disease. *Food Funct.* 2018;9(2):688-704.
2104. Daïen CI, Pinget GV, Tan JK, Macia L. Detrimental impact of microbiota-accessible carbohydrate-deprived diet on gut and immune homeostasis: an overview. *Front Immunol.* 2017;8:548.

2105. Hoy MK, Goldman JD. Fiber intake of the U.S. population: what we eat in America, NHANES 2009–2010. Food Surveys Research Group. Dietary Data Brief No. 12. Published September 2014. Available at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/dbrief/12_fiber_intake_0910.pdf. Accessed April 1, 2019.
2106. Han M, Wang C, Liu P, Li D, Li Y, Ma X. Dietary fiber gap and host gut microbiota. *Protein Pept Lett*. 2017;24(5):388–96.
2107. Røytiö H, Mokkala K, Vahlberg T, Laitinen K. Dietary intake of fat and fibre according to reference values relates to higher gut microbiota richness in overweight pregnant women. *Br J Nutr*. 2017;118(5):343–52.
2108. Han M, Wang C, Liu P, Li D, Li Y, Ma X. Dietary fiber gap and host gut microbiota. *Protein Pept Lett*. 2017;24(5):388–96.
2109. Martens E. Microbiome: fibre for the future. *Nature*. 2016;529(7585):158–9.
2110. Tap J, Furet JP, Bensaada M, et al. Gut microbiota richness promotes its stability upon increased dietary fibre intake in healthy adults. *Environ Microbiol*. 2015;17(12):4954–64.
2111. Martínez I, Lattimer JM, Hubach KL, et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. *ISME J*. 2013;7(2):269–80.
2112. Walter J, Martínez I, Rose DJ. Holobiont nutrition: considering the role of the gastrointestinal microbiota in the health benefits of whole grains. *Gut Microbes*. 2013;4(4):340–6.
2113. Bodinham CL, Hitchen KL, Youngman PJ, Frost GS, Robertson MD. Short-term effects of whole-grain wheat on appetite and food intake in healthy adults: a pilot study. *Br J Nutr*. 2011;106(3):327–30.
2114. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat Rev Gastroenterol Hepatol*. 2016;13(1):13–27.
2115. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56(7):1761–72.
2116. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology*. 2013;145(5):970–7.
2117. Greathouse KL, Faucher MA, Hastings-Tolsma M. The gut microbiome, obesity, and weight control in women's reproductive health. *West J Nurs Res*. 2017;39(8):1094–119.
2118. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease *Escherichia coli* across M-cells: contrasting effects of soluble plant fibres and emulsifiers. *Gut*. 2010;59(10):1331–9.
2119. CFR—Code of Federal Regulations Title 21. United States Food and Drug Administration. Updated September 4, 2018. Available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>. Accessed April 1, 2019.
2120. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. 2015;519(7541):92–6.
2121. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;38(10):1156–71.
2122. Fechner A, Fenske K, Jahreis G. Effects of legume kernel fibres and citrus fibre on putative risk factors for colorectal cancer: a randomised, double-blind, crossover human intervention trial. *Nutr J*. 2013;12:101.
2123. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab*. 2014;20(5):779–86.
2124. Ilyin VK. Microbiological status of cosmonauts during orbital spaceflights on Salyut and Mir orbital stations. *Acta Astronaut*. 2005;56(9–12):839–50.
2125. Finegold S, Sutter V, Mathisen G. Normal indigenous intestinal flora. In: Hentges D, ed. *Human Intestinal Microflora in Health and Disease*. 1st ed. New York: Academic Press; 1983:3–31.
2126. David LA, Materna AC, Friedman J, et al. Host lifestyle affects human microbiota on daily timescales. *Genome Biol*. 2014;15(7):R89.
2127. Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *Br J Nutr*. 2014;111(7):1147–61.
2128. Seganfredo FB, Blume CA, Moehlecke M, et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. *Obes Rev*. 2017;18(8):832–51.
2129. Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterology*. 2017;153(3):711–22.
2130. Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. *J Pediatr*. 2007;151(3):293–8.
2131. Foerster J, Maskarinec G, Reichardt N, et al. The influence of whole grain products and red meat on intestinal microbiota composition in normal weight adults: a randomized crossover intervention trial. *PLoS ONE*. 2014;9(10):e109606.
2132. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65(2):330–9.
2133. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65(2):330–9.
2134. Eid HM, Wright ML, Anil Kumar NV, et al. Significance of microbiota in obesity and metabolic diseases and the modulatory potential by medicinal plant and food ingredients. *Front Pharmacol*. 2017;8:387.
2135. Hooper PL, Hooper PL, Tytell M, Vigh L. Xenohormesis: health benefits from an eon of plant stress response evolution. *Cell Stress Chaperones*. 2010;15(6):761–70.
2136. Schultz JC. Shared signals and the potential for phylogenetic espionage between plants and animals. *Integr Comp Biol*. 2002;42(3):454–62.
2137. Schultz JC. Shared signals and the potential for phylogenetic espionage between plants and animals. *Integr Comp Biol*. 2002;42(3):454–62.
2138. Kahle K, Kraus M, Scheppach W, Ackermann M, Ridder F, Richling E. Studies on apple and blueberry fruit constituents: do the polyphenols reach the colon after ingestion? *Mol Nutr Food Res*. 2006;50(4–5):418–23.
2139. Routray W, Orsat V. Blueberries and their anthocyanins: factors affecting biosynthesis and properties. *Comp Rev Food Sci and Food Saf*. 2011;10(6):303–20.

2140. Hidalgo M, Oruna-Concha MJ, Kolida S, et al. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J Agric Food Chem*. 2012;60:3882-90.
2141. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. *J Nutr*. 2000;130(8S Suppl):2073S-85S.
2142. Delzenne NM, Neyrinck AM, Cani PD. Gut microbiota and metabolic disorders: how prebiotic can work? *Br J Nutr*. 2013;109 Suppl 2:S81-5.
2143. Delzenne NM, Neyrinck AM, Cani PD. Gut microbiota and metabolic disorders: how prebiotic can work? *Br J Nutr*. 2013;109 Suppl 2:S81-5.
2144. Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. *Gastroenterology*. 2017;153(3):711-22.
2145. Dewulf EM, Cani PD, Claus SP, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut*. 2013;62(8):1112-21.
2146. Hill P, Muir JG, Gibson PR. Controversies and recent developments of the low-FODMAP diet. *Gastroenterol Hepatol (N Y)*. 2017;13(1):36-45.
2147. Hidalgo M, Oruna-Concha MJ, Kolida S, et al. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J Agric Food Chem*. 2012;60(15):3882-90.
2148. Stevenson D, Scalzo J. Anthocyanin composition and content of blueberries. *J Berry Res*. 2012;2(4):179-89.
2149. Vendrame S, Guglielmetti S, Riso P, Arioli S, Klimis-Zacas D, Porrini M. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *J Agric Food Chem*. 2011;59(24):12815-20.
2150. Shinohara K, Ohashi Y, Kawasumi K, Terada A, Fujisawa T. Effect of apple intake on fecal microbiota and metabolites in humans. *Anaerobe*. 2010;16(5):510-5.
2151. Drasar B, Jenkins D. Bacteria, diet, and large bowel cancer. *Am J Clin Nutr*. 1976;29:1410-6.
2152. Mitsou EK, Kougia E, Nomikos T, Yannakoulia M, Mountzouris KC, Kyriacou A. Effect of banana consumption on faecal microbiota: a randomised, controlled trial. *Anaerobe*. 2011;17(6):384-7.
2153. Jin JS, Touyama M, Hisada T, Benno Y. Effects of green tea consumption on human fecal microbiota with special reference to *Bifidobacterium* species. *Microbiol Immunol*. 2012;56(11):729-39.
2154. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol*. 2009;130(2):117-21.
2155. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol*. 2009;130(2):117-21.
2156. Budryn G, Pałecz B, Rachwał-Rosiak D, et al. Effect of inclusion of hydroxycinnamic and chlorogenic acids from green coffee bean in β -cyclodextrin on their interactions with whey, egg white and soy protein isolates. *Food Chem*. 2015;168:276-87.
2157. Felberg I, Farah A, Monteiro M, et al. Effect of simultaneous consumption of soymilk and coffee on the urinary excretion of isoflavones, chlorogenic acids and metabolites in healthy adults. *J Funct Foods*. 2015;19:688-99.
2158. Bertola ML, Rimm EB, Mukamal KJ, Hu FB, Willett WC, Cassidy A. Dietary flavonoid intake and weight maintenance: three prospective cohorts of 124,086 US men and women followed for up to 24 years. *BMJ*. 2016;352:i17.
2159. de Oliveira MC, Sichieri R, Venturim Mozzier R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite*. 2008;51(2):291-5.
2160. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. *PLoS ONE*. 2012;7(4):e34938.
2161. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9613):651-9.
2162. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9613):651-9.
2163. Hooijmans CR, de Vries RB, Rovers MM, Gooszen HG, Ritskes-Hoitinga M. The effects of probiotic supplementation on experimental acute pancreatitis: a systematic review and meta-analysis. *PLoS ONE*. 2012;7(11):e48811.
2164. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9613):651-9.
2165. Besselink MG, Timmerman HM, Buskens E, et al. Probiotic prophylaxis in patients with predicted severe acute pancreatitis (PROPATRIA): design and rationale of a double-blind, placebo-controlled randomised multicenter trial [ISRCTN38327949]. *BMC Surg*. 2004;4:12.
2166. Gooszen HG. The PROPATRIA trial: best practices at the time were followed. *Lancet*. 2010;375(9722):1249-50.
2167. Hempel S, Newberry S, Ruelaz A, et al. (Prepared by the Southern California Evidence-based Practice Center). Safety of probiotics to reduce risk and prevent or treat disease. Agency for Healthcare Research and Quality. *AHRQ Publication No. 11-E007*. Updated July 2018. Available at: <http://www.ahrq.gov/clinic/tp/probiotictp.htm>. Accessed April 1, 2019.
2168. Raoult D. Human microbiome: take-home lesson on growth promoters? *Nature*. 2008;454(7205):690-1.
2169. Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of *Lactobacillus* species on weight gain in humans and animals. *Microb Pathog*. 2012;53(2):100-8.
2170. Abe F, Ishibashi N, Shimamura S. Effect of administration of bifidobacteria and lactic acid bacteria to newborn calves and piglets. *J Dairy Sci*. 1995;78(12):2838-46.
2171. Robinson E, Thompson W. Effect on weight gain of the addition of *Lactobacillus acidophilus* to the formula of newborn infants. *J Pediatr*. 1952;41(4):395-8.
2172. Million M, Raoult D. Species and strain specificity of *Lactobacillus* probiotics effect on weight regulation. *Microb Pathog*. 2013;55:52-4.
2173. Lexchin J. Those who have the gold make the evidence: how the pharmaceutical industry biases the outcomes of clinical trials of medications. *Sci Eng Ethics*. 2012;18(2):247-61.
2174. Million M, Raoult D. Publication biases in probiotics. *Eur J Epidemiol*. 2012;27(11):885-6.
2175. Borgeraas H, Johnson LK, Skattebu J, Hertel JK, Hjelmestaeth J. Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2018;19(2):219-32.

2176. Kadooka Y, Sato M, Imaizumi K, et al. Regulation of abdominal adiposity by probiotics (*Lactobacillus gasseri* SBT2055) in adults with obese tendencies in a randomized controlled trial. *Eur J Clin Nutr.* 2010;64(6):636–43.
2177. Vitali B, Minervini G, Rizzello CG, et al. Novel probiotic candidates for humans isolated from raw fruits and vegetables. *Food Microbiol.* 2012;31(1):116–25.
2178. Wassermann B, Rybakova D, Müller C, Berg G. Harnessing the microbiomes of *Brassica* vegetables for health issues. *Sci Rep.* 2017;7(1):17649.
2179. Leff JW, Fierer N. Bacterial communities associated with the surfaces of fresh fruits and vegetables. *PLoS ONE.* 2013;8(3):e59310.
2180. Jackson C, Stone B, Tyler H. Emerging perspectives on the natural microbiome of fresh produce vegetables. *Agriculture.* 2015;5(2):170–87.
2181. Gardner A, Mattiuzzi G, Faderl S, et al. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. *J Clin Oncol.* 2008;26(35):5684–8.
2182. Trifilio S, Helenowski I, Giel M, et al. Questioning the role of a neutropenic diet following hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2012;18(9):1385–90.
2183. Martinez KB, Leone V, Chang EB. Western diets, gut dysbiosis, and metabolic diseases: are they linked? *Gut Microbes.* 2017;8(2):130–42.
2184. Bakker GJ, Nieuwdorp M. Fecal microbiota transplantation: therapeutic potential for a multitude of diseases beyond *Clostridium difficile*. *Microbiol Spectr.* 2017;5(4).
2185. Bakker GJ, Nieuwdorp M. Fecal microbiota transplantation: therapeutic potential for a multitude of diseases beyond *Clostridium difficile*. *Microbiol Spectr.* 2017;5(4).
2186. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol.* 2012;107(11):1755.
2187. Kong LY, Tan RX. Artemisinin, a miracle of traditional Chinese medicine. *Nat Prod Rep.* 2015;32(12):1617–21.
2188. Dao MC, Clément K. Gut microbiota and obesity: concepts relevant to clinical care. *Eur J Intern Med.* 2018;48:18–24.
2189. Panchal P, Budree S, Scheeler A, et al. Scaling safe access to fecal microbiota transplantation: past, present, and future. *Curr Gastroenterol Rep.* 2018;20(4):14.
2190. Panchal P, Budree S, Scheeler A, et al. Scaling safe access to fecal microbiota transplantation: past, present, and future. *Curr Gastroenterol Rep.* 2018;20(4):14.
2191. Bakker GJ, Nieuwdorp M. Fecal microbiota transplantation: therapeutic potential for a multitude of diseases beyond *Clostridium difficile*. *Microbiol Spectr.* 2017;5(4).
2192. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. *Curr Gastroenterol Rep.* 2013;15(8):337.
2193. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: a systematic review. *Ann Intern Med.* 2015;162(9):630–8.
2194. Fecal microbiota transplantation. Infectious Diseases Society of America. 2019. Available at: <https://www.idsociety.org/public-health/emerging-clinical-issues/emerging-clinical-issues/fecal-microbiota-transplantation>. Accessed April 1, 2019.
2195. Panchal P, Budree S, Scheeler A, et al. Scaling safe access to fecal microbiota transplantation: past, present, and future. *Curr Gastroenterol Rep.* 2018;20(4):14.
2196. Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis.* 2015;2(1):ofv004.
2197. Hamzelou J. Not just obesity—faecal transplants’ weird effects. *New Scientist.* Published February 11, 2015. Available at: <https://www.newscientist.com/article/mg22530083-600-not-just-obesity-faecal-transplants-weird-effects>. Accessed April 1, 2019.
2198. Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis.* 2015;2(1):ofv004.
2199. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JL. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature.* 2006;444(7122):1027–31.
2200. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science.* 2013;341(6150):1241–4.
2201. Walker AW, Parkhill J. Microbiology. Fighting obesity with bacteria. *Science.* 2013;341(6150):1069–70.
2202. Hamzelou J. Not just obesity—faecal transplants’ weird effects. *New Scientist.* Published February 11, 2015. Available at: <https://www.newscientist.com/article/mg22530083-600-not-just-obesity-faecal-transplants-weird-effects>. Accessed April 1, 2019.
2203. Yu EW. Fecal microbiota transplant for obesity and metabolism. *Clinicaltrials.gov.* Published August 21, 2015. Available at: <https://clinicaltrials.gov/ct2/show/NCT02530385>. Accessed April 1, 2019.
2204. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology.* 2012;143(4):913–6.e7.
2205. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology.* 2012;143(4):913–6.e7.
2206. Udayappan SD, Hartstra AV, Dallinga-Thie GM, Nieuwdorp M. Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus. *Clin Exp Immunol.* 2014;177(1):24–9.
2207. Konstantinov SR, Peppelenbosch MP. Fecal microbiota transfer may increase irritable bowel syndrome and inflammatory bowel diseases-associated bacteria. *Gastroenterology.* 2013;144(4):e19–20.
2208. Tuohy KM, Conterno L, Gasperotti M, Viola R. Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J Agric Food Chem.* 2012;60(36):8776–82.
2209. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature.* 2012;486(7402):222–7.
2210. Song SJ, Lauber C, Costello EK, et al. Cohabiting family members share microbiota with one another and with their dogs. *Elife.* 2013;2:e00458.
2211. Lax S, Smith DP, Hampton-Marcell J, et al. Longitudinal analysis of microbial interaction between humans and the indoor environment. *Science.* 2014;345(6200):1048–52.

2212. Udayappan SD, Hartstra AV, Dallinga-Thie GM, Nieuwdorp M. Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus. *Clin Exp Immunol*. 2014;177(1):24-9.
2213. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. *N Engl J Med*. 2007;357(4):370-9.
2214. Alcock J, Maley CC, Aktipis CA. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. *Bioessays*. 2014;36(10):940-9.
2215. Kaplan LM, Brancale J. Eat well, or get roommates who do. *Cell Host Microbe*. 2017;21(2):123-5.
2216. Boeing H, Bechthold A, Bub A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr*. 2012;51(6):637-63.
2217. Fisher JO, Birch LL. Restricting access to palatable foods affects children's behavioral response, food selection, and intake. *Am J Clin Nutr*. 1999;69(6):1264-72.
2218. Schwingshackl L, Hoffmann G, Kalle-Uhlmann T, Arregui M, Buijsse B, Boeing H. Fruit and vegetable consumption and changes in anthropometric variables in adult populations: a systematic review and meta-analysis of prospective cohort studies. *PLoS ONE*. 2015;10(10):e0140846.
2219. Kahn H, Tatham L, Rodriguez C, Calle E, Thun M, Heath C. Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. *Am J Public Health*. 1997;87(5):747-54.
2220. Grosso G, Micek A, Godos J, et al. Health risk factors associated with meat, fruit and vegetable consumption in cohort studies: a comprehensive meta-analysis. *PLoS ONE*. 2017;12(8):e0183787.
2221. Kahn H, Tatham L, Rodriguez C, Calle E, Thun M, Heath C. Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. *Am J Public Health*. 1997;87(5):747-54.
2222. Bertoina ML, Mukamal KJ, Cahill LE, et al. Changes in intake of fruits and vegetables and weight change in United States men and women followed for up to 24 years: analysis from three prospective cohort studies. *PLoS Med*. 2015;12(9):e1001878.
2223. de Oliveira MC, Sichieri R, Venturim Mozzier R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite*. 2008;51(2):291-5.
2224. Dow CA, Going SB, Chow HH, Patil BS, Thomson CA. The effects of daily consumption of grapefruit on body weight, lipids, and blood pressure in healthy, overweight adults. *Metab Clin Exp*. 2012;61(7):1026-35.
2225. Rush E, Ferguson L, Cumin M, Thakur V, Karunasinghe N, Plank L. Kiwifruit consumption reduces DNA fragility: a randomized controlled pilot study in volunteers. *Nutr Res*. 2006;26(5):197-201.
2226. Evans SF, Meister M, Mahmood M, et al. Mango supplementation improves blood glucose in obese individuals. *Nutr Metab Insights*. 2014;7:77-84.
2227. Ledoux TA, Hingle MD, Baranowski T. Relationship of fruit and vegetable intake with adiposity: a systematic review. *Obes Rev*. 2011;12(5):e143-50.
2228. Mytton OT, Nnoaham K, Eyles H, Scarborough P, Ni Mhurchu C. Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. *BMC Public Health*. 2014;14:886.
2229. Kaiser K, Brown A, Bohan Brown M, Shikany J, Mattes R, Allison D. Increased fruit and vegetable intake has no discernible effect on weight loss: a systematic review and meta-analysis. *Am J Clin Nutr*. 2014;100(2):567-76.
2230. Mytton OT, Nnoaham K, Eyles H, Scarborough P, Ni Mhurchu C. Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. *BMC Public Health*. 2014;14:886.
2231. Rolls BJ, Ello-Martin JA, Tohill BC. What can intervention studies tell us about the relationship between fruit and vegetable consumption and weight management? *Nutr Rev*. 2004;62(1):1-17.
2232. Djuric Z, Poore KM, Depper JB, et al. Methods to increase fruit and vegetable intake with and without a decrease in fat intake: compliance and effects on body weight in the nutrition and breast health study. *Nutr Cancer*. 2002;43(2):141-51.
2233. Bertoina ML, Mukamal KJ, Cahill LE, et al. Changes in intake of fruits and vegetables and weight change in United States men and women followed for up to 24 years: analysis from three prospective cohort studies. *PLoS Med*. 2015;12(9):e1001878.
2234. Walker RW, Dumke KA, Goran MI. Fructose content in popular beverages made with and without high-fructose corn syrup. *Nutrition*. 2014;30(7-8):928-35.
2235. Muraki I, Imamura F, Manson JE, et al. Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies. *BMJ*. 2013;347:f5001.
2236. Hebden L, O'Leary F, Rangan A, Singgih Lie E, Hirani V, Allman-Farinelli M. Fruit consumption and adiposity status in adults: a systematic review of current evidence. *Crit Rev Food Sci Nutr*. 2017;57(12):2526-40.
2237. Shefferly A, Scharf RJ, DeBoer MD. Longitudinal evaluation of 100% fruit juice consumption on BMI status in 2-5-year-old children. *Pediatr Obes*. 2016;11(3):221-7.
2238. Sonnevile KR, Long MW, Rifas-Shiman SL, Kleinman K, Gillman MW, Taveras EM. Juice and water intake in infancy and later beverage intake and adiposity: could juice be a gateway drink? *Obesity (Silver Spring)*. 2015;23(1):170-6.
2239. Wojcicki JM, Heyman MB. Reducing childhood obesity by eliminating 100% fruit juice. *Am J Public Health*. 2012;102(9):1630-3.
2240. Houchins JA, Tan SY, Campbell WW, Mattes RD. Effects of fruit and vegetable, consumed in solid vs beverage forms, on acute and chronic appetitive responses in lean and obese adults. *Int J Obes (Lond)*. 2013;37(8):1109-15.
2241. Haber GB, Heaton KW, Murphy D, Burroughs LF. Depletion and disruption of dietary fibre. Effects on satiety, plasma-glucose, and serum-insulin. *Lancet*. 1977;2(8040):679-82.
2242. Mytton OT, Nnoaham K, Eyles H, Scarborough P, Ni Mhurchu C. Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. *BMC Public Health*. 2014;14:886.
2243. Elia M, Cummings JH. Physiological aspects of energy metabolism and gastrointestinal effects of carbohydrates. *Eur J Clin Nutr*. 2007;61 Suppl 1:S40-74.
2244. Wisker E, Feldheim W. Metabolizable energy of diets low or high in dietary fiber from fruits and vegetables when consumed by humans. *J Nutr*. 1990;120(11):1331-7.
2245. Pasma WJ, van Erk MJ, Klöpping WA, et al. Nutrigenomics approach elucidates health-promoting effects of high vegetable intake in lean and obese men. *Genes Nutr*. 2013;8(5):507-21.

2246. Shenoy SF, Poston WS, Reeves RS, et al. Weight loss in individuals with metabolic syndrome given DASH diet counseling when provided a low sodium vegetable juice: a randomized controlled trial. *Nutr J*. 2010;9:8.
2247. Sharma SP, Chung HJ, Kim HJ, Hong ST. Paradoxical effects of fruit on obesity. *Nutrients*. 2016;8(10):633.
2248. Madero M, Arriaga JC, Jalal D, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. *Metab Clin Exp*. 2011;60(11):1551-9.
2249. Bowman S, Clemens J, Martin C, Anand J, Steinfeldt L, Moshfegh A. Added sugars intake of Americans: what we eat in America, NHANES 2013-2014. United States Department of Agriculture. Published May 2017. Available at: https://www.ars.usda.gov/arsuserfiles/80400530/pdf/dbrief/18_added_sugars_intake_of_americans_2013-2014.pdf. Accessed April 1, 2019.
2250. Agricultural Research Service, United States Department of Agriculture. Basic report: 09003, apples, raw, with skin (includes foods for USDA's Food Distribution Program). National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/09003>. Accessed April 1, 2019.
2251. Agricultural Research Service, United States Department of Agriculture. Basic report: 09326, watermelon, raw. National Nutrient Database for Standard Reference. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/09326>. Accessed April 1, 2019.
2252. Harvard Health Letter. Rethinking fructose in your diet. *Harvard Health Publications*. Published June 2013. Available at: <https://www.health.harvard.edu/staying-healthy/rethinking-fructose-in-your-diet>. Accessed May 12, 2018.
2253. Meyer BJ, van der Merwe M, Du Plessis DG, de Bruin EJ, Meyer AC. Some physiological effects of a mainly fruit diet in man. *S Afr Med J*. 1971;45(8):191-5.
2254. Meyer BJ, de Bruin EJ, Du Plessis DG, van der Merwe M, Meyer AC. Some biochemical effects of a mainly fruit diet in man. *S Afr Med J*. 1971;45(10):253-61.
2255. Törrönen R, Kolehmainen M, Sarkkinen E, Mykkänen H, Niskanen L. Postprandial glucose, insulin, and free fatty acid responses to sucrose consumed with blackcurrants and lingonberries in healthy women. *Am J Clin Nutr*. 2012;96(3):527-33.
2256. Törrönen R, Kolehmainen M, Sarkkinen E, Mykkänen H, Niskanen L. Postprandial glucose, insulin, and free fatty acid responses to sucrose consumed with blackcurrants and lingonberries in healthy women. *Am J Clin Nutr*. 2012;96(3):527-33.
2257. Törrönen R, Kolehmainen M, Sarkkinen E, Mykkänen H, Niskanen L. Postprandial glucose, insulin, and free fatty acid responses to sucrose consumed with blackcurrants and lingonberries in healthy women. *Am J Clin Nutr*. 2012;96(3):527-33.
2258. Sugars and sweeteners: U.S. sugar production. Economic Research Service, United States Department of Agriculture. Updated May 31, 2018. Available at: <https://www.ers.usda.gov/topics/crops/sugar-sweeteners/background/>. Accessed April 1, 2019.
2259. Manzano S, Williamson G. Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal Caco-2 cells. *Mol Nutr Food Res*. 2010;54(12):1773-80.
2260. Törrönen R, Kolehmainen M, Sarkkinen E, Poutanen K, Mykkänen H, Niskanen L. Berries reduce postprandial insulin responses to wheat and rye breads in healthy women. *J Nutr*. 2013;143(4):430-6.
2261. Ravn-Haren G, Dragsted LO, Buch-Andersen T, et al. Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers. *Eur J Nutr*. 2013;52(8):1875-89.
2262. Barth SW, Koch TC, Watzl B, Dietrich H, Will F, Bub A. Moderate effects of apple juice consumption on obesity-related markers in obese men: impact of diet-gene interaction on body fat content. *Eur J Nutr*. 2012;51(7):841-50.
2263. Hollis JH, Houchins JA, Blumberg JB, Mattes RD. Effects of Concord grape juice on appetite, diet, body weight, lipid profile, and antioxidant status of adults. *J Am Coll Nutr*. 2009;28(5):574-82.
2264. Cohen DA, Sturm R, Scott M, Farley TA, Bluthenthal R. Not enough fruit and vegetables or too many cookies, candies, salty snacks, and soft drinks? *Public Health Rep*. 2010;125(1):88-95.
2265. Fielding J, Simon P. Food deserts or food swamps? *Arch Intern Med*. 2011;171(13):1171.
2266. Cohen DA, Sturm R, Scott M, Farley TA, Bluthenthal R. Not enough fruit and vegetables or too many cookies, candies, salty snacks, and soft drinks? *Public Health Rep*. 2010;125(1):88-95.
2267. Lapointe A, Weisnagel SJ, Provencher V, et al. Using restrictive messages to limit high-fat foods or nonrestrictive messages to increase fruit and vegetable intake: what works better for postmenopausal women? *Eur J Clin Nutr*. 2010;64(2):194-202.
2268. Lachat CK, Verstraeten R, De Meulenaer B, et al. Availability of free fruits and vegetables at canteen lunch improves lunch and daily nutritional profiles: a randomised controlled trial. *Br J Nutr*. 2009;102(7):1030-7.
2269. Bere E, Klepp KI, Overby NC. Free school fruit: can an extra piece of fruit every school day contribute to the prevention of future weight gain? A cluster randomized trial. *Food Nutr Res*. 2014;58.
2270. Mytton OT, Nnoaham K, Eyles H, Scarborough P, Ni Mhurchu C. Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. *BMC Public Health*. 2014;14:886.
2271. Weerts SE, Amoran A. Pass the fruits and vegetables! A community-university-industry partnership promotes weight loss in African American women. *Health Promot Pract*. 2011;12(2):252-60.
2272. Jenkins DJA, Boucher BA, Ashbury FD, et al. Effect of current dietary recommendations on weight loss and cardiovascular risk factors. *J Am Coll Cardiol*. 2017;69(9):1103-12.
2273. Erinosho TO, Moser RP, Oh AY, Nebeling LC, Yaroch AL. Awareness of the Fruits and Veggies—More Matters campaign, knowledge of the fruit and vegetable recommendation, and fruit and vegetable intake of adults in the 2007 Food Attitudes and Behaviors (FAB) survey. *Appetite*. 2012;59(1):155-60.
2274. Pivonka E, Seymour J, McKenna J, Baxter SD, Williams S. Development of the behaviorally focused Fruits & Veggies—More Matters public health initiative. *J Am Diet Assoc*. 2011;111(10):1570-7.
2275. Fisher JO, Dwyer JT. Next steps for science and policy on promoting vegetable consumption among US infants and young children. *Adv Nutr*. 2016;7(1):261S-71S.
2276. Fisher JO, Dwyer JT. Next steps for science and policy on promoting vegetable consumption among US infants and young children. *Adv Nutr*. 2016;7(1):261S-71S.

2277. A review of food marketing to children and adolescents. Federal Trade Commission. Published December 2012. Available at: <https://www.ftc.gov/sites/default/files/documents/reports/review-food-marketing-children-and-adolescents-follow-report/121221foodmarketingreport.pdf>. Accessed April 1, 2019.
2278. Bertoia ML, Mukamal KJ, Cahill LE, et al. Changes in intake of fruits and vegetables and weight change in United States men and women followed for up to 24 years: analysis from three prospective cohort studies. *PLoS Med*. 2015;12(9):e1001878.
2279. de Oliveira MC, Sichiari R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite*. 2008;51(2):291-5.
2280. Joo H, Kim CT, Kim IH, Kim Y. Anti-obesity effects of hot water extract and high hydrostatic pressure extract of garlic in rats fed a high-fat diet. *Food Chem Toxicol*. 2013;55:100-5.
2281. Lee MS, Kim IH, Kim CT, Kim Y. Reduction of body weight by dietary garlic is associated with an increase in uncoupling protein mRNA expression and activation of AMP-activated protein kinase in diet-induced obese mice. *J Nutr*. 2011;141(11):1947-53.
2282. Fenni S, Hammou H, Astier J, et al. Lycopene and tomato powder supplementation similarly inhibit high-fat diet induced obesity, inflammatory response, and associated metabolic disorders. *Mol Nutr Food Res*. 2017;61(9):1601083.
2283. Thies F, Masson LF, Rudd A, et al. Effect of a tomato-rich diet on markers of cardiovascular disease risk in moderately overweight, disease-free, middle-aged adults: a randomized controlled trial. *Am J Clin Nutr*. 2012;95(5):1013-22.
2284. Choudhary PR, Jani RD, Sharma MS. Effect of raw crushed garlic (*Allium sativum* L.) on components of metabolic syndrome. *J Diet Suppl*. 2018;15(4):499-506.
2285. Sharifi F, Sheikhi AK, Behdad M, Mousavinasab N. Effect of garlic on serum adiponectin and interleukin levels in women with metabolic syndrome. *Int J Endocrinol Metab*. 2010;8(2):68-73.
2286. Xu C, Mathews AE, Rodrigues C, et al. Aged garlic extract supplementation modifies inflammation and immunity of adults with obesity: a randomized, double-blind, placebo-controlled clinical trial. *Clin Nutr ESPEN*. 2018;24:148-55.
2287. Seo DY, Lee SR, Kim HK, et al. Independent beneficial effects of aged garlic extract intake with regular exercise on cardiovascular risk in postmenopausal women. *Nutr Res Pract*. 2012;6(3):226-31.
2288. Soleimani D, Paknahad Z, Askari G, Iraj B, Feizi A. Effect of garlic powder consumption on body composition in patients with nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Adv Biomed Res*. 2016;5:2.
2289. Wong A, Townley S. Herbal medicines and anaesthesia. *CEACCP*. 2011;11(1):14-7.
2290. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis*. 2002;34(2):234-8.
2291. Tani Y, Fujiwara T, Ochi M, Isumi A, Kato T. Does eating vegetables at start of meal prevent childhood overweight in Japan? A-CHILD Study. *Front Pediatr*. 2018;6:134.
2292. Shukla AP, Aronne LJ. Response to comment on Shukla et al. Food order has a significant impact on postprandial glucose and insulin levels. 2015;38:e98-9. *Diabetes Care*. 2015;38(11):e197.
2293. Shukla AP, Dickison M, Coughlin N, et al. The impact of food order on postprandial glycaemic excursions in prediabetes. *Diabetes Obes Metab*. 2019;21(2):377-81.
2294. Imai S, Fukui M, Kajiyama S. Effect of eating vegetables before carbohydrates on glucose excursions in patients with type 2 diabetes. *J Clin Biochem Nutr*. 2014;54(1):7-11.
2295. Imai S, Matsuda M, Hasegawa G, et al. A simple meal plan of "eating vegetables before carbohydrate" was more effective for achieving glycemic control than an exchange-based meal plan in Japanese patients with type 2 diabetes. *Asia Pac J Clin Nutr*. 2011;20(2):161-8.
2296. Tani Y, Fujiwara T, Ochi M, Isumi A, Kato T. Does eating vegetables at start of meal prevent childhood overweight in Japan? A-CHILD Study. *Front Pediatr*. 2018;6:134.
2297. Wansink B, Painter JE, Lee YK. The office candy dish: proximity's influence on estimated and actual consumption. *Int J Obes (Lond)*. 2006;30(5):871-5. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
2298. Rolls BJ. The oversizing of America: portion size and the obesity epidemic. *Nutr Today*. 2003;38(2):42-53.
2299. Spill MK, Birch LL, Roe LS, Rolls BJ. Eating vegetables first: the use of portion size to increase vegetable intake in preschool children. *Am J Clin Nutr*. 2010;91(5):1237-43.
2300. Rolls BJ, Roe LS, Meengs JS. Portion size can be used strategically to increase vegetable consumption in adults. *Am J Clin Nutr*. 2010;91(4):913-22.
2301. Lally P, Chipperfield A, Wardle J. Healthy habits: efficacy of simple advice on weight control based on a habit-formation model. *Int J Obes (Lond)*. 2008;32(4):700-7.
2302. Zylke JW, Bauchner H. The unrelenting challenge of obesity. *JAMA*. 2016;315(21):2277-8.
2303. Keeping apples crunchy and flavorful after storage. *AgResearch Magazine*. Published October 2007. Available at: <https://agresearchmag.ars.usda.gov/2007/oct/apples>. Accessed March 1, 2019.
2304. Papanikolaou Y, Fulgoni VL. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight, and a smaller waist circumference in adults: results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008;27(5):569-76.
2305. Schneiderman N, Chirinos DA, Avilés-Santa ML, Heiss G. Challenges in preventing heart disease in Hispanics: early lessons learned from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prog Cardiovasc Dis*. 2014;57(3):253-61.
2306. Kochanek K, Murphy S, Xu J, Arias E. Mortality in the United States, 2013. Centers for Disease Control and Prevention. NCHS Data Brief. No. 178. Published December 2014. Available at: <https://www.cdc.gov/nchs/data/databriefs/db178.pdf>. Accessed April 1, 2019.
2307. The Hispanic paradox. *Lancet*. 2015;385(9981):1918.
2308. Lopez-Jimenez F, Lavie CJ. Hispanics and cardiovascular health and the "Hispanic Paradox": what is known and what needs to be discovered? *Prog Cardiovasc Dis*. 2014;57(3):227-9.

2309. Young RP, Hopkins RJ. A review of the Hispanic paradox: time to spill the beans? *Eur Respir Rev.* 2014;23(134):439-49.
2310. Anderson JW, Smith BM, Washnock CS. Cardiovascular and renal benefits of dry bean and soybean intake. *Am J Clin Nutr.* 1999;70(3 Suppl):464S-74S.
2311. Papanikolaou Y, Fulgoni VL. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight, and a smaller waist circumference in adults: results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr.* 2008;27(5):569-76.
2312. Hosseinpour-Niazi S, Mirmiran P, Hedayati M, Azizi F. Substitution of red meat with legumes in the therapeutic lifestyle change diet based on dietary advice improves cardiometabolic risk factors in overweight type 2 diabetes patients: a cross-over randomized clinical trial. *Eur J Clin Nutr.* 2015;69(5):592-7.
2313. Bertoia ML, Mukamal KJ, Cahill LE, et al. Changes in intake of fruits and vegetables and weight change in United States men and women followed for up to 24 years: analysis from three prospective cohort studies. *PLoS Med.* 2015;12(9):e1001878.
2314. Mitchell DC, Lawrence FR, Hartman TJ, Curran JM. Consumption of dry beans, peas, and lentils could improve diet quality in the US population. *J Am Diet Assoc.* 2009;109(5):909-13.
2315. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djoussé L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. *Br J Nutr.* 2015;114(6):831-43.
2316. Kou T, Wang Q, Cai J, et al. Effect of soybean protein on blood pressure in postmenopausal women: a meta-analysis of randomized controlled trials. *Food Funct.* 2017;8(8):2663-71.
2317. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2011;21(2):94-103.
2318. Sievenpiper JL, Kendall CW, Esfahani A, et al. Effect of non-oil-seed pulses on glycaemic control: a systematic review and meta-analysis of randomised controlled experimental trials in people with and without diabetes. *Diabetologia.* 2009;52(8):1479-95.
2319. Palmer SM, Winham DM, Hradek C. Knowledge gaps of the health benefits of beans among low-income women. *Am J Health Behav.* 2018;42(1):27-38.
2320. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr.* 1995;49(9):675-90.
2321. Havemeier S, Erickson J, Slavin J. Dietary guidance for pulses: the challenge and opportunity to be part of both the vegetable and protein food groups. *Ann NY Acad Sci.* 2017;1392(1):58-66.
2322. Leathwood P, Pollet P. Effects of slow release carbohydrates in the form of bean flakes on the evolution of hunger and satiety in man. *Appetite.* 1988;10(1):1-11.
2323. Zafar TA, Kabir Y. Chickpeas suppress postprandial blood glucose concentration, and appetite and reduce energy intake at the next meal. *J Food Sci Technol.* 2017;54(4):987-94.
2324. Mollard RC, Zyklus A, Luhovyy BL, Nunez MF, Wong CL, Anderson GH. The acute effects of a pulse-containing meal on glycaemic responses and measures of satiety and satiation within and at a later meal. *Br J Nutr.* 2012;108(3):509-17.
2325. Kristensen MD, Bendsen NT, Christensen SM, Astrup A, Raben A. Meals based on vegetable protein sources (beans and peas) are more satiating than meals based on animal protein sources (veal and pork)—a randomized cross-over meal test study. *Food Nutr Res.* 2016;60:32634.
2326. Halkjær J, Olsen A, Overvad K, et al. Intake of total, animal and plant protein and subsequent changes in weight or waist circumference in European men and women: the Diogenes project. *Int J Obes (Lond).* 2011;35(8):1104-13.
2327. Nielsen LV, Kristensen MD, Klingenberg L, et al. Protein from meat or vegetable sources in meals matched for fiber content has similar effects on subjective appetite sensations and energy intake—a randomized acute cross-over meal test study. *Nutrients.* 2018;10(1):96.
2328. Li SS, Kendall CW, de Souza RJ, et al. Dietary pulses, satiety and food intake: a systematic review and meta-analysis of acute feeding trials. *Obesity (Silver Spring).* 2014;22(8):1773-80.
2329. Jenkins D, Wolever T, Taylor R, Barker H, Fielden H. Exceptionally low blood glucose response to dried beans: comparison with other carbohydrate foods. *BMJ.* 1980;281(6240):578-80.
2330. Jenkins DJ, Wolever TM, Taylor RH, et al. Slow release dietary carbohydrate improves second meal tolerance. *Am J Clin Nutr.* 1982;35(6):1339-46.
2331. Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr.* 1988;48(4):1041-7.
2332. Mollard RC, Wong CL, Luhovyy BL, Anderson GH. First and second meal effects of pulses on blood glucose, appetite, and food intake at a later meal. *Appl Physiol Nutr Metab.* 2011;36(5):634-42.
2333. Nilsson A, Johansson E, Ekström L, Björck I. Effects of a brown beans evening meal on metabolic risk markers and appetite regulating hormones at a subsequent standardized breakfast: a randomized cross-over study. *PLoS ONE.* 2013;8(4):e59985.
2334. Ropert A, Cherbut C, Rozé C, et al. Colonic fermentation and proximal gastric tone in humans. *Gastroenterology.* 1996;111(2):289-96.
2335. Luhovyy BL, Mollard RC, Panahi S, Nunez MF, Cho F, Anderson GH. Canned navy bean consumption reduces metabolic risk factors associated with obesity. *Can J Diet Pract Res.* 2015;76(1):33-7.
2336. Murty CM, Pittaway JK, Ball MJ. Chickpea supplementation in an Australian diet affects food choice, satiety and bowel health. *Appetite.* 2010;54(2):282-8.
2337. Vigiouliou E, Blanco Mejia S, Kendall CW, Sievenpiper JL. Can pulses play a role in improving cardiometabolic health? Evidence from systematic reviews and meta-analyses. *Ann NY Acad Sci.* 2017;1392(1):43-57.
2338. Kim SJ, de Souza RJ, Choo VL, et al. Effects of dietary pulse consumption on body weight: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2016;103(5):1213-23.
2339. Jenkins DJ, Kendall CW, Augustin LS, et al. Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med.* 2012;172(21):1653-60.
2340. Mollard RC, Luhovyy BL, Panahi S, Nunez M, Hanley A, Anderson GH. Regular consumption of pulses for 8 weeks reduces metabolic syndrome risk factors in overweight and obese adults. *Br J Nutr.* 2012;108 Suppl 1:S111-22.

2341. Mollard RC, Luhovyy BL, Panahi S, Nunez M, Hanley A, Anderson GH. Regular consumption of pulses for 8 weeks reduces metabolic syndrome risk factors in overweight and obese adults. *Br J Nutr*. 2012;108 Suppl 1:S111-22.
2342. Kim SJ, de Souza RJ, Choo VL, et al. Effects of dietary pulse consumption on body weight: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2016;103(5):1213-23.
2343. Noah L, Guillon F, Bouchet B, et al. Digestion of carbohydrate from white beans (*Phaseolus vulgaris* L.) in healthy humans. *J Nutr*. 1998;128(6):977-85.
2344. Rebello CJ, Greenway FL, Finley JW. Whole grains and pulses: a comparison of the nutritional and health benefits. *J Agric Food Chem*. 2014;62(29):7029-49.
2345. Bo-Linn G, Santa Ana C, Morawski S, Fordtran J. Starch blockers—their effect on calorie absorption from a high-starch meal. *N Engl J Med*. 1982;307(23):1413-6.
2346. Drew R. Whatever happened to starch blockers? *N C Med J*. 1983;44(8):498.
2347. Garrow JS, Scott PF, Heels S, Nair KS, Halliday D. “Starch blockers” are ineffective in man. *Lancet*. 1983;1(8314-5):60-1.
2348. Starch blockers do not block starch digestion. *Nutr Rev*. 1985;43(2):46-8.
2349. Barrett ML, Udani JK. A proprietary alpha-amylase inhibitor from white bean (*Phaseolus vulgaris*): a review of clinical studies on weight loss and glycemic control. *Nutr J*. 2011;10:24.
2350. Drew R. Whatever happened to starch blockers? *N C Med J*. 1983;44(8):498.
2351. Layer P, Carlson GL, DiMagno EP. Partially purified white bean amylase inhibitor reduces starch digestion in vitro and inactivates intraduodenal amylase in humans. *Gastroenterology*. 1985;88(6):1895-902.
2352. Onakpoya I, Aldaas S, Terry R, Ernst E. The efficacy of *Phaseolus vulgaris* as a weight-loss supplement: a systematic review and meta-analysis of randomised clinical trials. *Br J Nutr*. 2011;106(2):196-202.
2353. Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med*. 2013;11:222.
2354. Ombra MN, d’Acierno A, Nazzaro F, et al. Alpha-amylase, α -glucosidase and lipase inhibiting activities of polyphenol-rich extracts from six common bean cultivars of Southern Italy, before and after cooking. *Int J Food Sci Nutr*. 2018;69(7):824-34.
2355. Larhammar D. Fakes and fraud in commercial diets. *Scand J Food Nutr*. 2005;49(2):78-80.
2356. Darmadi-Blackberry I, Wahlqvist ML, Kouris-Blazos A, et al. Legumes: the most important dietary predictor of survival in older people of different ethnicities. *Asia Pac J Clin Nutr*. 2004;13(2):217-20.
2357. Buettner D. *The Blue Zones: 9 Lessons for Living Longer from the People Who’ve Lived the Longest*. Washington, D.C.: National Geographic; 2012.
2358. Nachbar MS, Oppenheim JD. Lectins in the United States diet: a survey of lectins in commonly consumed foods and a review of the literature. *Am J Clin Nutr*. 1980;33(11):2338-45.
2359. Knight B. Ricin—a potent homicidal poison. *Br Med J*. 1979;1(6159):350-1.
2360. de Mejía EG, Priscearu VI. Lectins as bioactive plant proteins: a potential in cancer treatment. *Crit Rev Food Sci Nutr*. 2005;45(6):425-45.
2361. Deshpande S, Singh R. Research note: hemagglutinating activity of lectins in selected varieties of raw and processed dry beans. *J Food Process Preserv*. 1991;15(2):81-7.
2362. Noah ND, Bender AE, Reaidi GB, Gilbert RJ. Food poisoning from raw red kidney beans. *Br Med J*. 1980;281(6234):236-7.
2363. Noah ND, Bender AE, Reaidi GB, Gilbert RJ. Food poisoning from raw red kidney beans. *Br Med J*. 1980;281(6234):236-7.
2364. Kumar S, Verma AK, Das M, Jain SK, Dwivedi PD. Clinical complications of kidney bean (*Phaseolus vulgaris* L.) consumption. *Nutrition*. 2013;29(6):821-7.
2365. Thompson L, Rea R, Jenkins D. Effect of heat processing on hemagglutinin activity in red kidney beans. *J Food Sci*. 1983;48(1):235-6.
2366. Thompson L, Rea R, Jenkins D. Effect of heat processing on hemagglutinin activity in red kidney beans. *J Food Sci*. 1983;48(1):235-6.
2367. Rodhouse JC, Haugh CA, Roberts D, Gilbert RJ. Red kidney bean poisoning in the UK: an analysis of 50 suspected incidents between 1976 and 1989. *Epidemiol Infect*. 1990;105(3):485-91.
2368. Hermsdorff HH, Zulet MÁ, Abete I, Martínez JA. A legume-based hypocaloric diet reduces proinflammatory status and improves metabolic features in overweight/obese subjects. *Eur J Nutr*. 2011;50(1):61-9.
2369. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2017;105(6):1462-73.
2370. Mitchell DC, Lawrence FR, Hartman TJ, Curran JM. Consumption of dry beans, peas, and lentils could improve diet quality in the US population. *J Am Diet Assoc*. 2009;109(5):909-13.
2371. Havemeier S, Erickson J, Slavin J. Dietary guidance for pulses: the challenge and opportunity to be part of both the vegetable and protein food groups. *Ann NY Acad Sci*. 2017;1392(1):58-66.
2372. Havemeier S, Erickson J, Slavin J. Dietary guidance for pulses: the challenge and opportunity to be part of both the vegetable and protein food groups. *Ann NY Acad Sci*. 2017;1392(1):58-66.
2373. Winham DM, Hutchins AM. Perceptions of flatulence from bean consumption among adults in 3 feeding studies. *Nutr J*. 2011;10:128.
2374. Smoyak SA. Is satiety (lack thereof) the culprit with obesity? *J Psychosoc Nurs Ment Health Serv*. 2015;53(3):3-4.
2375. Gerstein DE, Woodward-Lopez G, Evans AE, Kelsey K, Drewnowski A. Clarifying concepts about macronutrients’ effects on satiation and satiety. *J Am Diet Assoc*. 2004;104(7):1151-3.
2376. Booth DA, Nouwen A. Satiety. No way to slim. *Appetite*. 2010;55(3):718-21.
2377. Leidy HJ, Clifton PM, Astrup A, et al. The role of protein in weight loss and maintenance. *Am J Clin Nutr*. 2015;101(6):1320S-9S.
2378. Nilsson A, Johansson E, Ekström L, Björck I. Effects of a brown beans evening meal on metabolic risk markers and appetite regulating hormones at a subsequent standardized breakfast: a randomized cross-over study. *PLoS ONE*. 2013;8(4):e59985.

2379. Mollard RC, Wong CL, Luhovyy BL, Anderson GH. First and second meal effects of pulses on blood glucose, appetite, and food intake at a later meal. *Appl Physiol Nutr Metab*. 2011;36(5):634-42.
2380. Poppitt SD, Shin HS, McGill AT, et al. Duodenal and ileal glucose infusions differentially alter gastrointestinal peptides, appetite response, and food intake: a tube feeding study. *Am J Clin Nutr*. 2017;106(3):725-35.
2381. Santoro S. Stomachs: does the size matter? Aspects of intestinal satiety, gastric satiety, hunger and gluttony. *Clinics (Sao Paulo)*. 2012;67(4):301-3.
2382. Hashim SA, Van Itallie TB. Studies in normal and obese subjects with a monitored food dispensing device. *Ann NY Acad Sci*. 1965;131(1):654-61.
2383. Hashim SA, Van Itallie TB. Studies in normal and obese subjects with a monitored food dispensing device. *Ann NY Acad Sci*. 1965;131(1):654-61.
2384. Hashim SA, Van Itallie TB. Studies in normal and obese subjects with a monitored food dispensing device. *Ann NY Acad Sci*. 1965;131(1):654-61.
2385. Campbell RG, Hashim SA, Van Itallie TB. Studies of food-intake regulation in man. Responses to variations in nutritive density in lean and obese subjects. *N Engl J Med*. 1971;285(25):1402-7.
2386. Hashim SA, Van Itallie TB. Studies in normal and obese subjects with a monitored food dispensing device. *Ann NY Acad Sci*. 1965;131(1):654-61.
2387. Campbell RG, Hashim SA, Van Itallie TB. Studies of food-intake regulation in man. Responses to variations in nutritive density in lean and obese subjects. *N Engl J Med*. 1971;285(25):1402-7.
2388. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr*. 2009;139(3):629-32.
2389. Ahlstrom B, Dinh T, Haselton MG, Tomiyama AJ. Understanding eating interventions through an evolutionary lens. *Health Psychol Rev*. 2017;11(1):72-88.
2390. Rolls B, Rowe E, Rolls E, Kingston B, Megson A, Gunary R. Variety in a meal enhances food intake in man. *Physiol Behav*. 1981;26(2):215-21.
2391. Davis CM. Self selection of diet by newly weaned infants. *Am J Dis Child*. 1928;36(4):651-79.
2392. Rolls B. Sensory-specific satiety. *Nutr Rev*. 1986;44(3):93-101.
2393. Rolls B. Sensory-specific satiety. *Nutr Rev*. 1986;44(3):93-101.
2394. Remick AK, Polivy J, Pliner P. Internal and external moderators of the effect of variety on food intake. *Psychol Bull*. 2009;135(3):434-51.
2395. Raynor HA, Epstein LH. Dietary variety, energy regulation, and obesity. *Psychol Bull*. 2001;127(3):325-41.
2396. Epstein LH, Rodefer JS, Wisniewski L, Caggiola AR. Habituation and dishabituation of human salivary response. *Physiol Behav*. 1992;51(5):945-50.
2397. Levitsky DA, Iyer S, Pacanowski CR. Number of foods available at a meal determines the amount consumed. *Eat Behav*. 2012;13(3):183-7.
2398. McCrory MA, Burke A, Roberts SB. Dietary (sensory) variety and energy balance. *Physiol Behav*. 2012;107(4):576-83.
2399. Epstein LH, Carr KA, Cavanaugh MD, Paluch RA, Bouton ME. Long-term habituation to food in obese and nonobese women. *Am J Clin Nutr*. 2011;94(2):371-6.
2400. Epstein LH, Fletcher KD, O'Neill J, Roemmich JN, Raynor H, Bouton ME. Food characteristics, long-term habituation and energy intake. Laboratory and field studies. *Appetite*. 2013;60(1):40-50.
2401. Epstein LH, Robinson JL, Roemmich JN, Marusewski AL, Roba LG. What constitutes food variety? Stimulus specificity of food. *Appetite*. 2010;54(1):23-9.
2402. Kahn B, Wansink B. The influence of assortment structure on perceived variety and consumption quantities. *J Consum Res*. 2004;30(4):519-33. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
2403. Remick AK, Polivy J, Pliner P. Internal and external moderators of the effect of variety on food intake. *Psychol Bull*. 2009;135(3):434-51.
2404. Levitsky DA, Iyer S, Pacanowski CR. Number of foods available at a meal determines the amount consumed. *Eat Behav*. 2012;13(3):183-7.
2405. Argilles JM. The rise and fall of the cafeteria diet: some observations. *J Nutr*. 1988;118(12):1593-4.
2406. Larson DE, Tataranni PA, Ferraro RT, Ravussin E. Ad libitum food intake on a "cafeteria diet" in Native American women: relations with body composition and 24-h energy expenditure. *Am J Clin Nutr*. 1995;62(5):911-7.
2407. Raynor HA, Niemeier HM, Wing RR. Effect of limiting snack food variety on long-term sensory-specific satiety and monotony during obesity treatment. *Eat Behav*. 2006;7(1):1-14.
2408. Raynor HA, Steeves EA, Hecht J, Fava JL, Wing RR. Limiting variety in non-nutrient-dense, energy-dense foods during a lifestyle intervention: a randomized controlled trial. *Am J Clin Nutr*. 2012;95(6):1305-14.
2409. Johnson F, Wardle J. Variety, palatability, and obesity. *Adv Nutr*. 2014;5(6):851-9.
2410. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr*. 1995;49(9):675-90.
2411. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr*. 1995;49(9):675-90.
2412. Tanoue K, Matsui K, Takamasu T. Fried-potato diet causes vitamin A deficiency in an autistic child. *JPEN J Parenteral Enteral Nutr*. 2012;36(6):753-5.
2413. Erdmann J, Hebeisen Y, Lippl F, Wagenpfeil S, Schusdziarra V. Food intake and plasma ghrelin response during potato-, rice- and pasta-rich test meals. *Eur J Nutr*. 2007;46(4):196-203.
2414. Akilen R, Deljomanesh N, Hunschede S, et al. The effects of potatoes and other carbohydrate side dishes consumed with meat on food intake, glycemia and satiety response in children. *Nutr Diabetes*. 2016;6:e195.
2415. Vadeloo MK, Parekh N. Dietary variety: an overlooked strategy for obesity and chronic disease control. *Am J Prev Med*. 2015;49(6):974-9.
2416. McCrory MA, Burke A, Roberts SB. Dietary (sensory) variety and energy balance. *Physiol Behav*. 2012;107(4):576-83.
2417. Burns RJ, Rothman AJ. Offering variety: a subtle manipulation to promote healthy food choice throughout the day. *Health Psychol*. 2015;34(5):566-70.

2418. Meengs JS, Roe LS, Rolls BJ. Vegetable variety: an effective strategy to increase vegetable intake in adults. *J Acad Nutr Diet.* 2012;112(8):1211-5.
2419. Vadiveloo MK, Campos H, Mattei J. Seasoning ingredient variety, but not quality, is associated with greater intake of beans and rice among urban Costa Rican adults. *Nutr Res.* 2016;36(8):780-8.
2420. Vadiveloo MK, Parekh N. Dietary variety: an overlooked strategy for obesity and chronic disease control. *Am J Prev Med.* 2015;49(6):974-9.

Chapter 3

2421. Katz DL. Why dieting should die. *Child Obes.* 2014;10(6):443-4.
2422. Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. *Circulation.* 1979;60(6):1401-12.
2423. Milea D, Cassoux N, Lehoang P. Blindness in a strict vegan. *N Engl J Med.* 2000;342(12):897-8.
2424. Kuo SC, Yeh CB, Yeh YW, Tzeng NS. Schizophrenia-like psychotic episode precipitated by cobalamin deficiency. *Gen Hosp Psychiatry.* 2009;31(6):586-8.
2425. Brocadello F, Levedianos G, Piccione F, Manara R, Pesenti FF. Irreversible subacute sclerotic combined degeneration of the spinal cord in a vegan subject. *Nutrition.* 2007;23(7-8):622-4.
2426. Haler D. Death after vegan diet. *Lancet.* 1968;2(7560):170.
2427. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. *Am Fam Physician.* 2017;96(6):384-9.
2428. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014;312(9):923-33.
2429. Kelly JH. Comparison of diets for weight loss and heart disease risk reduction. *JAMA.* 2005;293(13):1590.
2430. Rehkamp S. A look at calorie sources in the American Diet. Economic Research Service, United States Department of Agriculture. Published December 5, 2016. Available at: <https://www.ers.usda.gov/amber-waves/2016/december/a-look-at-calorie-sources-in-the-american-diet>. Accessed April 1, 2019.
2431. Yang MU, Van Itallie TB. Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. *J Clin Invest.* 1976;58(3):722-30.
2432. Rouillier MA, David-Riel S, Brazeau AS, St-Pierre DH, Karelis AD. Effect of an acute high carbohydrate diet on body composition using DXA in young men. *Ann Nutr Metab.* 2015;66(4):233-6.
2433. Denke MA. Metabolic effects of high-protein, low-carbohydrate diets. *Am J Cardiol.* 2001;88(1):59-61.
2434. Polivy J, Herman CP. If at first you don't succeed. False hopes of self-change. *Am Psychol.* 2002;57(9):677-89.
2435. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014;312(9):923-33.
2436. Obert J, Pearlman M, Obert L, Chapin S. Popular weight loss strategies: a review of four weight loss techniques. *Curr Gastroenterol Rep.* 2017;19(12):61.
2437. Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. *Circulation.* 1979;60(6):1401-12.
2438. Appleton H. The First Amendment: is the freedom of speech more important than the protection of human life? *LA Ent L Rev.* 1992;12(2):585-614.
2439. Anderson JW, Konz EC, Jenkins DJ. Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J Am Coll Nutr.* 2000;19(5):578-90.
2440. Miller M, Beach V, Sorkin JD, et al. Comparative effects of three popular diets on lipids, endothelial function, and C-reactive protein during weight maintenance. *J Am Diet Assoc.* 2009;109(4):713-7.
2441. Fleming RM. The effect of high-protein diets on coronary blood flow. *Angiology.* 2000;51(10):817-26.
2442. Jenkins DJ, Wong JM, Kendall CW, et al. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009;169(11):1046-54.
2443. Ornish D. Comparison of diets for weight loss and heart disease risk reduction. *JAMA.* 2005;293(13):1589.
2444. Fleming RM. The effect of high-protein diets on coronary blood flow. *Angiology.* 2000;51(10):817-26.
2445. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA.* 1998;280(23):2001-7.
2446. Calton JB. Prevalence of micronutrient deficiency in popular diet plans. *J Int Soc Sports Nutr.* 2010;7:24.
2447. Ma Y, Pagoto SL, Griffith JA, et al. A dietary quality comparison of popular weight-loss plans. *J Am Diet Assoc.* 2007;107(10):1786-91.
2448. Clarys P, Deliens T, Huybrechts I, et al. Comparison of nutritional quality of the vegan, vegetarian, semi-vegetarian, pesco-vegetarian and omnivorous diet. *Nutrients.* 2014;6(3):1318-32.
2449. Farmer B, Larson BT, Fulgoni VL, Rainville AJ, Liepa GU. A vegetarian dietary pattern as a nutrient-dense approach to weight management: an analysis of the national health and nutrition examination survey 1999-2004. *J Am Diet Assoc.* 2011;111(6):819-27.
2450. Van Horn L. Achieving nutrient density: a vegetarian approach. *J Am Diet Assoc.* 2011;111(6):799.
2451. Keenan S, Mitts KG, Kurtz CA. Scurvy presenting as a medial head tear of the gastrocnemius. *Orthopedics.* 2002;25(6):689-91.
2452. Eitenmiller R, Ye L, Landen W. *Vitamin Analysis for the Health and Food Sciences.* Boca Raton, FL: CRC; 2007:469.
2453. Del Bo' C, Riso P, Gardana C, Brusamolino A, Battezzati A, Ciappellano S. Effect of two different sublingual dosages of vitamin B on cobalamin nutritional status in vegans and vegetarians with a marginal deficiency: a randomized controlled trial. *Clin Nutr.* 2019;38(2):575-83.
2454. Siebert AK, Obeid R, Weder S, et al. Vitamin B-12-fortified toothpaste improves vitamin status in vegans: a 12-wk randomized placebo-controlled study. *Am J Clin Nutr.* 2017;105(3):618-25.
2455. Tuso PJ, Ismail MH, Ha BP, Bartolotto C. Nutritional update for physicians: plant-based diets. *Perm J.* 2013;17(2):61-6.
2456. Fardet A, Boirie Y. Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. *Nutr Rev.* 2014;72(12):741-62.
2457. Ornish D. Comparison of diets for weight loss and heart disease risk reduction. *JAMA.* 2005;293(13):1589.
2458. Estruch R, Ros E. Mediterranean diet for primary prevention of cardiovascular disease. *N Engl J Med.* 2013;369(7):676-7.

2459. Barnard N, Scherwitz L, Ornish D. Adherence and acceptability of a low-fat, vegetarian diet among patients with cardiac disease. *J Cardiopulm Rehabil.* 1992;12(6):423-31.
2460. Franklin TL, Kolasa KM, Griffin K, Mayo C, Badenhop DT. Adherence to very-low-fat diet by a group of cardiac rehabilitation patients in the rural southeastern United States. *Arch Fam Med.* 1995;4(6):551-4.
2461. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA.* 1998;280(23):2001-7.
2462. Barnard N, Scialli A, Bertron P, Hurlock D, Edmonds K. Acceptability of a therapeutic low-fat, vegan diet in premenopausal women. *J Nutr Educ Behav.* 2000;32(6):314-9.
2463. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes.* 2017;7(3):e256.
2464. Carter JP, Furman T, Hutcheson HR. Preeclampsia and reproductive performance in a community of vegans. *South Med J.* 1987;80(6):692-7.
2465. Sacks FM, Castelli WP, Donner A, Kass EH. Plasma lipids and lipoproteins in vegetarians and controls. *N Engl J Med.* 1975;292(22):1148-51.
2466. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr.* 2010;91(5):1525S-9S.
2467. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr.* 2010;91(5):1525S-9S.
2468. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr.* 2010;91(5):1525S-9S.
2469. Vincent HK, Bourguignon CM, Taylor AG. Relationship of the dietary phytochemical index to weight gain, oxidative stress and inflammation in overweight young adults. *J Hum Nutr Diet.* 2010;23(1):20-9.
2470. Mirmiran P, Bahadoran Z, Golzarand M, Shiva N, Azizi F. Association between dietary phytochemical index and 3-year changes in weight, waist circumference and body adiposity index in adults: Tehran Lipid and Glucose study. *Nutr Metab (Lond).* 2012;9(1):108.
2471. Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006;30(9):1389-96.
2472. Chiu YF, Hsu CC, Chiu TH, et al. Cross-sectional and longitudinal comparisons of metabolic profiles between vegetarian and non-vegetarian subjects: a matched cohort study. *Br J Nutr.* 2015;114(8):1313-20.
2473. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr.* 2010;91(5):1525S-9S.
2474. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr.* 2010;91(5):1525S-9S.
2475. Spock B, Parker SJ. *Dr. Spock's Baby and Child Care: A Handbook for Parents of Developing Children from Birth through Adolescence.* 7th edition. New York: Pocket Books; 1998.
2476. Cali AM, Caprio S. Prediabetes and type 2 diabetes in youth: an emerging epidemic disease? *Curr Opin Endocrinol Diabetes Obes.* 2008;15(2):123-7.
2477. Key T, Davey G. Prevalence of obesity is low in people who do not eat meat. *BMJ.* 1996;313(7060):816-7.
2478. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term low-calorie low-protein vegan diet and endurance exercise are associated with low cardiometabolic risk. *Rejuvenation Res.* 2007;10(2):225-34.
2479. Kennedy ET, Bowman SA, Spence JT, Freedman M, King J. Popular diets: correlation to health, nutrition, and obesity. *J Am Diet Assoc.* 2001;101(4):411-20.
2480. Carels RA, Young KM, Coit C, Clayton AM, Spencer A, Hobbs M. Can following the caloric restriction recommendations from the Dietary Guidelines for Americans help individuals lose weight? *Eat Behav.* 2008;9(3):328-35.
2481. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet.* 2013;113(12):1610-9.
2482. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet.* 2013;113(12):1610-9.
2483. Carter JP, Furman T, Hutcheson HR. Preeclampsia and reproductive performance in a community of vegans. *South Med J.* 1987;80(6):692-7.
2484. Levin N, Rattan J, Gilat T. Energy intake and body weight in ovo-lacto vegetarians. *J Clin Gastroenterol.* 1986;8(4):451-3.
2485. Campbell TC, Chen J. Energy balance: interpretation of data from rural China. *Toxicol Sci.* 1999;52(2 Suppl):87-94.
2486. Levin N, Rattan J, Gilat T. Energy intake and body weight in ovo-lacto vegetarians. *J Clin Gastroenterol.* 1986;8(4):451-3.
2487. Mirmiran P, Bahadoran Z, Golzarand M, Shiva N, Azizi F. Association between dietary phytochemical index and 3-year changes in weight, waist circumference and body adiposity index in adults: Tehran Lipid and Glucose study. *Nutr Metab (Lond).* 2012;9(1):108.
2488. Campbell TC, Chen J. Energy balance: interpretation of data from rural China. *Toxicol Sci.* 1999;52(2 Suppl):87-94.
2489. Campbell TC, Chen J. Energy balance: interpretation of data from rural China. *Toxicol Sci.* 1999;52(2 Suppl):87-94.
2490. Toth MJ, Poehlman ET. Sympathetic nervous system activity and resting metabolic rate in vegetarians. *Metab Clin Exp.* 1994;43(5):621-5.
2491. Nadimi H, Yousefinejad A, Djazayeri A, Hosseini M, Hosseini S. Association of vegan diet with RMR, body composition and oxidative stress. *Acta Sci Pol Technol Aliment.* 2013;12(3):311-8.
2492. Oberlin P, Melby C, Poehlman E. Resting energy expenditure in young vegetarian and nonvegetarian women. *Nutr Res.* 1990;10(1):39-49.
2493. Poehlman ET, Arciero PJ, Melby CL, Badylak SF. Resting metabolic rate and postprandial thermogenesis in vegetarians and nonvegetarians. *Am J Clin Nutr.* 1988;48(2):209-13.
2494. Montalcini T, De Bonis D, Ferro Y, et al. High vegetable fats intake is associated with high resting energy expenditure in vegetarians. *Nutrients.* 2015;7(7):5933-47.
2495. Orlich MJ, Jaceldo-Siegl K, Sabaté J, Fan J, Singh PN, Fraser GE. Patterns of food consumption among vegetarians and non-vegetarians. *Br J Nutr.* 2014;112(10):1644-53.
2496. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian diets and weight reduction: a meta-analysis of randomized controlled trials. *J Gen Intern Med.* 2016;31(1):109-16.

2497. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. *J Acad Nutr Diet*. 2015;115(6):954-69.
2498. Turner-McGrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. *Nutrition*. 2015;31(2):350-8.
2499. Turner-McGrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. *Nutrition*. 2015;31(2):350-8.
2500. Sarter B, Campbell TC, Fuhrman J. Effect of a high nutrient density diet on long-term weight loss: a retrospective chart review. *Altern Ther Health Med*. 2008;14(3):48-53.
2501. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280(23):2001-7.
2502. McDougall J, Thomas LE, McDougall C, et al. Effects of 7 days on an ad libitum low-fat vegan diet: the McDougall Program cohort. *Nutr J*. 2014;13:99.
2503. Hänninen O, Nenonen M, Ling WH, Li DS, Sihvonen L. Effects of eating an uncooked vegetable diet for 1 week. *Appetite*. 1992;19(3):243-54.
2504. Hunnicutt D, Diehl H, Vedro P. The CHIP prescription for health. *Absolute Advantage*. 2004;3(8)3-5.
2505. Morton D, Rankin P, Kent L, et al. The Complete Health Improvement Program (CHIP) and reduction of chronic disease risk factors in Canada. *Can J Diet Pract Res*. 2014;75(2):72-7.
2506. Diehl HA. Coronary risk reduction through intensive community-based lifestyle intervention: the Coronary Health Improvement Project (CHIP) experience. *Am J Cardiol*. 1998;82(10B):83T-7T.
2507. Merrill RM, Aldana SG, Greenlaw RL, Diehl HA, Salberg A, Englert H. Can newly acquired healthy behaviors persist? An analysis of health behavior decay. *Prev Chronic Dis*. 2008;5(1):1-13.
2508. Merrill RM, Aldana SG, Greenlaw RL, Diehl HA, Salberg A, Englert H. Can newly acquired healthy behaviors persist? An analysis of health behavior decay. *Prev Chronic Dis*. 2008;5(1):1-13.
2509. Morton D, Rankin P, Kent L, Dysinger W. The Complete Health Improvement Program (CHIP): history, evaluation, and outcomes. *Am J Lifestyle Med*. 2016;10(1):64-73.
2510. Morton D, Rankin P, Kent L, Dysinger W. The Complete Health Improvement Program (CHIP): history, evaluation, and outcomes. *Am J Lifestyle Med*. 2016;10(1):64-73.
2511. Rankin P, Morton DP, Diehl H, Gobble J, Morey P, Chang E. Effectiveness of a volunteer-delivered lifestyle modification program for reducing cardiovascular disease risk factors. *Am J Cardiol*. 2012;109(1):82-6.
2512. Merrill RM, Aldana SG, Greenlaw RL, Diehl HA, Salberg A. The effects of an intensive lifestyle modification program on sleep and stress disorders. *J Nutr Health Aging*. 2007;11(3):242-8.
2513. Aldana SG, Greenlaw RL, Diehl HA, et al. Effects of an intensive diet and physical activity modification program on the health risks of adults. *J Am Diet Assoc*. 2005;105(3):371-81.
2514. Merrill RM, Aldana SG. Improving overall health status through the CHIP intervention. *Am J Health Behav*. 2009;33(2):135-46.
2515. Hunnicutt D, Diehl H, Vedro P. The CHIP prescription for health. *Absolute Advantage*. 2004;3(8):3-5.
2516. Bloomer RJ, Toline AH. Participant compliance to a six-month traditional and modified Daniel Fast. *J Fasting and Health*. 2014;2(3):90-5.
2517. Trapp C, Barnard N, Katcher H. A plant-based diet for type 2 diabetes: scientific support and practical strategies. *Diabetes Educ*. 2010;36(1):33-48.
2518. Can a problem drinker simply cut down? National Institute on Alcohol Abuse and Alcoholism. Available at: <https://web.archive.org/web/20051112172730/http://www.niaaa.nih.gov/FAQs/General-English/FAQs11.htm>. Published 1996. Accessed April 1, 2019.
2519. Barnard ND, Akhtar A, Nicholson A. Factors that facilitate compliance to lower fat intake. *Arch Fam Med*. 1995;4(2):153-8.
2520. Moore WJ, McGrievy ME, Turner-McGrievy GM. Dietary adherence and acceptability of five different diets, including vegan and vegetarian diets, for weight loss: the New DIETs study. *Eat Behav*. 2015;19:33-8.
2521. Moore WJ, McGrievy ME, Turner-McGrievy GM. Dietary adherence and acceptability of five different diets, including vegan and vegetarian diets, for weight loss: the New DIETs study. *Eat Behav*. 2015;19:33-8.
2522. Trapp C, Barnard N, Katcher H. A plant-based diet for type 2 diabetes: scientific support and practical strategies. *Diabetes Educ*. 2010;36(1):33-48.
2523. Cramer H, Kessler CS, Sundberg T, et al. Characteristics of Americans choosing vegetarian and vegan diets for health reasons. *J Nutr Educ Behav*. 2017;49(7):561-7. e1.
2524. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes*. 2017;7(3):e256.
2525. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes*. 2017;7(3):e256.
2526. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes*. 2017;7(3):e256.
2527. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes*. 2017;7(3):e256.
2528. Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann Intern Med*. 2005;142(1):56-66.
2529. Saslow LR, Daubenmier JJ, Moskowitz JT, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr Diabetes*. 2017;7(12):304.
2530. Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med*. 2004;140(10):769-77.

2531. Noto H, Goto A, Tsujimoto T, Noda M. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS ONE*. 2013;8(1):e55030.
2532. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645-52.
2533. Kim H, Caulfield LE, Rebholz CM. Healthy plant-based diets are associated with lower risk of all-cause mortality in us adults. *J Nutr*. 2018;148(4):624-31.
2534. Singh PN, Arthur KN, Orlich MJ, et al. Global epidemiology of obesity, vegetarian dietary patterns, and noncommunicable disease in Asian Indians. *Am J Clin Nutr*. 2014;100 Suppl 1:359S-64S.
2535. Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br J Nutr*. 2013;110(5):969-70.
2536. Fleming RM. The effect of high-protein diets on coronary blood flow. *Angiology*. 2000;51(10):817-26.
2537. Esselstyn CB. A plant-based diet and coronary artery disease: a mandate for effective therapy. *J Geriatr Cardiol*. 2017;14(5):317-20.
2538. Jenkins DJ, Kendall CW. The garden of Eden: plant-based diets, the genetic drive to store fat and conserve cholesterol, and implications for epidemiology in the 21st century. *Epidemiology*. 2006;17(2):128-30.
2539. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med*. 1985;312(5):283-9.
2540. Anderson JW, Konz EC, Jenkins DJ. Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J Am Coll Nutr*. 2000;19(5):578-90.
2541. Buja LM, Nikolai N. Anitschkow and the lipid hypothesis of atherosclerosis. *Cardiovasc Pathol*. 2014;23(3):183-4.
2542. Roberts WC. We think we are one, we act as if we are one, but we are not one. *Am J Cardiol*. 1990;66(10):896.

Chapter 4

2543. Kahleova H, Tura A, Hill M, Holubkov R, Barnard ND. A plant-based dietary intervention improves beta-cell function and insulin resistance in overweight adults: a 16-week randomized clinical trial. *Nutrients*. 2018;10(2):189.
2544. Sabaté J, Wien M. Vegetarian diets and childhood obesity prevention. *Am J Clin Nutr*. 2010;91(5):1525S-95S.
2545. Latner JD, Wilson GT, Stunkard AJ, Jackson ML. Self-help and long-term behavior therapy for obesity. *Behav Res Ther*. 2002;40(7):805-12.
2546. Wohl J. Weight Watchers keeps gaining (because, well, Oprah). *Ad Age*. Published August 3, 2017. Available at: <http://adage.com/article/cmo-strategy/weight-watchers-gaining-oprah-winfrey/310024>. Accessed April 9, 2019.
2547. Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. *JAMA*. 2003;289(14):1792-8.
2548. Latner JD, Stunkard AJ, Wilson GT, Jackson ML, Zelitch DS, Labouvie E. Effective long-term treatment of obesity: a continuing care model. *Int J Obes Relat Metab Disord*. 2000;24(7):893-8.
2549. Gudzone KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. *Ann Intern Med*. 2015;162(7):501-12.
2550. Latner JD, Stunkard AJ, Wilson GT, Jackson ML, Zelitch DS, Labouvie E. Effective long-term treatment of obesity: a continuing care model. *Int J Obes Relat Metab Disord*. 2000;24(7):893-8.
2551. Latner JD, Stunkard AJ, Wilson GT, Jackson ML, Zelitch DS, Labouvie E. Effective long-term treatment of obesity: a continuing care model. *Int J Obes Relat Metab Disord*. 2000;24(7):893-8.
2552. Volkmar FR, Stunkard AJ, Woolston J, Bailey RA. High attrition rates in commercial weight reduction programs. *Arch Intern Med*. 1981;141(4):426-8.
2553. WebMD Health News. Scared skinny: weight-loss boot camp is tough but effective. WebMD. Published July 31, 2000. Available at: <https://www.webmd.com/diet/news/20000731/weight-loss-boot-camp>. Accessed April 9, 2019.
2554. Latner JD, Stunkard AJ, Wilson GT, Jackson ML, Zelitch DS, Labouvie E. Effective long-term treatment of obesity: a continuing care model. *Int J Obes Relat Metab Disord*. 2000;24(7):893-8.
2555. Renjilian DA, Perri MG, Nezu AM, McKelvey WF, Shermer RL, Anton SD. Individual versus group therapy for obesity: effects of matching participants to their treatment preferences. *J Consult Clin Psychol*. 2001;69(4):717-21.
2556. Painter SL, Ahmed R, Kushner RF, et al. Expert coaching in weight loss: retrospective analysis. *J Med Internet Res*. 2018;20(3):e92.
2557. Zheng Y, Klem ML, Sereika SM, Danford CA, Ewing LJ, Burke LE. Self-weighing in weight management: a systematic literature review. *Obesity (Silver Spring)*. 2015;23(2):256-65.
2558. Cheatham SW, Stull KR, Fantigrassi M, Motel I. The efficacy of wearable activity tracking technology as part of a weight loss program: a systematic review. *J Sports Med Phys Fitness*. 2018;58(4):534-48.
2559. Pacanowski CR, Bertz FC, Levitsky DA. Daily self-weighing to control body weight in adults: a critical review of the literature. *Sage Open*. 2014;4(4):1-16.
2560. Zheng Y, Klem ML, Sereika SM, Danford CA, Ewing LJ, Burke LE. Self-weighing in weight management: a systematic literature review. *Obesity (Silver Spring)*. 2015;23(2):256-65.
2561. Pacanowski CR, Bertz FC, Levitsky DA. Daily self-weighing to control body weight in adults: a critical review of the literature. *Sage Open*. 2014;4(4):1-16.
2562. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr*. 1997;66(2):239-46.
2563. Butryn ML, Phelan S, Hill JO, Wing RR. Consistent self-monitoring of weight: a key component of successful weight loss maintenance. *Obesity (Silver Spring)*. 2007;15(12):3091-6.
2564. Zheng Y, Klem ML, Sereika SM, Danford CA, Ewing LJ, Burke LE. Self-weighing in weight management: a systematic literature review. *Obesity (Silver Spring)*. 2015;23(2):256-65.
2565. Wilkinson L. Questions regarding weighing every day. *J Acad Nutr Diet*. 2016;116(3):405.
2566. Steinberg DM, Tate DF, Bennett GG, Ennett S, Samuel-Hodge C, Ward DS. The efficacy of a daily self-weighing weight loss intervention using smart scales and e-mail. *Obesity (Silver Spring)*. 2013;21(9):1789-97.
2567. Levitsky DA, Garay J, Nausbaum M, Neighbors L, Dellavalle DM. Monitoring weight daily blocks the freshman weight gain: a model for combating the epidemic of obesity. *Int J Obes (Lond)*. 2006;30(6):1003-10.
2568. Pacanowski CR, Levitsky DA. Frequent self-weighing and visual feedback for weight loss in overweight adults. *J Obes*. 2015;2015:763680.
2569. Madigan CD, Jolly K, Lewis AL, Aveyard P, Daley AJ. A randomised controlled trial of the effectiveness of self-weighing as a weight loss intervention. *Int J Behav Nutr Phys Act*. 2014;11:125.
2570. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol*. 2009;28(6):690-701.
2571. Michie S, Whittington C, Hamoudi Z, Zarnani F, Tober G, West R. Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction*. 2012;107(8):1431-40.
2572. Madigan CD, Daley AJ, Lewis AL, Aveyard P, Jolly K. Is self-weighing an effective tool for weight loss: a systematic literature review and meta-analysis. *Int J Behav Nutr Phys Act*. 2015;12:104.
2573. Pacanowski CR, Bertz FC, Levitsky DA. Daily self-weighing to control body weight in adults: a critical review of the literature. *Sage Open*. 2014;4(4):1-16.
2574. Shieh C, Knisely MR, Clark D, Carpenter JS. Self-weighing in weight management interventions: a systematic review of literature. *Obes Res Clin Pract*. 2016;10(5):493-519.
2575. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. *Circulation*. 2014;129(25 Suppl 2):S102-38.
2576. National Heart, Lung, and Blood Institute's Obesity Education Initiative Working Group. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. NIH Publication No. 00-4084. Published October 2000. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf. Accessed April 9, 2019.

2577. Zheng Y, Klem ML, Sereika SM, Danford CA, Ewing LJ, Burke LE. Self-weighing in weight management: a systematic literature review. *Obesity (Silver Spring)*. 2015;23(2):256–65.
2578. Oshima Y, Matsuoka Y, Sakane N. Effect of weight-loss program using self-weighing twice a day and feedback in overweight and obese subject: a randomized controlled trial. *Obes Res Clin Pract*. 2013;7(5):e361–6.
2579. Zheng Y, Klem ML, Sereika SM, Danford CA, Ewing LJ, Burke LE. Self-weighing in weight management: a systematic literature review. *Obesity (Silver Spring)*. 2015;23(2):256–65.
2580. Benn Y, Webb TL, Chang BP, Harkin B. What is the psychological impact of self-weighing? A meta-analysis. *Health Psychol Rev*. 2016;10(2):187–203.
2581. Benn Y, Webb TL, Chang BP, Harkin B. What is the psychological impact of self-weighing? A meta-analysis. *Health Psychol Rev*. 2016;10(2):187–203.
2582. Shieh C, Knisely MR, Clark D, Carpenter JS. Self-weighing in weight management interventions: a systematic review of literature. *Obes Res Clin Pract*. 2016;10(5):493–519.
2583. Pacanowski CR, Linde JA, Neumark-Sztainer D. Self-weighing: helpful or harmful for psychological well-being? A review of the literature. *Curr Obes Rep*. 2015;4(1):65–72.
2584. López M. Hypothalamic AMPK: a golden target against obesity? *Eur J Endocrinol*. 2017;176(5):R235–46.
2585. Steinberg GR, Macaulay SL, Febbraio MA, Kemp BE. AMP-activated protein kinase—the fat controller of the energy railroad. *Can J Physiol Pharmacol*. 2006;84(7):655–65.
2586. López M. Hypothalamic AMPK: a golden target against obesity? *Eur J Endocrinol*. 2017;176(5):R235–46.
2587. Musi N, Fujii N, Hirshman MF, et al. AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. *Diabetes*. 2001;50(5):921–7.
2588. Kola B, Grossman AB, Korbonits M. The role of AMP-activated protein kinase in obesity. *Front Horm Res*. 2008;36:198–211.
2589. Narkar VA, Downes M, Yu RT, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell*. 2008;134(3):405–15.
2590. Benkimoun P. Police find range of drugs after trawling bins used by Tour de France cyclists. *BMJ*. 2009;339:b4201.
2591. Niederberger E, King TS, Russe OQ, Geisslinger G. Activation of AMPK and its impact on exercise capacity. *Sports Med*. 2015;45(11):1497–509.
2592. Niederberger E, King TS, Russe OQ, Geisslinger G. Activation of AMPK and its impact on exercise capacity. *Sports Med*. 2015;45(11):1497–509.
2593. McCarty MF. AMPK activation—protean potential for boosting healthspan. *Age (Dordr)*. 2014;36(2):641–63.
2594. López M. Hypothalamic AMPK: a golden target against obesity? *Eur J Endocrinol*. 2017;176(5):R235–46.
2595. Martínez de Morentin PB, Urisarri A, Couce ML, López M. Molecular mechanisms of appetite and obesity: a role for brain AMPK. *Clin Sci*. 2016;130(19):1697–709.
2596. Novak CM, Gavini CK. Smokeless weight loss. *Diabetes*. 2012;61(4):776–7.
2597. Novak CM, Gavini CK. Smokeless weight loss. *Diabetes*. 2012;61(4):776–7.
2598. Pilhatsch M, Scheuing H, Kroemer N, et al. Nicotine administration in healthy non-smokers reduces appetite but does not alter plasma ghrelin. *Hum Psychopharmacol*. 2014;29(4):384–7.
2599. Perkins KA, Epstein LH, Stiller RL, et al. Acute effects of nicotine on hunger and caloric intake in smokers and nonsmokers. *Psychopharmacology (Berl)*. 1991;103(1):103–9.
2600. Wu Y, Song P, Zhang W, et al. Activation of AMPK α 2 in adipocytes is essential for nicotine-induced insulin resistance in vivo. *Nat Med*. 2015;21(4):373–82.
2601. Martínez de Morentin PB, Whittle AJ, Fernø J, et al. Nicotine induces negative energy balance through hypothalamic AMP-activated protein kinase. *Diabetes*. 2012;61(4):807–17.
2602. Ferguson SG, Shiffman S, Rohay JM, Gitchell JG, Garvey AJ. Effect of compliance with nicotine gum dosing on weight gained during a quit attempt. *Addiction*. 2011;106(3):651–6.
2603. Nielsen SS, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. Nicotine from edible *Solanaceae* and risk of Parkinson disease. *Ann Neurol*. 2013;74(3):472–7.
2604. Schütte-Borkovec K, Heppel CW, Helling AK, Richter E. Analysis of myosmine, cotinine and nicotine in human toenail, plasma and saliva. *Biomarkers*. 2009;14(5):278–84.
2605. Siegmund B, Leitner E, Pfannhauser W. Determination of the nicotine content of various edible nightshades (*Solanaceae*) and their products and estimation of the associated dietary nicotine intake. *J Agric Food Chem*. 1999;47(8):3113–20.
2606. Brody AL, Mandelkern MA, London ED, et al. Cigarette smoking saturates brain α β 2 nicotinic acetylcholine receptors. *Arch Gen Psychiatry*. 2006;63(8):907–15.
2607. Searles Nielsen S, Gallagher LG, Lundin JL, et al. Environmental tobacco smoke and Parkinson's disease. *Mov Disord*. 2012;27(2):293–6.
2608. Siegmund B, Leitner E, Pfannhauser W. Determination of the nicotine content of various edible nightshades (*Solanaceae*) and their products and estimation of the associated dietary nicotine intake. *J Agric Food Chem*. 1999;47(8):3113–20.
2609. Hellenbrand W, Seidler A, Boeing H, et al. Diet and Parkinson's disease. I: a possible role for the past intake of specific foods and food groups: results from a self-administered food-frequency questionnaire in a case-control study. *Neurology*. 1996;47(3):636–43.
2610. Nielsen SS, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. Nicotine from edible *Solanaceae* and risk of Parkinson disease. *Ann Neurol*. 2013;74(3):472–7.
2611. Kim NH, Park SH. Evaluation of green pepper (*Capsicum annuum* L.) juice on the weight gain and changes in lipid profile in C57BL/6 mice fed a high-fat diet. *J Sci Food Agric*. 2015;95(1):79–87.
2612. Reinbach HC, Smeets A, Martinussen T, Møller P, Westerterp-Plantenga MS. Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans in negative and positive energy balance. *Clin Nutr*. 2009;28(3):260–5.
2613. Kawabata F, Inoue N, Yazawa S, Kawada T, Inoue K, Fushiki T. Effects of CH-19 sweet, a non-pungent cultivar of red pepper, in decreasing the body weight and suppressing body fat accumulation by sympathetic nerve activation in humans. *Biosci Biotechnol Biochem*. 2006;70(12):2824–35.
2614. Etter JF. Addiction to the nicotine gum in never smokers. *BMC Public Health*. 2007;7:159.

2615. Grahame Hardie D. Regulation of AMP-activated protein kinase by natural and synthetic activators. *Acta Pharm Sin B*. 2016;6(1):1-19.
2616. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J*. 2010;9:3.
2617. Arayne MS, Sultana N, Bahadur SS. The berberis story: *Berberis vulgaris* in therapeutics. *Pak J Pharm Sci*. 2007;20(1):83-92.
2618. Arayne MS, Sultana N, Bahadur SS. The berberis story: *Berberis vulgaris* in therapeutics. *Pak J Pharm Sci*. 2007;20(1):83-92.
2619. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. *Phytother Res*. 2008;22(8):999-1012.
2620. Imanshahidi M, Hosseinzadeh H. Pharmacological and therapeutic effects of *Berberis vulgaris* and its active constituent, berberine. *Phytother Res*. 2008;22(8):999-1012.
2621. Chiou WF, Chen J, Chen CF. Relaxation of corpus cavernosum and raised intracavernous pressure by berberine in rabbit. *Br J Pharmacol*. 1998;125(8):1677-84.
2622. Fouladi RF. Aqueous extract of dried fruit of *Berberis vulgaris* L. in acne vulgaris, a clinical trial. *J Diet Suppl*. 2012;9(4):253-61.
2623. Yan HM, Xia MF, Wang Y, et al. Efficacy of berberine in patients with non-alcoholic fatty liver disease. *PLoS ONE*. 2015;10(8):e0134172.
2624. Pérez-Rubio KG, González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, Espinel-Bermúdez MC. Effect of berberine administration on metabolic syndrome, insulin sensitivity, and insulin secretion. *Metab Syndr Relat Disord*. 2013;11(5):366-9.
2625. Zhang Y, Li X, Zou D, et al. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *J Clin Endocrinol Metab*. 2008;93(7):2559-65.
2626. Jin Y, Khadka DB, Cho WJ. Pharmacological effects of berberine and its derivatives: a patent update. *Expert Opin Ther Pat*. 2016;26(2):229-43.
2627. Funk RS, Singh RK, Winefield RD, et al. Variability in potency among commercial preparations of berberine. *J Diet Suppl*. 2018;15(3):343-51.
2628. Lazavi F, Mirmiran P, Sohrab G, Nikpayam O, Angoorani P, Hedayati M. The barberry juice effects on metabolic factors and oxidative stress in patients with type 2 diabetes: a randomized clinical trial. *Complement Ther Clin Pract*. 2018;31:170-4.
2629. Arayne MS, Sultana N, Bahadur SS. The berberis story: *Berberis vulgaris* in therapeutics. *Pak J Pharm Sci*. 2007;20(1):83-92.
2630. Grahame Hardie D. Regulation of AMP-activated protein kinase by natural and synthetic activators. *Acta Pharm Sin B*. 2016;6(1):1-19.
2631. Chen H, Chen T, Giudici P, Chen F. Vinegar functions on health: constituents, sources, and formation mechanisms. *Compr Rev Food Sci Food Saf*. 2016;15(6):1124-38.
2632. Ali Z, Wang Z, Amir RM, et al. Potential uses of vinegar as a medicine and related in vivo mechanisms. *Int J Vitam Nutr Res*. 2018;86(3-4):1-12.
2633. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580-93.
2634. Shield KD, Soerjomataram I, Rehm J. Alcohol use and breast cancer: a critical review. *Alcohol Clin Exp Res*. 2016;40(6):1166-81.
2635. Ceddia RB. The role of AMP-activated protein kinase in regulating white adipose tissue metabolism. *Mol Cell Endocrinol*. 2013;366(2):194-203.
2636. CPG sec. 525.825 vinegar, definitions—adulteration with vinegar eels. United States Food and Drug Administration. Published March 1995. Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-ice/documents/webcontent/ucm074471.pdf>. Accessed April 9, 2019.
2637. Ali Z, Wang Z, Amir RM, et al. Potential uses of vinegar as a medicine and related in vivo mechanisms. *Int J Vitam Nutr Res*. 2018;86(3-4):1-12.
2638. Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. *Biosci Biotechnol Biochem*. 2009;73(8):1837-43.
2639. Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. *Biosci Biotechnol Biochem*. 2009;73(8):1837-43.
2640. Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. *Biosci Biotechnol Biochem*. 2009;73(8):1837-43.
2641. Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. *Biosci Biotechnol Biochem*. 2009;73(8):1837-43.
2642. Darzi J, Frost GS, Montaser R, Yap J, Robertson MD. Influence of the tolerability of vinegar as an oral source of short-chain fatty acids on appetite control and food intake. *Int J Obes (Lond)*. 2014;38(5):675-81.
2643. Sakakibara S, Murakami R, Takahashi M, et al. Vinegar intake enhances flow-mediated vasodilatation via upregulation of endothelial nitric oxide synthase activity. *Biosci Biotechnol Biochem*. 2010;74(5):1055-61.
2644. Park J, Kim J, Kim J, et al. Pomegranate vinegar beverage reduces visceral fat accumulation in association with AMPK activation in overweight women: a double-blind, randomized, and placebo-controlled trial. *J Funct Foods*. 2014;8:274-81.
2645. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol*. 2008;51(3):249-55.
2646. Ebihara K, Nakajima A. Effect of acetic acid and vinegar on blood glucose and insulin responses to orally administered sucrose and starch. *Agric Biol Chem*. 1988;52(5):1311-2.
2647. Region of the U.S. Vinegar Users. Market trends. Vinegar Institute. Published 2018. Available at: <https://versatilevinegar.org/market-trends>. Accessed April 9, 2019.
2648. Gale EA. Lessons from the glitazones: a story of drug development. *Lancet*. 2001;357(9271):1870-5.

2649. Feeley J. Pfizer ends Rezulin cases with \$205 million to spare (update1). *Bloomberg*. Published March 31, 2009. Available at: <http://web.archive.org/web/20140407071232/https://www.bloomberg.com/apps/news?pid=newsarchive&sid=act0akCefQwo>. Accessed April 10, 2019.
2650. Johnston C, Quagliano S, White S. Vinegar ingestion at mealtime reduced fasting blood glucose concentrations in healthy adults at risk for type 2 diabetes. *J Funct Foods*. 2013;5(4):2007-11.
2651. Johnston CS, Steplewska I, Long CA, Harris LN, Ryals RH. Examination of the antiglycemic properties of vinegar in healthy adults. *Ann Nutr Metab*. 2010;56(1):74-9.
2652. Shishehbor F, Mansoori A, Shirani F. Vinegar consumption can attenuate postprandial glucose and insulin responses; a systematic review and meta-analysis of clinical trials. *Diabetes Res Clin Pract*. 2017;127:1-9.
2653. Liljeberg H, Björck I. Delayed gastric emptying rate may explain improved glycaemia in healthy subjects to a starchy meal with added vinegar. *Eur J Clin Nutr*. 1998;52(5):368-71.
2654. White AM, Johnston CS. Vinegar ingestion at bedtime moderates waking glucose concentrations in adults with well-controlled type 2 diabetes. *Diabetes Care*. 2007;30(11):2814-5.
2655. Mitrou P, Petsiou E, Papakonstantinou E, et al. Vinegar consumption increases insulin-stimulated glucose uptake by the forearm muscle in humans with type 2 diabetes. *J Diabetes Res*. 2015;2015:175204.
2656. Hu GX, Chen GR, Xu H, Ge RS, Lin J. Activation of the AMP activated protein kinase by short-chain fatty acids is the main mechanism underlying the beneficial effect of a high fiber diet on the metabolic syndrome. *Med Hypotheses*. 2010;74(1):123-6.
2657. Ostman E, Granfeldt Y, Persson L, Björck I. Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. *Eur J Clin Nutr*. 2005;59(9):983-8.
2658. Ostman E, Granfeldt Y, Persson L, Björck I. Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. *Eur J Clin Nutr*. 2005;59(9):983-8.
2659. Maioli M, Pes GM, Sanna M, et al. Sourdough-leavened bread improves postprandial glucose and insulin plasma levels in subjects with impaired glucose tolerance. *Acta Diabetol*. 2008;45(2):91-6.
2660. Novotni D, Curic D, Bituh M, Colic Barić I, Skevin D, Cukelj N. Glycemic index and phenolics of partially-baked frozen bread with sourdough. *Int J Food Sci Nutr*. 2011;62(1):26-33.
2661. Leeman M, Ostman E, Björck I. Vinegar dressing and cold storage of potatoes lowers postprandial glycaemic and insulinaemic responses in healthy subjects. *Eur J Clin Nutr*. 2005;59(11):1266-71.
2662. Varvarelis N, Khallafi H, Pappachen B, Krishnamurthy M. Natural therapies—when ignorance is not bliss!! *J Am Geriatr Soc*. 2007;55(11):1892-3.
2663. Chung CH. Corrosive oesophageal injury following vinegar ingestion. *Hong Kong Med J*. 2002;8(5):365-6.
2664. Hill LL, Woodruff LH, Foote JC, Barreto-Alcoba M. Esophageal injury by apple cider vinegar tablets and subsequent evaluation of products. *J Am Diet Assoc*. 2005;105(7):1141-4.
2665. Hill LL, Woodruff LH, Foote JC, Barreto-Alcoba M. Esophageal injury by apple cider vinegar tablets and subsequent evaluation of products. *J Am Diet Assoc*. 2005;105(7):1141-4.
2666. Kuniyuki S, Oonishi H. Chemical burn from acetic acid with deep ulceration. *Contact Derm*. 1997;36(3):169-70.
2667. Petsiou EI, Mitrou PI, Raptis SA, Dimitriadis GD. Effect and mechanisms of action of vinegar on glucose metabolism, lipid profile, and body weight. *Nutr Rev*. 2014;72(10):651-61.
2668. McCarty MF. AMPK activation—protean potential for boosting healthspan. *Age (Dordr)*. 2014;36(2):641-63.
2669. Hu GX, Chen GR, Xu H, Ge RS, Lin J. Activation of the AMP activated protein kinase by short-chain fatty acids is the main mechanism underlying the beneficial effect of a high fiber diet on the metabolic syndrome. *Med Hypotheses*. 2010;74(1):123-6.
2670. Wanders AJ, van den Borne JJ, de Graaf C, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obes Rev*. 2011;12(9):724-39.
2671. Gardner E. Alternative sugars: yacon syrup (nectar). *BDJ*. 2017;223(9):625.
2672. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45241184, organic yacon syrup, UPC: 845772170502. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45241184>. Accessed April 9, 2019.
2673. Genta S, Cabrera W, Habib N, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr*. 2009;28(2):182-7.
2674. Genta S, Cabrera W, Habib N, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr*. 2009;28(2):182-7.
2675. Genta S, Cabrera W, Habib N, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr*. 2009;28(2):182-7.
2676. Krogsgaard LR, Lyngesen M, Bytzer P. Systematic review: quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome. *Aliment Pharmacol Ther*. 2017;45(12):1506-13.
2677. Ford AC, Moayyedi P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2010;32(2):144-58.
2678. Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. *J Nutr*. 2012;142(8):1510-8.
2679. Barrett J, Gibson P. Response to comment on low FODMAP diet. *Nutr Clin Pract*. 2013;28(6):775-6.
2680. Raatz SK, Johnson LK, Picklo MJ. Consumption of honey, sucrose, and high-fructose corn syrup produces similar metabolic effects in glucose-tolerant and—intolerant individuals. *J Nutr*. 2015;145(10):2265-72.
2681. Marcinek K, Krejpcio Z. Chia seeds (*Salvia hispanica*): health promoting properties and therapeutic applications—a review. *Rocz Panstw Zakl Hig*. 2017;68(2):123-9.
2682. Valdivia-López MA, Tecante A. Chia (*Salvia hispanica*): a review of native Mexican seed and its nutritional and functional properties. *Adv Food Nutr Res*. 2015;75:53-75.
2683. Valdivia-López MA, Tecante A. Chia (*Salvia hispanica*): a review of native Mexican seed and its nutritional and functional properties. *Adv Food Nutr Res*. 2015;75:53-75.
2684. Valdivia-López MA, Tecante A. Chia (*Salvia hispanica*): a review of native Mexican seed and its nutritional and functional properties. *Adv Food Nutr Res*. 2015;75:53-75.

2685. Chicco AG, D'Alessandro ME, Hein GJ, Oliva ME, Lombardo YB. Dietary chia seed (*Salvia hispanica* L.) rich in alpha-linolenic acid improves adiposity and normalises hypertriglycerolaemia and insulin resistance in dyslipaemic rats. *Br J Nutr*. 2009;101(1):41-50.
2686. Ayerza R, Coates W, Lauria M. Chia seed (*Salvia hispanica* L.) as an omega-3 fatty acid source for broilers: influence on fatty acid composition, cholesterol and fat content of white and dark meats, growth performance, and sensory characteristics. *Poult Sci*. 2002;81(6):826-37.
2687. Ayaz A, Akyol A, Inan-Eroglu E, Kabasakal Cetin A, Samur G, Akbiyik F. Chia seed (*Salvia Hispanica* L.) added yogurt reduces short-term food intake and increases satiety: randomised controlled trial. *Nutr Res Pract*. 2017;11(5):412-8.
2688. Nieman DC, Cayea EJ, Austin MD, Henson DA, McAnulty SR, Jin F. Chia seed does not promote weight loss or alter disease risk factors in overweight adults. *Nutr Res*. 2009;29(6):414-8.
2689. Austria JA, Richard MN, Chahine MN, et al. Bioavailability of alpha-linolenic acid in subjects after ingestion of three different forms of flaxseed. *J Am Coll Nutr*. 2008;27(2):214-21.
2690. Ratnayake W, Behrens W, Fischer P, L'Abbé M, Mongeau R, Beare-Rogers J. Chemical and nutritional studies of flaxseed (variety Linott) in rats. *J Nutr Biochem*. 1992;3(5):232-40.
2691. Nieman DC, Gillitt N, Jin F, et al. Chia seed supplementation and disease risk factors in overweight women: a metabolomics investigation. *J Altern Complement Med*. 2012;18(7):700-8.
2692. Vuksan V, Jenkins AL, Brissette C, et al. Salba-chia (*Salvia hispanica* L.) in the treatment of overweight and obese patients with type 2 diabetes: a double-blind randomized controlled trial. *Nutr Metab Cardiovasc Dis*. 2017;27(2):138-46.
2693. Teoh SL, Lai NM, Vanichkulpitak P, Vuksan V, Ho H, Chaiyakunapruk N. Clinical evidence on dietary supplementation with chia seed (*Salvia hispanica* L.): a systematic review and meta-analysis. *Nutr Rev*. 2018;76(4):219-42.
2694. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosty de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obes Rev*. 2017;18(9):1096-107.
2695. Vuksan V, Choleva L, Jovanovski E, et al. Comparison of flax (*Linum usitatissimum*) and Salba-chia (*Salvia hispanica* L.) seeds on postprandial glycemia and satiety in healthy individuals: a randomized, controlled, crossover study. *Eur J Clin Nutr*. 2017;71(2):234-8.
2696. Miller R, Schneiderman LJ. A clinical study of the use of human chorionic gonadotrophin in weight reduction. *J Fam Pract*. 1977;4(3):445-8.
2697. Yari Z, Rahimlou M, Poustchi H, Hekmatdoost A. Flaxseed supplementation in metabolic syndrome management: a pilot randomized, open-labeled, controlled study. *Phytother Res*. 2016;30(8):1339-44.
2698. Yari Z, Rahimlou M, Poustchi H, Hekmatdoost A. Flaxseed supplementation in metabolic syndrome management: a pilot randomized, open-labeled, controlled study. *Phytother Res*. 2016;30(8):1339-44.
2699. Xu J, Gao H, Song L, et al. Flaxseed oil and alpha-lipoic acid combination ameliorates hepatic oxidative stress and lipid accumulation in comparison to lard. *Lipids Health Dis*. 2013;12:58.
2700. Xu J, Gao H, Song L, et al. Flaxseed oil and alpha-lipoic acid combination ameliorates hepatic oxidative stress and lipid accumulation in comparison to lard. *Lipids Health Dis*. 2013;12:58.
2701. Yari Z, Rahimlou M, Eslamparast T, Ebrahimi-Daryani N, Poustchi H, Hekmatdoost A. Flaxseed supplementation in non-alcoholic fatty liver disease: a pilot randomized, open labeled, controlled study. *Int J Food Sci Nutr*. 2016;67(4):461-9.
2702. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosty de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. *Obes Rev*. 2017;18(9):1096-107.
2703. Cyanogena glykosider och vätecyanid. Livsmedelsverket. Published April 18, 2017. Available at: <https://www.livsmedelsverket.se/livsmedel-och-innehall/oonskade-amnen/vaxtgifter/cyanogena-glykosider-och-vatecyanid>. Accessed April 9, 2019.
2704. Prasad K. Flaxseed and cardiovascular health. *J Cardiovasc Pharmacol*. 2009;54(5):369-77.
2705. Jones DA. Why are so many food plants cyanogenic? *Phytochemistry*. 1998;47(2):155-62.
2706. Chaudhary M, Gupta R. Cyanide detoxifying enzyme: rhodanese. *Current Biotechnology*. 2012;1:327-35.
2707. Jones DA. Why are so many food plants cyanogenic? *Phytochemistry*. 1998;47(2):155-62.
2708. Jones DA. Why are so many food plants cyanogenic? *Phytochemistry*. 1998;47(2):155-62.
2709. Shragg TA, Albertson TE, Fisher CJ. Cyanide poisoning after bitter almond ingestion. *West J Med*. 1982;136(1):65-9.
2710. Chaouali N, Gana I, Dorra A, et al. Potential toxic levels of cyanide in almonds (*Prunus amygdalus*), apricot kernels (*Prunus armeniaca*), and almond syrup. *ISRN Toxicol*. 2013;2013:610648.
2711. Parikh M, Netticadan T, Pierce GN. Flaxseed: its bioactive components and their cardiovascular benefits. *Am J Physiol Heart Circ Physiol*. 2018;314(2):H146-59.
2712. Abraham K, Buhrike T, Lampen A. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. *Arch Toxicol*. 2016;90(3):559-74.
2713. Cunnane SC, Ganguli S, Menard C, et al. High α -linolenic acid flaxseed (*Linum usitatissimum*): some nutritional properties in humans. *Br J Nutr*. 1993;69(2):443-53.
2714. Abraham K, Buhrike T, Lampen A. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. *Arch Toxicol*. 2016;90(3):559-74.
2715. Fukuda T, Ito H, Mukainaka T, Tokuda H, Nishino H, Yoshida T. Anti-tumor promoting effect of glycosides from *Prunus persica* seeds. *Biol Pharm Bull*. 2003;26(2):271-3.
2716. Abraham K, Buhrike T, Lampen A. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. *Arch Toxicol*. 2016;90(3):559-74.
2717. Parikh M, Netticadan T, Pierce GN. Flaxseed: its bioactive components and their cardiovascular benefits. *Am J Physiol Heart Circ Physiol*. 2018;314(2):H146-59.
2718. Abraham K, Buhrike T, Lampen A. Bioavailability of cyanide after consumption of a single meal of foods containing high levels of cyanogenic glycosides: a crossover study in humans. *Arch Toxicol*. 2016;90(3):559-74.
2719. Rosling H. Cyanide exposure from linseed. *Lancet*. 1993;341(8838):177.

2720. Mnif S, Aifa S. Cumin (*Cuminum cyminum* L.) from traditional uses to potential biomedical applications. *Chem Biodivers*. 2015;12(5):733–42.
2721. Shavakhi A, Torki M, Khodadoostan M, Shavakhi S. Effects of cumin on nonalcoholic steatohepatitis: a double blind, randomised, controlled trial. *Adv Biomed Res*. 2015;4:212.
2722. Taghizadeh M, Memarzadeh MR, Asemi Z, Esmaillzadeh A. Effect of the *Cuminum cyminum* L. intake on weight loss, metabolic profiles and biomarkers of oxidative stress in overweight subjects: a randomized double-blind placebo-controlled clinical trial. *Ann Nutr Metab*. 2015;66(2-3):117–24.
2723. Zheljzkov VD, Shiwakoti S. Yield, composition, and antioxidant capacity of ground cumin seed oil fractions obtained at different time points during the hydrodistillation. *Hort Science*. 2015;50(8):1213–7.
2724. Taghizadeh M, Memarzadeh MR, Abedi F, et al. The effect of *Cuminum cyminum* L. plus lime administration on weight loss and metabolic status in overweight subjects: a randomized double-blind placebo-controlled clinical trial. *Iran Red Crescent Med J*. 2016;18(8):e34212.
2725. Jafari S, Sattari R, Ghavamzadeh S. Evaluation the effect of 50 and 100 mg doses of *Cuminum cyminum* essential oil on glycemic indices, insulin resistance and serum inflammatory factors on patients with diabetes type II: a double-blind randomized placebo-controlled clinical trial. *J Tradit Complement Med*. 2017;7(3):332–8.
2726. Coutinho Moraes DF, Still DW, Lum MR, Hirsch AM. DNA-based authentication of botanicals and plant-derived dietary supplements: where have we been and where are we going? *Planta Med*. 2015;81(9):687–95.
2727. Zare R, Heshmati F, Fallahzadeh H, Nadjarzadeh A. Effect of cumin powder on body composition and lipid profile in overweight and obese women. *Complement Ther Clin Pract*. 2014;20(4):297–301.
2728. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of *Nigella sativa*: a miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337–52.
2729. Sharma NK, Ahirwar D, Jhade D, Gupta S. Medicinal and pharmacological potential of *Nigella sativa*: a review. *Ethnobotanical Review*. 2009;13:946–55.
2730. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45205519, Sweet Sunnah, whole black seeds *Nigella sativa*, UPC: 680274444443. USDA Branded Food Products Database. Published July 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45205519>. Accessed April 9, 2019.
2731. Sahebkar A, Beccuti G, Simental-Mendía LE, Nobili V, Bo S. *Nigella sativa* (black seed) effects on plasma lipid concentrations in humans: a systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res*. 2016;106:37–50.
2732. Sahebkar A, Soranna D, Liu X, et al. A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with *Nigella sativa* (black seed) on blood pressure. *J Hypertens*. 2016;34(11):2127–35.
2733. Daryabeygi-Khotbehshara R, Golzarand M, Ghaffari MP, Djafarian K. *Nigella sativa* improves glucose homeostasis and serum lipids in type 2 diabetes: a systematic review and meta-analysis. *Complement Ther Med*. 2017;35:6–13.
2734. Ibrahim RM, Hamdan NS, Mahmud R, et al. A randomised controlled trial on hypolipidemic effects of *Nigella sativa* seeds powder in menopausal women. *J Transl Med*. 2014;12:82.
2735. Latiff LA, Parhizkar S, Dollah MA, Hassan ST. Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: a novel role of *Nigella sativa*. *Iran J Basic Med Sci*. 2014;17(12):980–5.
2736. Ibrahim RM, Hamdan NS, Mahmud R, et al. A randomised controlled trial on hypolipidemic effects of *Nigella sativa* seeds powder in menopausal women. *J Transl Med*. 2014;12:82.
2737. Sahebkar A, Beccuti G, Simental-Mendía LE, Nobili V, Bo S. *Nigella sativa* (black seed) effects on plasma lipid concentrations in humans: a systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res*. 2016;106:37–50.
2738. Mousavi SM, Sheikh A, Varkaneh HK, Zarezadeh M, Rahmani J, Milajerdi A. Effect of *Nigella sativa* supplementation on obesity indices: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2018;38:48–57.
2739. Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (*Crocus sativus* L.) and major depressive disorder: a meta-analysis of randomized clinical trials. *J Integr Med*. 2013;11(6):377–83.
2740. Abedimanesh N, Bathaie SZ, Abedimanesh S, Motlagh B, Separham A, Ostadrahimi A. Saffron and crocin improved appetite, dietary intakes and body composition in patients with coronary artery disease. *J Cardiovasc Thorac Res*. 2017;9(4):200–8.
2741. Samarghandian S, Azimi-Nezhad M, Samini F. Ameliorative effect of saffron aqueous extract on hyperglycemia, hyperlipidemia, and oxidative stress on diabetic encephalopathy in streptozotocin induced experimental diabetes mellitus. *Biomed Res Int*. 2014;2014:920857.
2742. Abedimanesh N, Bathaie SZ, Abedimanesh S, Motlagh B, Separham A, Ostadrahimi A. Saffron and crocin improved appetite, dietary intakes and body composition in patients with coronary artery disease. *J Cardiovasc Thorac Res*. 2017;9(4):200–8.
2743. Gout B, Bourges C, Paineau-Dubreuil S. Satiereal, a *Crocus sativus* L extract, reduces snacking and increases satiety in a randomized placebo-controlled study of mildly overweight, healthy women. *Nutr Res*. 2010;30(5):305–13.
2744. Hosseinzadeh H, Younesi HM. Antinociceptive and anti-inflammatory effects of *Crocus sativus* L. stigma and petal extracts in mice. *BMC Pharmacol*. 2002;2:7.
2745. Casazza K, Brown A, Astrup A, et al. Weighing the evidence of common beliefs in obesity research. *Crit Rev Food Sci Nutr*. 2015;55(14):2014–53.
2746. Johns Hopkins Bloomberg School of Public Health. Breakfast. Johns Hopkins University. Published 2012. Available at: <https://web.archive.org/web/20120723060928/https://www.jhsph.edu/offices-and-services/student-affairs/Breakfast>. Accessed April 9, 2019.
2747. Che C. Myths and realities: is breakfast the most important meal of the day? *Clinical Correlations*. Published June 18, 2009. Available at: <https://www.clinicalcorrelations.org/?p=1525>. Accessed April 9, 2019.
2748. Salge Blake J. Want to trim your waist? Try eating breakfast. American Dietetic Association. Published November 15, 2010. Available at: <https://web.archive.org/web/20101223233855/http://www.eatright.org/Media/Blog.aspx?>

- id=4294969065&blogid=269. Accessed April 9, 2019.
2749. Che C. Myths and realities: is breakfast the most important meal of the day? *Clinical Correlations*. Published June 18, 2009. Available at: <https://www.clinicalcorrelations.org/?p=1525>. Accessed April 9, 2019.
2750. Muhlfeld D. Breakfast: pro and con. *Duke Med Health News*. 2014;20(11).
2751. Brown AW, Bohan Brown MM, Allison DB. Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence. *Am J Clin Nutr*. 2013;98(5):1298-308.
2752. Brown AW, Bohan Brown MM, Allison DB. Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence. *Am J Clin Nutr*. 2013;98(5):1298-308.
2753. Adams AM, Smith AF. Risk perception and communication: recent developments and implications for anaesthesia. *Anaesthesia*. 2001;56(8):745-55.
2754. Hornick B, Duyff RL, Murphy MM, Shumow L. Proposing a definition of candy in moderation. *Nutr Today*. 2014;49(2):87-94.
2755. O'Neil CE, Fulgoni VL, Nicklas TA. Association of candy consumption with body weight measures, other health risk factors for cardiovascular disease, and diet quality in US children and adolescents: NHANES 1999-2004. *Food Nutr Res*. 2011;55:5794.
2756. Brown AW, Bohan Brown MM, Allison DB. Reply to RA Mekary and E Giovannucci. *Am J Clin Nutr*. 2014;99(1):213.
2757. Betts JA, Richardson JD, Chowdhury EA, Holman GD, Tsintzas K, Thompson D. The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults. *Am J Clin Nutr*. 2014;100(2):539-47.
2758. Leidy HJ, Gwin JA, Roenfeldt CA, Zino AZ, Shafer RS. Evaluating the intervention-based evidence surrounding the causal role of breakfast on markers of weight management, with specific focus on breakfast composition and size. *Adv Nutr*. 2016;7(3):563S-75S.
2759. Brown AW, Bohan Brown MM, Allison DB. Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence. *Am J Clin Nutr*. 2013;98(5):1298-308.
2760. Chowdhury EA, Richardson JD, Tsintzas K, Thompson D, Betts JA. Carbohydrate-rich breakfast attenuates glycaemic, insulinaemic and ghrelin response to ad libitum lunch relative to morning fasting in lean adults. *Br J Nutr*. 2015;114(1):98-107.
2761. LeCheminant GM, LeCheminant JD, Tucker LA, Bailey BW. A randomized controlled trial to study the effects of breakfast on energy intake, physical activity, and body fat in women who are nonhabitual breakfast eaters. *Appetite*. 2017;112:44-51.
2762. Levitsky DA, Pacanowski CR. Effect of skipping breakfast on subsequent energy intake. *Physiol Behav*. 2013;119:9-16.
2763. Chowdhury EA, Richardson JD, Tsintzas K, Thompson D, Betts JA. Effect of extended morning fasting upon ad libitum lunch intake and associated metabolic and hormonal responses in obese adults. *Int J Obes (Lond)*. 2016;40(2):305-11.
2764. Bayham BE, Greenway FL, Johnson WD, Dhurandhar NV. A randomized trial to manipulate the quality instead of quantity of dietary proteins to influence the markers of satiety. *J Diabetes Complicat*. 2014;28(4):547-52.
2765. Geliebter A, Grillot CL, Aviram-Friedman R, Haq S, Yahav E, Hashim SA. Effects of oatmeal and corn flakes cereal breakfasts on satiety, gastric emptying, glucose, and appetite-related hormones. *Ann Nutr Metab*. 2015;66(2-3):93-103.
2766. Geliebter A, Grillot CL, Aviram-Friedman R, Haq S, Yahav E, Hashim SA. Effects of oatmeal and corn flakes cereal breakfasts on satiety, gastric emptying, glucose, and appetite-related hormones. *Ann Nutr Metab*. 2015;66(2-3):93-103.
2767. Musa-Veloso K, Fallah S, O'Shea M, Chu Y. Assessment of intakes and patterns of cooked oatmeal consumption in the U.S. using data from the National Health and Nutrition Examination Surveys. *Nutrients*. 2016;8(8):503.
2768. Kant AK, Graubard BI. Within-person comparison of eating behaviors, time of eating, and dietary intake on days with and without breakfast: NHANES 2005-2010. *Am J Clin Nutr*. 2015;102(3):661-70.
2769. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716.
2770. Xu M, Huang T, Lee AW, Qi L, Cho S. Ready-to-eat cereal consumption with total and cause-specific mortality: prospective analysis of 367,442 individuals. *J Am Coll Nutr*. 2016;35(3):217-23.
2771. Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the Physicians' Health Study I. *Arch Intern Med*. 2007;167(19):2080-5.
2772. Harris JL, Schwartz MB, Brownell KD, et al. Cereal FACTS 2012: limited progress in the nutrition quality and marketing of children's cereals. Rudd Center for Food Policy & Obesity. Published June 2012. Available at: http://www.cerealfacts.org/media/cereal_facts_report_2012_7.12.pdf. Accessed April 9, 2019.
2773. LoDolce ME, Harris JL, Schwartz MB. Sugar as part of a balanced breakfast? What cereal advertisements teach children about healthy eating. *J Health Commun*. 2013;18(11):1293-309.
2774. Breaking the fast. *Harvard Health Letter*. Published June 2011. Available at: <https://www.health.harvard.edu/staying-healthy/breaking-the-fast>. Accessed April 9, 2019.
2775. Wootan M, Ludwig D. Sugary cereal: breakfast candy or obesity cure? *Atlantic*. Published April 24, 2012. Available at: <https://www.theatlantic.com/health/archive/2012/04/sugary-cereal-breakfast-candy-or-obesity-cure/256293>. Accessed April 9, 2019.
2776. Scrinis G. Reformulation, fortification and functionalization: Big Food corporations' nutritional engineering and marketing strategies. *J Peasant Stud*. 2015;43(1):17-37.
2777. Stanton RA. Changing eating patterns versus adding nutrients to processed foods. *Med J Aust*. 2016;204(11):398.
2778. Undurraga D, Naidenko O, Sharp R. Children's cereals: sugar by the pound. Environmental Working Group. Published May 2014. Available at: <https://static.ewg.org/reports/2014/cereals/pdf/2014-EWG-Cereals-Report.pdf>. Accessed April 9, 2019.
2779. Goldfein K, Slavin J. Why sugar is added to food: food science 101. *Compr Rev Food Sci Food Saf*. 2015;14(5):644-56.

2780. Goldfein K, Slavin J. Why sugar is added to food: food science 101. *Compr Rev Food Sci Food Saf*. 2015;14(5):644-56.
2781. General Mills, Inc. Re: Interagency Working Group on food marketed to children: FTC project no. P094513. Comments on proposed nutrition principles and general comments and proposed marketing definitions. [Letter to Donald Clark, Secretary, Federal Trade Commission.] Published July 14, 2011.
2782. Scrinis G, Monteiro CA. Ultra-processed foods and the limits of product reformulation. *Public Health Nutr*. 2018;21(1):247-52.
2783. Hayden EB, Shannon IL, Brenner C, et al. Letters from our readers. *J Dent Child*. 1975:88-90.
2784. Hanks AS, Just DR, Wansink B. Chocolate milk consequences: a pilot study evaluating the consequences of banning chocolate milk in school cafeterias. *PLoS ONE*. 2014;9(4):e91022. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
2785. Hayden EB, Shannon IL, Brenner C, et al. Letters from our readers. *J Dent Child*. 1975:88-90.
2786. Hearings before the Select Committee on Nutrition and Human Needs of the United States Senate, Ninety-third Congress, first session. Nutrition Education—1973. Part 3—TV Advertising of Food to Children. Washington, D.C.: U.S. Government Printing Office; 1973. Available at: https://archive.org/details/ERIC_ED079441. Accessed April 1, 2019.
2787. Gregory EM. Edward Bernays, Uncle Freud, and Betty Crocker. *Psychology Today*. Published April 6, 2016. Available at: <https://www.psychologytoday.com/gb/blog/the-secular-shepherd/201604/edward-bernays-uncle-freud-and-betty-crocker>. Accessed April 9, 2019.
2788. Givel M. Consent and counter-mobilization: the case of the national smokers alliance. *J Health Commun*. 2007;12(4):339-57.
2789. Levitsky DA. Next will be apple pie. *Am J Clin Nutr*. 2014;100(2):503-4.
2790. Levitsky DA. Next will be apple pie. *Am J Clin Nutr*. 2014;100(2):503-4.
2791. Levitsky DA. Breaking the feast. *Am J Clin Nutr*. 2015;102(3):531-2.
2792. McCrory MA, Shaw AC, Lee JA. Energy and nutrient timing for weight control: does timing of ingestion matter? *Endocrinol Metab Clin North Am*. 2016;45(3):689-718.
2793. Betts JA, Richardson JD, Chowdhury EA, Holman GD, Tsintzas K, Thompson D. The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults. *Am J Clin Nutr*. 2014;100(2):539-47.
2794. Betts JA, Richardson JD, Chowdhury EA, Holman GD, Tsintzas K, Thompson D. The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults. *Am J Clin Nutr*. 2014;100(2):539-47.
2795. Betts JA, Chowdhury EA, Gonzalez JT, Richardson JD, Tsintzas K, Thompson D. Is breakfast the most important meal of the day? *Proc Nutr Soc*. 2016;75(4):464-74.
2796. Betts JA, Richardson JD, Chowdhury EA, Holman GD, Tsintzas K, Thompson D. The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults. *Am J Clin Nutr*. 2014;100(2):539-47.
2797. Chowdhury EA, Richardson JD, Holman GD, Tsintzas K, Thompson D, Betts JA. The causal role of breakfast in energy balance and health: a randomized controlled trial in obese adults. *Am J Clin Nutr*. 2016;103(3):747-56.
2798. Hirsh E, Halberg E, Halberg F, et al. Body weight change during 1 week on a single daily 2000-calorie meal consumed as breakfast (B) or dinner (D). *Chronobiologia*. 1975;2(Suppl 1):31-2.
2799. Sehgal A. Physiology flies with time. *Cell*. 2017;171(6):1232-5.
2800. Froy O, Miskin R. Effect of feeding regimens on circadian rhythms: implications for aging and longevity. *Aging (Albany NY)*. 2010;2(1):7-27.
2801. Ruddick-Collins LC, Johnston JD, Morgan PJ, Johnstone AM. The big breakfast study: chrono-nutrition influence on energy expenditure and bodyweight. *Nutr Bull*. 2018;43(2):174-83.
2802. Challet E. Circadian clocks, food intake, and metabolism. *Prog Mol Biol Transl Sci*. 2013;119:105-35.
2803. Green CB, Takahashi JS, Bass J. The meter of metabolism. *Cell*. 2008;134(5):728-42.
2804. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev*. 2007;11(6):465-84.
2805. Panda S. Circadian physiology of metabolism. *Science*. 2016;354(6315):1008-15.
2806. Oda H. Chrononutrition. *J Nutr Sci Vitaminol*. 2015;61 Suppl:S92-4.
2807. Carroll R, Metcalfe C, Gunnell D, Mohamed F, Eddleston M. Diurnal variation in probability of death following self-poisoning in Sri Lanka—evidence for chronotoxicity in humans. *Int J Epidemiol*. 2012;41(6):1821-8.
2808. Dallmann R, Okyar A, Lévi F. Dosing-time makes the poison: circadian regulation and pharmacotherapy. *Trends Mol Med*. 2016;22(5):430-45.
2809. Kirley K, Sharma U, Rowland K. PURLs: BP meds: this simple change improves outcomes. *J Fam Pract*. 2012;61(3):153-5.
2810. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int*. 2010;27(8):1629-51.
2811. Beccuti G, Monagheddu C, Evangelista A, et al. Timing of food intake: sounding the alarm about metabolic impairments? A systematic review. *Pharmacol Res*. 2017;125(Pt B):132-41.
2812. Raynor HA, Champagne CM. Position of the Academy of Nutrition and Dietetics: interventions for the treatment of overweight and obesity in adults. *J Acad Nutr Diet*. 2016;116(1):129-47.
2813. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. *Int J Obes (Lond)*. 2010;34(12):1667-83.
2814. Almoosawi S, Winter J, Prynne CJ, Hardy R, Stephen AM. Daily profiles of energy and nutrient intakes: are eating profiles changing over time? *Eur J Clin Nutr*. 2012;66(6):678-86.
2815. Purslow LR, Sandhu MS, Forouhi N, et al. Energy intake at breakfast and weight change: prospective study of 6,764 middle-aged men and women. *Am J Epidemiol*. 2008;167(2):188-92.
2816. de Castro JM. The time of day of food intake influences overall intake in humans. *J Nutr*. 2004;134(1):104-11.
2817. Thomson M, Spence JC, Raine K, Laing L. The association of television viewing with snacking behavior and body weight of young adults. *Am J Health Promot*. 2008;22(5):329-35.
2818. Baron KG, Reid KJ, Kern AS, Zee PC. Role of sleep timing in caloric intake and BMI. *Obesity (Silver Spring)*. 2011;19(7):1374-81.

2819. Haynes A, Kemps E, Moffitt R. Is cake more appealing in the afternoon? Time of day is associated with control over automatic positive responses to unhealthy food. *Food Qual Prefer*. 2016;54:67-74.
2820. Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. *Int J Obes (Lond)*. 2013;37(4):604-11.
2821. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring)*. 2009;17(11):2100-2.
2822. Lecheminant JD, Christenson E, Bailey BW, Tucker LA. Restricting night-time eating reduces daily energy intake in healthy young men: a short-term cross-over study. *Br J Nutr*. 2013;110(11):2108-13.
2823. Halberg F, Haus E, Cornélissen G. From biologic rhythms to chronomes relevant for nutrition. In: Marriott B, ed. *Not Eating Enough: Overcoming Underconsumption of Military Operational Rations*. Washington, D.C.: National Academies Press; 1995.
2824. Scheer FA, Morris CJ, Shea SA. The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity (Silver Spring)*. 2013;21(3):421-3.
2825. Stack N, Barker D, Carskadon M, Diniz Behn C. A model-based approach to optimizing ultradian forced desynchrony protocols for human circadian research. *J Biol Rhythms*. 2017;32(5):485-98.
2826. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev*. 2007;11(6):465-84.
2827. Reilly T, Waterhouse J, Edwards B. Some chronobiological and physiological problems associated with long-distance journeys. *Travel Med Infect Dis*. 2009;7(2):88-101.
2828. Bo S, Broglio F, Settanni F, et al. Effects of meal timing on changes in circulating epinephrine, norepinephrine, and acylated ghrelin concentrations: a pilot study. *Nutr Diabetes*. 2017;7(12):303.
2829. Halberg F, Haus E, Cornélissen G. From biologic rhythms to chronomes relevant for nutrition. In: Marriott B, ed. *Not Eating Enough: Overcoming Underconsumption of Military Operational Rations*. Washington, D.C.: National Academies Press; 1995.
2830. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504-12.
2831. Raynor HA, Li F, Cardoso C. Daily pattern of energy distribution and weight loss. *Physiol Behav*. 2018;192:167-72.
2832. Lombardo M, Bellia A, Padua E, et al. Morning meal more efficient for fat loss in a 3-month lifestyle intervention. *J Am Coll Nutr*. 2014;33(3):198-205.
2833. Madjd A, Taylor MA, Delavari A, Malekzadeh R, Macdonald IA, Farshchi HR. Beneficial effect of high energy intake at lunch rather than dinner on weight loss in healthy obese women in a weight-loss program: a randomized clinical trial. *Am J Clin Nutr*. 2016;104(4):982-9.
2834. Fong M, Caterson ID, Madigan CD. Are large dinners associated with excess weight, and does eating a smaller dinner achieve greater weight loss? A systematic review and meta-analysis. *Br J Nutr*. 2017;118(8):616-28.
2835. Jakubowicz D, Froy O, Wainstein J, Boaz M. Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. *Steroids*. 2012;77(4):323-31.
2836. Romon M, Edme JL, Boulenguez C, Lescroart JL, Frimat P. Circadian variation of diet-induced thermogenesis. *Am J Clin Nutr*. 1993;57(4):476-80.
2837. Bo S, Fadda M, Castiglione A, et al. Is the timing of caloric intake associated with variation in diet-induced thermogenesis and in the metabolic pattern? A randomized cross-over study. *Int J Obes (Lond)*. 2015;39(12):1689-95.
2838. Morris CJ, Garcia JI, Myers S, Yang JN, Trienekens N, Scheer FA. The human circadian system has a dominating role in causing the morning/evening difference in diet-induced thermogenesis. *Obesity (Silver Spring)*. 2015;23(10):2053-8.
2839. Yoshino J, Almeda-Valdes P, Patterson BW, et al. Diurnal variation in insulin sensitivity of glucose metabolism is associated with diurnal variations in whole-body and cellular fatty acid metabolism in metabolically normal women. *J Clin Endocrinol Metab*. 2014;99(9):E1666-70.
2840. Morris CJ, Garcia JI, Myers S, Yang JN, Trienekens N, Scheer FA. The human circadian system has a dominating role in causing the morning/evening difference in diet-induced thermogenesis. *Obesity (Silver Spring)*. 2015;23(10):2053-8.
2841. Ravussin E, Acheson KJ, Vernet O, Danforth E, Jéquier E. Evidence that insulin resistance is responsible for the decreased thermic effect of glucose in human obesity. *J Clin Invest*. 1985;76(3):1268-73.
2842. Bo S, Fadda M, Castiglione A, et al. Is the timing of caloric intake associated with variation in diet-induced thermogenesis and in the metabolic pattern? A randomized cross-over study. *Int J Obes (Lond)*. 2015;39(12):1689-95.
2843. Bowen AJ, Reeves RL. Diurnal variation in glucose tolerance. *Arch Intern Med*. 1967;119(3):261-4.
2844. Van Cauter E. Diurnal and ultradian rhythms in human endocrine function: a minireview. *Horm Res*. 1990;34(2):45-53.
2845. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev*. 1997;18(5):716-38.
2846. Gangwisch JE. Invited commentary: nighttime light exposure as a risk factor for obesity through disruption of circadian and circannual rhythms. *Am J Epidemiol*. 2014;180(3):251-3.
2847. Mayo Clinic. Glucose tolerance test. MayoClinic.org. Published March 20, 2018. Available at: <https://www.mayoclinic.org/tests-procedures/glucose-tolerance-test/about/pac-20394296>. Accessed March 2, 2019.
2848. Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metab Clin Exp*. 2018;84:11-27.
2849. Sonnier T, Rood J, Gimble JM, Peterson CM. Glycemic control is impaired in the evening in prediabetes through multiple diurnal rhythms. *J Diabetes Complicat*. 2014;28(6):836-43.
2850. Morris CJ, Yang JN, Garcia JI, et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc Natl Acad Sci USA*. 2015;112(17):E2225-34.
2851. Gibbs M, Harrington D, Starkey S, Williams P, Hampton S. Diurnal postprandial responses to low and high glycaemic index mixed meals. *Clin Nutr*. 2014;33(5):889-94.

2852. Morgan LM, Shi JW, Hampton SM, Frost G. Effect of meal timing and glycaemic index on glucose control and insulin secretion in healthy volunteers. *Br J Nutr*. 2012;108(7):1286-91.
2853. Gibbs M, Harrington D, Starkey S, Williams P, Hampton S. Diurnal postprandial responses to low and high glycaemic index mixed meals. *Clin Nutr*. 2014;33(5):889-94.
2854. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504-12.
2855. Bandín C, Scheer FA, Luque AJ, et al. Meal timing affects glucose tolerance, substrate oxidation and circadian-related variables: a randomized, crossover trial. *Int J Obes (Lond)*. 2015;39(5):828-33.
2856. Saad A, Dalla Man C, Nandy DK, et al. Diurnal pattern to insulin secretion and insulin action in healthy individuals. *Diabetes*. 2012;61(11):2691-700.
2857. Leung GKW, Huggins CE, Bonham MP. Effect of meal timing on postprandial glucose responses to a low glycemic index meal: a crossover trial in healthy volunteers. *Clin Nutr*. 2019;38(1):465-71.
2858. Tsuchida Y, Hata S, Sone Y. Effects of a late supper on digestion and the absorption of dietary carbohydrates in the following morning. *J Physiol Anthropol*. 2013;32(1):9.
2859. Jakubowicz D, Wainstein J, Ahren B, Landau Z, Bar-Dayán Y, Froy O. Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Care*. 2015;38(10):1820-6.
2860. Kobayashi F, Ogata H, Omi N, et al. Effect of breakfast skipping on diurnal variation of energy metabolism and blood glucose. *Obes Res Clin Pract*. 2014;8(3):e201-98.
2861. Bi H, Gan Y, Yang C, Chen Y, Tong X, Lu Z. Breakfast skipping and the risk of type 2 diabetes: a meta-analysis of observational studies. *Public Health Nutr*. 2015;18(16):3013-9.
2862. Cahill LE, Chiuve SE, Mekary RA, et al. Prospective study of breakfast eating and incident coronary heart disease in a cohort of male US health professionals. *Circulation*. 2013;128(4):337-43.
2863. Uzhova I, Fuster V, Fernández-Ortiz A, et al. The importance of breakfast in atherosclerosis disease: insights from the PESA study. *J Am Coll Cardiol*. 2017;70(15):1833-42.
2864. Uzhova I, Peñalvo JL. Reply: skipping breakfast is a marker of unhealthy lifestyle. *J Am Coll Cardiol*. 2018;71(6):708-9.
2865. Yokoyama Y, Onishi K, Hosoda T, et al. Skipping breakfast and risk of mortality from cancer, circulatory diseases and all causes: findings from the Japan collaborative cohort study. *Yonago Acta Med*. 2016;59(1):55-60.
2866. Farshchi HR, Taylor MA, MacDonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. *Am J Clin Nutr*. 2005;81(2):388-96.
2867. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504-12.
2868. Garaulet M, Gómez-Abellán P. Timing of food intake and obesity: a novel association. *Physiol Behav*. 2014;134:44-50.
2869. Weaver DR. The suprachiasmatic nucleus: a 25-year retrospective. *J Biol Rhythms*. 1998;13(2):100-12.
2870. Challet E. Circadian clocks, food intake, and metabolism. *Prog Mol Biol Transl Sci*. 2013;119:105-35.
2871. Dashti HS, Mogensen KM. Recommending small, frequent meals in the clinical care of adults: a review of the evidence and important considerations. *Nutr Clin Pract*. 2017;32(3):365-77.
2872. Coomans CP, Lucassen EA, Kooijman S, et al. Plasticity of circadian clocks and consequences for metabolism. *Diabetes Obes Metab*. 2015;17 Suppl 1:65-75.
2873. Carrasco-Benso MP, Rivero-Gutierrez B, Lopez-Minguez J, et al. Human adipose tissue expresses intrinsic circadian rhythm in insulin sensitivity. *FASEB J*. 2016;30(9):3117-23.
2874. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. *Sleep Med Rev*. 2007;11(6):465-84.
2875. Thaiss CA, Zeevi D, Levy M, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*. 2014;159(3):514-29.
2876. Liang X, Bushman FD, Fitzgerald GA. Time in motion: the molecular clock meets the microbiome. *Cell*. 2014;159(3):469-70.
2877. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. *Int J Obes (Lond)*. 2010;34(12):1667-83.
2878. Garaulet M, Gómez-Abellán P. Timing of food intake and obesity: a novel association. *Physiol Behav*. 2014;134:44-50.
2879. Kuehn BM. Resetting the circadian clock might boost metabolic health. *JAMA*. 2017;317(13):1303-5.
2880. Wehrens SMT, Christou S, Isherwood C, et al. Meal timing regulates the human circadian system. *Curr Biol*. 2017;27(12):1768-75.e3.
2881. Jakubowicz D, Wainstein J, Landau Z, et al. Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: a randomized clinical trial. *Diabetes Care*. 2017;40(11):1573-9.
2882. Yoshizaki T, Tada Y, Hida A, et al. Effects of feeding schedule changes on the circadian phase of the cardiac autonomic nervous system and serum lipid levels. *Eur J Appl Physiol*. 2013;113(10):2603-11.
2883. Cella LK, Van Cauter E, Schoeller DA. Effect of meal timing on diurnal rhythm of human cholesterol synthesis. *Am J Physiol*. 1995;269(5 Pt 1):E878-83.
2884. Matheson A, O'Brien L, Reid JA. The impact of shiftwork on health: a literature review. *J Clin Nurs*. 2014;23(23-24):3309-20.
2885. Jiang P, Turek FW. The endogenous circadian clock programs animals to eat at certain times of the 24-hour day: what if we ignore the clock? *Physiol Behav*. 2018;193(Pt B):211-7.
2886. Morris CJ, Purvis TE, Hu K, Scheer FA. Circadian misalignment increases cardiovascular disease risk factors in humans. *Proc Natl Acad Sci USA*. 2016;113(10):E1402-11.
2887. Lennernäs M, Akerstedt T, Hambaer L. Nocturnal eating and serum cholesterol of three-shift workers. *Scand J Work Environ Health*. 1994;20(6):401-6.

2888. Morris CJ, Purvis TE, Mistretta J, Hu K, Scheer FAJL. Circadian misalignment increases C-reactive protein and blood pressure in chronic shift workers. *J Biol Rhythms*. 2017;32(2):154-64.
2889. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA*. 2009;106(11):4453-8.
2890. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. *Proc Natl Acad Sci USA*. 2014;111(47):16647-53.
2891. Grant CL, Coates AM, Dorrian J, et al. Timing of food intake during simulated night shift impacts glucose metabolism: a controlled study. *Chronobiol Int*. 2017;34(8):1003-13.
2892. Cain SW, Filtzess AJ, Phillips CL, Anderson C. Enhanced preference for high-fat foods following a simulated night shift. *Scand J Work Environ Health*. 2015;41(3):288-93.
2893. McHill AW, Melanson EL, Higgins J, et al. Impact of circadian misalignment on energy metabolism during simulated nightshift work. *Proc Natl Acad Sci USA*. 2014;111(48):17302-7.
2894. Hibi M, Masumoto A, Naito Y, et al. Nighttime snacking reduces whole body fat oxidation and increases LDL cholesterol in healthy young women. *Am J Physiol Regul Integr Comp Physiol*. 2013;304(2):R94-101.
2895. Agricultural Research Service, United States Department of Agriculture. Basic report: 01001, butter, salted. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/01001>. Accessed April 9, 2019.
2896. Parsons MJ, Moffitt TE, Gregory AM, et al. Social jetlag, obesity and metabolic disorder: investigation in a cohort study. *Int J Obes (Lond)*. 2015;39(5):842-8.
2897. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol*. 2012;22(10):939-43.
2898. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol*. 2012;22(10):939-43.
2899. Mota MC, Silva CM, Balieiro LCT, Fahmy WM, Crispim CA. Social jetlag and metabolic control in non-communicable chronic diseases: a study addressing different obesity statuses. *Sci Rep*. 2017;7(1):6358.
2900. Pot GK, Almoosawi S, Stephen AM. Meal irregularity and cardiometabolic consequences: results from observational and intervention studies. *Proc Nutr Soc*. 2016;75(4):475-86.
2901. Pot GK, Almoosawi S, Stephen AM. Meal irregularity and cardiometabolic consequences: results from observational and intervention studies. *Proc Nutr Soc*. 2016;75(4):475-86.
2902. Farshchi HR, Taylor MA, MacDonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. *Am J Clin Nutr*. 2005;81(1):16-24.
2903. Farshchi HR, Taylor MA, MacDonald IA. Decreased thermic effect of food after an irregular compared with a regular meal pattern in healthy lean women. *Int J Obes Relat Metab Disord*. 2004;28(5):653-60.
2904. Farshchi HR, Taylor MA, MacDonald IA. Regular meal frequency creates more appropriate insulin sensitivity and lipid profiles compared with irregular meal frequency in healthy lean women. *Eur J Clin Nutr*. 2004;58(7):1071-7.
2905. Alhussain MH, MacDonald IA, Taylor MA. Irregular meal-pattern effects on energy expenditure, metabolism, and appetite regulation: a randomized controlled trial in healthy normal-weight women. *Am J Clin Nutr*. 2016;104(1):21-32.
2906. Parks EJ, McCrory MA. When to eat and how often? *Am J Clin Nutr*. 2005;81(1):3-4.
2907. Alhussain MH, MacDonald IA, Taylor MA. Irregular meal-pattern effects on energy expenditure, metabolism, and appetite regulation: a randomized controlled trial in healthy normal-weight women. *Am J Clin Nutr*. 2016;104(1):21-32.
2908. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Alteration of internal circadian phase relationships after morning versus evening carbohydrate-rich meals in humans. *J Biol Rhythms*. 2002;17(4):364-76.
2909. Stevens RG, Zhu Y. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond, B, Biol Sci*. 2015;370(1667).
2910. Gangwisch JE. Invited commentary: nighttime light exposure as a risk factor for obesity through disruption of circadian and circannual rhythms. *Am J Epidemiol*. 2014;180(3):251-3.
2911. Reid KJ, Santostasi G, Baron KG, Wilson J, Kang J, Zee PC. Timing and intensity of light correlate with body weight in adults. *PLoS ONE*. 2014;9(4):e92251.
2912. Obayashi K, Saeki K, Kurumatani N. Ambient light exposure and changes in obesity parameters: a longitudinal study of the HEIJO-KYO Cohort. *J Clin Endocrinol Metab*. 2016;101(9):3539-47.
2913. McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. *Am J Epidemiol*. 2014;180(3):245-50.
2914. McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. *Am J Epidemiol*. 2014;180(3):245-50.
2915. Koo YS, Song JY, Joo EY, et al. Outdoor artificial light at night, obesity, and sleep health: cross-sectional analysis in the KoGES study. *Chronobiol Int*. 2016;33(3):301-14.
2916. Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metab Clin Exp*. 2018;84:11-27.
2917. Reid KJ, Santostasi G, Baron KG, Wilson J, Kang J, Zee PC. Timing and intensity of light correlate with body weight in adults. *PLoS ONE*. 2014;9(4):e92251.
2918. Bylesjö EI, Boman K, Wetterberg L. Obesity treated with phototherapy: four case studies. *Int J Eat Disord*. 1996;20(4):443-6.
2919. Dunai A, Novak M, Chung SA, et al. Moderate exercise and bright light treatment in overweight and obese individuals. *Obesity (Silver Spring)*. 2007;15(7):1749-57.
2920. Zhang P, Tokura H. Influence of two different light intensities during daytime on endurance performance of handgrip exercise. *Eur J Appl Physiol Occup Physiol*. 1996;74(4):318-21.
2921. Danilenko KV, Mustafina SV, Pechenkina EA. Bright light for weight loss: results of a controlled crossover trial. *Obes Facts*. 2013;6(1):28-38.

2922. Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. Effect of sunlight and season on serotonin turnover in the brain. *Lancet*. 2002;360(9348):1840-2.
2923. Stoica E, Enulescu O. Catecholamine response to light in migraine. *Cephalalgia*. 1988;8(1):31-6.
2924. Ryan DH. Use of sibutramine and other noradrenergic and serotonergic drugs in the management of obesity. *Endocrine*. 2000;13(2):193-9.
2925. de Castro JM. Seasonal rhythms of human nutrient intake and meal pattern. *Physiol Behav*. 1991;50(1):243-8.
2926. Garaulet M, Ordovás JM, Madrid JA. The chronobiology, etiology and pathophysiology of obesity. *Int J Obes (Lond)*. 2010;34(12):1667-83.
2927. Gangwisch JE. Invited commentary: nighttime light exposure as a risk factor for obesity through disruption of circadian and circannual rhythms. *Am J Epidemiol*. 2014;180(3):251-3.
2928. de Castro JM. Seasonal rhythms of human nutrient intake and meal pattern. *Physiol Behav*. 1991;50(1):243-8.
2929. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162:656-62.
2930. Laermans J, Depoortere I. Chronobesity: role of the circadian system in the obesity epidemic. *Obes Rev*. 2016;17(2):108-25.
2931. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev*. 2002; (2):CD001520.
2932. Wolden-Hanson T, Mitton DR, McCants RL, et al. Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. *Endocrinology*. 2000;141(2):487-97.
2933. Favero G, Stacchiotti A, Castrezzati S, et al. Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice. *Nutr Res*. 2015;35(10):891-900.
2934. Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, et al. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. *Bipolar Disord*. 2014;16(4):410-21.
2935. Modabbernia A, Heidari P, Soleimani R, et al. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. *J Psychiatr Res*. 2014;53:133-40.
2936. Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, et al. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. *Bipolar Disord*. 2014;16(4):410-21.
2937. Chojnacki C, Walecka-Kapica E, Klupinska G, Pawlowicz M, Blonska A, Chojnacki J. Effects of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women. *J Physiol Pharmacol*. 2015;66(5):665-71.
2938. Gonçalves AL, Martini Ferreira A, Ribeiro RT, et al. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry*. 2016;87:1127-32.
2939. Mesri Alamdari N, Mahdavi R, Roshanravan N, Lotfi Yaghin N, Ostadrahimi AR, Faramarzi E. A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. *Horm Metab Res*. 2015;47(7):504-8.
2940. Lathrop NJ, Lentz M. Melatonin, light therapy, and jet lag. *Air Med J*. 2001;20(5):30-4.
2941. Reilly T, Waterhouse J, Edwards B. Some chronobiological and physiological problems associated with long-distance journeys. *Travel Med Infect Dis*. 2009;7(2):88-101.
2942. Grigg-Damberger MM, Lanakieva D. Poor quality control of over-the-counter melatonin: what they say is often not what you get. *J Clin Sleep Med*. 2017;13(2):163-5.
2943. Reiter RJ. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr Rev*. 1991;12(2):151-80.
2944. Reilly T, Waterhouse J, Edwards B. Some chronobiological and physiological problems associated with long-distance journeys. *Travel Med Infect Dis*. 2009;7(2):88-101.
2945. Grigg-Damberger MM, Lanakieva D. Poor quality control of over-the-counter melatonin: what they say is often not what you get. *J Clin Sleep Med*. 2017;13(2):163-5.
2946. Melatonin. *Med Lett Drugs Ther*. 1995;37(962):111-2.
2947. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev*. 2002; (2):CD001520.
2948. Naylor S, Johnson KL, Williamson BL, Klarskov K, Gleich GJ. Structural characterization of contaminants in commercial preparations of melatonin by on-line HPLC-electrospray ionization-tandem mass spectrometry. *Adv Exp Med Biol*. 1999;467:769-77.
2949. Williamson B, Tomlinson A, Naylor S, Gleich G. Contaminants in commercial preparations of melatonin. *Mayo Clin Proc*. 1997;72(11):1094-5.
2950. Reilly T, Waterhouse J, Edwards B. Some chronobiological and physiological problems associated with long-distance journeys. *Travel Med Infect Dis*. 2009;7(2):88-101.
2951. Feng X, Wang M, Zhao Y, Han P, Dai Y. Melatonin from different fruit sources, functional roles, and analytical methods. *Trends Food Sci Technol*. 2014;37(1):21-31.
2952. Oba S, Nakamura K, Sahashi Y, Hattori A, Nagata C. Consumption of vegetables alters morning urinary 6-sulfatoxymelatonin concentration. *J Pineal Res*. 2008;45(1):17-23.
2953. Sae-Teaw M, Johns J, Johns NP, Subongkot S. Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers. *J Pineal Res*. 2013;55(1):58-64.
2954. Tan DX, Zanghi BM, Manchester LC, Reiter RJ. Melatonin identified in meats and other food stuffs: potentially nutritional impact. *J Pineal Res*. 2014;57(2):213-8.
2955. Brown PN, Turi CE, Shipley PR, et al. Comparisons of large (*Vaccinium macrocarpon* Ait.) and small (*Vaccinium oxycoccos* L., *Vaccinium vitisidaea* L.) cranberry in British Columbia by phytochemical determination, antioxidant potential, and metabolomic profiling with chemometric analysis. *Planta Med*. 2012;78:630-40.

2956. Kirakosyan A, Seymour E, Llanes D, Kaufman P, Bolling S. Chemical profile and antioxidant capacities of tart cherry products. *Food Chem.* 2008;115(1):20-5.
2957. Oladi E, Mohamadi M, Shamspur T, Mostafavi A. Spectrofluorimetric determination of melatonin in kernels of four different Pistacia varieties after ultrasound-assisted solid-liquid extraction. *Spectrochim Acta A Mol Biomol Spectrosc.* 2014;132:326-9.
2958. Oladi E, Mohamadi M, Shamspur T, Mostafavi A. Spectrofluorimetric determination of melatonin in kernels of four different Pistacia varieties after ultrasound-assisted solid-liquid extraction. *Spectrochim Acta A Mol Biomol Spectrosc.* 2014;132:326-9.
2959. Lathrop NJ, Lentz M. Melatonin, light therapy, and jet lag. *Air Med J.* 2001;20(5):30-4.
2960. Oladi E, Mohamadi M, Shamspur T, Mostafavi A. "Expression of Concern to Spectrofluorimetric Determination of Melatonin in Kernels of Four Different Pistacia Varieties after Ultrasound-Assisted Solid-Liquid Extraction" [Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 132 (2014) 326-329]. *Spectrochim Acta A Mol Biomol Spectrosc.* 2019;217:322.
2961. Almoosawi S, Vingeliene S, Karagounis LG, Pot GK. Chrono-nutrition: a review of current evidence from observational studies on global trends in time-of-day of energy intake and its association with obesity. *Proc Nutr Soc.* 2016;75(4):487-500.
2962. Lopez-Minguez J, Gómez-Abellán P, Garaulet M. Circadian rhythms, food timing and obesity. *Proc Nutr Soc.* 2016;75(4):501-11.
2963. DiMeglio DP, Mattes RD. Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes Relat Metab Disord.* 2000;24(6):794-800.
2964. Martens MJ, Westerterp-Plantenga MS. Mode of consumption plays a role in alleviating hunger and thirst. *Obesity (Silver Spring).* 2012;20(3):517-24.
2965. Stafleu A, Zijlstra N, Hogenkamp P, Mars M. Texture and diet related behavior: a focus on satiety and satiation. In: Preedy V, Watson R, Martin C, eds. *Handbook of Behavior, Food and Nutrition.* New York: Springer; 2011:133-42.
2966. Smit HJ, Kemsley EK, Tapp HS, Henry CJ. Does prolonged chewing reduce food intake? Fletcherism revisited. *Appetite.* 2011;57(1):295-8.
2967. Clegg ME, Ranawana V, Shafat A, Henry CJ. Soups increase satiety through delayed gastric emptying yet increased glycaemic response. *Eur J Clin Nutr.* 2013;67(1):8-11.
2968. Flood JE, Rolls BJ. Soup preloads in a variety of forms reduce meal energy intake. *Appetite.* 2007;49(3):626-34.
2969. Mattes R. Soup and satiety. *Physiol Behav.* 2005;83(5):739-47.
2970. Smit HJ, Kemsley EK, Tapp HS, Henry CJ. Does prolonged chewing reduce food intake? Fletcherism revisited. *Appetite.* 2011;57(1):295-8.
2971. Wooley O, Wooley S, Dunham R. Can calories be perceived and do they affect hunger in obese and nonobese humans? *J Comp Physiol Psychol.* 1972;80(2):250-8.
2972. Rozin P, Dow S, Moscovitch M, Rajaram S. What causes humans to begin and end a meal? A role for memory for what has been eaten, as evidenced by a study of multiple meal eating in amnesic patients. *Psychol Sci.* 1998;9(5):392-6.
2973. Crum AJ, Corbin WR, Brownell KD, Salovey P. Mind over milkshakes: mindsets, not just nutrients, determine ghrelin response. *Health Psychol.* 2011;30(4):424-9.
2974. de Graaf C. Why liquid energy results in overconsumption. *Proc Nutr Soc.* 2011;70(2):162-70.
2975. Martens MJ, Westerterp-Plantenga MS. Mode of consumption plays a role in alleviating hunger and thirst. *Obesity (Silver Spring).* 2012;20(3):517-24.
2976. Conklin MT, Lambert LG, Anderson JB. How long does it take students to eat lunch? A summary of three studies. *J Child Nutr Manag.* 2002;26(2).
2977. Andrade AM, Greene GW, Melanson KJ. Eating slowly led to decreases in energy intake within meals in healthy women. *J Am Diet Assoc.* 2008;108(7):1186-91.
2978. Kokkinos A, le Roux CW, Alexiadou K, et al. Eating slowly increases the postprandial response of the anorexigenic gut hormones, peptide YY and glucagon-like peptide-1. *J Clin Endocrinol Metab.* 2010;95(1):333-7.
2979. Harvard T.H. Chan School of Public Health. Healthy weight checklist. Available at: <https://www.hsph.harvard.edu/obesity-prevention-source/diet-lifestyle-to-prevent-obesity>. Accessed April 9, 2019.
2980. Joseph A. Joey Chestnut ate an absurd number of calories from his record-breaking 72 hot dogs. For the win. *USA Today.* Published July 4, 2017. Available at: <https://ftw.usatoday.com/2017/07/joey-chestnut-72-hot-dogs-nathans-calories-nutrition-eating-contest-video-facts>. Accessed April 9, 2019.
2981. Walike BC, Jordan HA, Stellar E. Preloading and the regulation of food intake in man. *J Comp Physiol Psychol.* 1969;68(3):327-33.
2982. Andrade AM, Greene GW, Melanson KJ. Eating slowly led to decreases in energy intake within meals in healthy women. *J Am Diet Assoc.* 2008;108(7):1186-91.
2983. Viskaal-van Dongen M, Kok FJ, de Graaf C. Eating rate of commonly consumed foods promotes food and energy intake. *Appetite.* 2011;56(1):25-31.
2984. Ohkuma T, Hirakawa Y, Nakamura U, Kiyohara Y, Kitazono T, Ninomiya T. Association between eating rate and obesity: a systematic review and meta-analysis. *Int J Obes (Lond).* 2015;39(11):1589-96.
2985. Spiegel T, Wadden T, Foster G. Objective measurement of eating rate during behavioral treatment of obesity. *Behav Ther.* 1991;22(1):61-7.
2986. Yeomans MR, Gray RW, Mitchell CJ, True S. Independent effects of palatability and within-meal pauses on intake and appetite ratings in human volunteers. *Appetite.* 1997;29(1):61-76.
2987. Andrade AM, Greene GW, Melanson KJ. Eating slowly led to decreases in energy intake within meals in healthy women. *J Am Diet Assoc.* 2008;108(7):1186-91.
2988. Whorton JC. "Physiologic optimism": Horace Fletcher and hygienic ideology in progressive America. *Bull Hist Med.* 1981;55(1):59-87.
2989. Smit HJ, Kemsley EK, Tapp HS, Henry CJ. Does prolonged chewing reduce food intake? Fletcherism revisited. *Appetite.* 2011;57(1):295-8.

2990. Smit HJ, Kemsley EK, Tapp HS, Henry CJ. Does prolonged chewing reduce food intake? Fletcherism revisited. *Appetite*. 2011;57(1):295-8.
2991. Li J, Zhang N, Hu L, et al. Improvement in chewing activity reduces energy intake in one meal and modulates plasma gut hormone concentrations in obese and lean young Chinese men. *Am J Clin Nutr*. 2011;94(3):709-16.
2992. Smit HJ, Kemsley EK, Tapp HS, Henry CJ. Does prolonged chewing reduce food intake? Fletcherism revisited. *Appetite*. 2011;57(1):295-8.
2993. Fukuda H, Saito T, Mizuta M, et al. Chewing number is related to incremental increases in body weight from 20 years of age in Japanese middle-aged adults. *Gerodontology*. 2013;30(3):214-9.
2994. Forde CG, Leong C, Chia-Ming E, McCrickerd K. Fast or slow-foods? Describing natural variations in oral processing characteristics across a wide range of Asian foods. *Food Funct*. 2017;8(2):595-606.
2995. Zhu Y, Hollis JH. Relationship between chewing behavior and body weight status in fully dentate healthy adults. *Int J Food Sci Nutr*. 2015;66(2):135-9.
2996. Zhu Y, Hollis JH. Increasing the number of chews before swallowing reduces meal size in normal-weight, overweight, and obese adults. *J Acad Nutr Diet*. 2014;114(6):926-31.
2997. Zhu Y, Hollis JH. Increasing the number of chews before swallowing reduces meal size in normal-weight, overweight, and obese adults. *J Acad Nutr Diet*. 2014;114(6):926-31.
2998. Hollis JH. The effect of mastication on food intake, satiety and body weight. *Physiol Behav*. 2018;193(Pt B):242-5.
2999. Zhu Y, Hsu WH, Hollis JH. Increased number of chews during a fixed-amount meal suppresses postprandial appetite and modulates glycemic response in older males. *Physiol Behav*. 2014;133:136-40.
3000. Higgs S, Jones A. Prolonged chewing at lunch decreases later snack intake. *Appetite*. 2013;62:91-5.
3001. Higgs S, Jones A. Prolonged chewing at lunch decreases later snack intake. *Appetite*. 2013;62:91-5.
3002. Smeets PA, Erkner A, de Graaf C. Cephalic phase responses and appetite. *Nutr Rev*. 2010;68(11):643-55.
3003. Spetter MS, Mars M, Viergever MA, de Graaf C, Smeets PA. Taste matters—effects of bypassing oral stimulation on hormone and appetite responses. *Physiol Behav*. 2014;137:9-17.
3004. Cecil JE, Francis J, Read NW. Relative contributions of intestinal, gastric, oro-sensory influences and information to changes in appetite induced by the same liquid meal. *Appetite*. 1998;31(3):377-90.
3005. Robertson MD, Jackson KG, Williams CM, Fielding BA, Frayn KN. Prolonged effects of modified sham feeding on energy substrate mobilization. *Am J Clin Nutr*. 2001;73(1):111-7.
3006. Swithers SE, Martin AA, Davidson TL. High-intensity sweeteners and energy balance. *Physiol Behav*. 2010;100(1):55-62.
3007. Wijlens AG, Erkner A, Alexander E, Mars M, Smeets PA, de Graaf C. Effects of oral and gastric stimulation on appetite and energy intake. *Obesity (Silver Spring)*. 2012;20(11):2226-32.
3008. Viskaal-van Dongen M, Kok FJ, de Graaf C. Eating rate of commonly consumed foods promotes food and energy intake. *Appetite*. 2011;56(1):25-31.
3009. Agricultural Research Service, United States Department of Agriculture. Basic report: 09003, apples, raw, with skin (includes foods for USDA's Food Distribution Program). National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/09003>. Accessed April 9, 2019.
3010. Agricultural Research Service, United States Department of Agriculture. Basic report: 09016, apple juice, canned or bottled, unsweetened, without added ascorbic acid. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/09016>. Accessed April 9, 2019.
3011. De Jonge L, Agoues I, Garrel D. Decreased thermogenic response to food with intragastric vs. oral feeding. *Am J Physiol Endocrinol Metab*. 1991;260(2):E238-42.
3012. Brondel L, Fricker J, Fantino M. Postprandial thermogenesis and alimentary sensory stimulation in human subjects. *Int J Obes Relat Metab Disord*. 1999;23(1):34-40.
3013. LeBlanc J, Cabanac M, Samson P. Reduced postprandial heat production with gavage as compared with meal feeding in human subjects. *Am J Physiol*. 1984;246(1 Pt 1):E95-101.
3014. De Jonge L, Agoues I, Garrel D. Decreased thermogenic response to food with intragastric vs. oral feeding. *Am J Physiol Endocrinol Metab*. 1991;260(2):E238-42.
3015. Toyama K, Zhao X, Kuranuki S, et al. The effect of fast eating on the thermic effect of food in young Japanese women. *Int J Food Sci Nutr*. 2015;66(2):140-7.
3016. Hamada Y, Kashima H, Hayashi N. The number of chews and meal duration affect diet-induced thermogenesis and splanchnic circulation. *Obesity (Silver Spring)*. 2014;22(5):E62-9.
3017. Komai N, Motokubota N, Suzuki M, Hayashi I, Moritani T, Nagai N. Thorough mastication prior to swallowing increases postprandial satiety and the thermic effect of a meal in young women. *J Nutr Sci Vitaminol*. 2016;62(5):288-94.
3018. Bolhuis DP, Lakemond CM, de Wijk RA, Luning PA, de Graaf C. Both longer oral sensory exposure to and higher intensity of saltiness decrease ad libitum food intake in healthy normal-weight men. *J Nutr*. 2011;141(12):2242-8.
3019. Bolhuis DP, Lakemond CM, de Wijk RA, Luning PA, de Graaf C. Both longer oral sensory exposure to and higher intensity of saltiness decrease ad libitum food intake in healthy normal-weight men. *J Nutr*. 2011;141(12):2242-8.
3020. Weijzen PL, Smeets PA, de Graaf C. Sip size of orangeade: effects on intake and sensory-specific satiation. *Br J Nutr*. 2009;102(7):1091-7.
3021. Zijlstra N, de Wijk RA, Mars M, Stafleu A, de Graaf C. Effect of bite size and oral processing time of a semisolid food on satiation. *Am J Clin Nutr*. 2009;90(2):269-75.
3022. Leveille G, McMahon K, Alcantara E, Zibell S. Benefits of chewing gum: oral health and beyond. *Nutr Today*. 2008;43(2):75-81.
3023. Levine J, Baukol P, Pavlidis I. The energy expended in chewing gum. *N Engl J Med*. 1999;341(27):2100.
3024. Kresge DL, Melanson K. Chewing gum increases energy expenditure before and after controlled breakfasts. *Appl Physiol Nutr Metab*. 2015;40(4):401-6.
3025. Levine J, Baukol P, Pavlidis I. The energy expended in chewing gum. *N Engl J Med*. 1999;341(27):2100.
3026. Florman DA. More on chewing gum. *N Engl J Med*. 2000;342(20):1531-2.
3027. Levine J, Baukol P, Pavlidis I. The energy expended in chewing gum. *N Engl J Med*. 1999;341(27):2100.

3028. Hasegawa Y, Sakagami J, Ono T, Hori K, Zhang M, Maeda Y. Circulatory response and autonomic nervous activity during gum chewing. *Eur J Oral Sci.* 2009;117(4):470-3.
3029. Hamada Y, Yanaoka T, Kashiwabara K, et al. The effects of gum chewing while walking on physical and physiological functions. *J Phys Ther Sci.* 2018;30(4):625-9.
3030. Komai N, Motokubota N, Suzuki M, Hayashi I, Moritani T, Nagai N. Thorough mastication prior to swallowing increases postprandial satiety and the thermic effect of a meal in young women. *J Nutr Sci Vitaminol.* 2016;62(5):288-94.
3031. Kresge DL, Melanson K. Chewing gum increases energy expenditure before and after controlled breakfasts. *Appl Physiol Nutr Metab.* 2015;40(4):401-6.
3032. Hamada Y, Miyaji A, Hayashi N. Effect of postprandial gum chewing on diet-induced thermogenesis. *Obesity (Silver Spring).* 2016;24(4):878-85.
3033. Melanson KJ, Kresge DL. Chewing gum decreases energy intake at lunch following a controlled breakfast. *Appetite.* 2017;118:1-7.
3034. Swoboda C, Temple JL. Acute and chronic effects of gum chewing on food reinforcement and energy intake. *Eat Behav.* 2013;14(2):149-56.
3035. Julis RA, Mattes RD. Influence of sweetened chewing gum on appetite, meal patterning and energy intake. *Appetite.* 2007;48(2):167-75.
3036. Mattes RD, Considine RV. Oral processing effort, appetite and acute energy intake in lean and obese adults. *Physiol Behav.* 2013;120:173-81.
3037. Tordoff MG, Alleva AM. Oral stimulation with aspartame increases hunger. *Physiol Behav.* 1990;47(3):555-9.
3038. Julis RA, Mattes RD. Influence of sweetened chewing gum on appetite, meal patterning and energy intake. *Appetite.* 2007;48(2):167-75.
3039. Melanson KJ, Kresge DL. Chewing gum decreases energy intake at lunch following a controlled breakfast. *Appetite.* 2017;118:1-7.
3040. Swoboda C, Temple JL. Acute and chronic effects of gum chewing on food reinforcement and energy intake. *Eat Behav.* 2013;14(2):149-56.
3041. Allison A, Chambers D. Effects of residual toothpaste flavor on flavor profiles of common foods and beverages. *J Sens Stud.* 2005;20(2):167-86.
3042. Hutchings SC, Horner KM, Dible VA, Grigor JMV, O'Riordan D. Modification of aftertaste with a menthol mouthwash reduces food wanting, liking, and ad libitum intake of potato crisps. *Appetite.* 2017;108:57-67.
3043. Swoboda C, Temple JL. Acute and chronic effects of gum chewing on food reinforcement and energy intake. *Eat Behav.* 2013;14(2):149-56.
3044. Shikany JM, Thomas AS, McCubrey RO, Beasley TM, Allison DB. Randomized controlled trial of chewing gum for weight loss. *Obesity (Silver Spring).* 2012;20(3):547-52.
3045. Melanson KJ, Kresge DL. Chewing gum decreases energy intake at lunch following a controlled breakfast. *Appetite.* 2017;118:1-7.
3046. Weijzen PL, Smeets PA, de Graaf C. Sip size of orangeade: effects on intake and sensory-specific satiety. *Br J Nutr.* 2009;102(7):1091-7.
3047. Melanson KJ, Kresge DL. Chewing gum decreases energy intake at lunch following a controlled breakfast. *Appetite.* 2017;118:1-7.
3048. Hyams JS. Sorbitol intolerance: an unappreciated cause of functional gastrointestinal complaints. *Gastroenterology.* 1983;84(1):30-3.
3049. Greaves RR, Bown RL, Farthing MJ, Brown RL. An air stewardess with puzzling diarrhoea. *Lancet.* 1996;348(9040):1488.
3050. Bauditz J, Norman K, Biering H, Lochs H, Pirlich M. Severe weight loss caused by chewing gum. *BMJ.* 2008;336(7635):96-7.
3051. Hyams JS. Sorbitol intolerance: an unappreciated cause of functional gastrointestinal complaints. *Gastroenterology.* 1983;84(1):30-3.
3052. Shikany JM, Thomas AS, McCubrey RO, Beasley TM, Allison DB. Randomized controlled trial of chewing gum for weight loss. *Obesity (Silver Spring).* 2012;20(3):547-52.
3053. Bolhuis DP, Forde CG, Cheng Y, Xu H, Martin N, de Graaf C. Slow food: sustained impact of harder foods on the reduction in energy intake over the course of the day. *PLoS ONE.* 2014;9(4):e93370.
3054. de Graaf C, Kok FJ. Slow food, fast food and the control of food intake. *Nat Rev Endocrinol.* 2010;6(5):290-3.
3055. Hogenkamp PS, Mars M, Stafleu A, de Graaf C. Intake during repeated exposure to low-and high-energy-dense yogurts by different means of consumption. *Am J Clin Nutr.* 2010;91(4):841-7.
3056. de Wijk RA, Zijlstra N, Mars M, de Graaf C, Prinz JF. The effects of food viscosity on bite size, bite effort and food intake. *Physiol Behav.* 2008;95(3):527-32.
3057. Zijlstra N, Mars M, de Wijk RA, Westerterp-Plantenga MS, de Graaf C. The effect of viscosity on ad libitum food intake. *Int J Obes (Lond).* 2008;32(4):676-83.
3058. Camps G, Mars M, de Graaf C, Smeets PA. Empty calories and phantom fullness: a randomized trial studying the relative effects of energy density and viscosity on gastric emptying determined by MRI and satiety. *Am J Clin Nutr.* 2016;104(1):73-80.
3059. McCrickerd K, Lim CM, Leong C, Chia EM, Forde CG. Texture-based differences in eating rate reduce the impact of increased energy density and large portions on meal size in adults. *J Nutr.* 2017;147(6):1208-17.
3060. Tang J, Larsen DS, Ferguson LR, James BJ. The effect of textural complexity of solid foods on satiety. *Physiol Behav.* 2016;163:17-24.
3061. Hogenkamp P, Schiöth H. Effect of oral processing behaviour on food intake and satiety. *Trends Food Sci Technol.* 2013;34(1):67-75.
3062. Higgs S, Jones A. Prolonged chewing at lunch decreases later snack intake. *Appetite.* 2013;62:91-5.
3063. Hollis JH. The effect of mastication on food intake, satiety and body weight. *Physiol Behav.* 2018;193(Pt B):242-5.
3064. de Graaf C, Kok FJ. Slow food, fast food and the control of food intake. *Nat Rev Endocrinol.* 2010;6(5):290-3.

3065. Viskaal-van Dongen M, Kok FJ, de Graaf C. Eating rate of commonly consumed foods promotes food and energy intake. *Appetite*. 2011;56(1):25-31.
3066. Agricultural Research Service, United States Department of Agriculture. Basic report: 01102, milk, chocolate, fluid, commercial, whole, with added vitamin A and vitamin D. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/01102>. Accessed April 9, 2019.
3067. Agricultural Research Service, United States Department of Agriculture. Basic report: 11124, carrots, raw. National Nutrient Database for Standard Reference Legacy Release. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/11124>. Accessed April 9, 2019.
3068. Viskaal-van Dongen M, Kok FJ, de Graaf C. Eating rate of commonly consumed foods promotes food and energy intake. *Appetite*. 2011;56(1):25-31.
3069. Duncan KH, Bacon JA, Weinsier RL. The effects of high and low energy density diets on satiety, energy intake, and eating time of obese and nonobese subjects. *Am J Clin Nutr*. 1983;37(5):763-7.
3070. Norris DJ, Weinsier RL. The time-calorie displacement approach for long-term weight control. One aspect of the nutrition clinic. *Ala J Med Sci*. 1982;19(4):399-401.
3071. Norris DJ, Weinsier RL. The time-calorie displacement approach for long-term weight control. One aspect of the nutrition clinic. *Ala J Med Sci*. 1982;19(4):399-401.
3072. Heimbürger DC, Allison DB, Goran MI, et al. A *festchrift* for Roland L. Weinsier: nutrition scientist, educator, and clinician. *Obes Res*. 2003;11(10):1246-62.
3073. Weinsier RL, Johnston MH, Doleys DM, Bacon JA. Dietary management of obesity: evaluation of the time-energy displacement diet in terms of its efficacy and nutritional adequacy for long-term weight control. *Br J Nutr*. 1982;47(3):367-79.
3074. Weinsier RL, Johnston MH, Doleys DM, Bacon JA. Dietary management of obesity: evaluation of the time-energy displacement diet in terms of its efficacy and nutritional adequacy for long-term weight control. *Br J Nutr*. 1982;47(3):367-79.
3075. Chen Y, Henson S, Jackson AB, Richards JS. Obesity intervention in persons with spinal cord injury. *Spinal Cord*. 2006;44(2):82-91.
3076. Morgan S. Rational weight loss programs: a clinician's guide. *J Am Coll Nutr*. 1989;8(3):186-94.
3077. Robinson E, Almiron-Roig E, Rutters F, et al. A systematic review and meta-analysis examining the effect of eating rate on energy intake and hunger. *Am J Clin Nutr*. 2014;100(1):123-51.
3078. Sun L, Ranawana DV, Tan WJ, Quek YC, Henry CJ. The impact of eating methods on eating rate and glycemic response in healthy adults. *Physiol Behav*. 2015;139:505-10.
3079. Kokkinos A, le Roux CW, Alexiadou K, et al. Eating slowly increases the postprandial response of the anorexigenic gut hormones, peptide YY and glucagon-like peptide-1. *J Clin Endocrinol Metab*. 2010;95(1):333-7.
3080. 2011 Food & Health Survey: consumer attitudes toward food safety, nutrition & health. International Food Information Council Foundation. Published May 5, 2011. Available at: https://www.foodinsight.org/2011_food_health_survey_consumer_attitudes_toward_food_safety_nutrition_health. Accessed April 9, 2019.
3081. Speakman JR, Selman C. Physical activity and resting metabolic rate. *Proc Nutr Soc*. 2003;62(3):621-34.
3082. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest*. 1986;78(6):1568-78.
3083. Levine JA. Nonexercise activity thermogenesis—liberating the life-force. *J Intern Med*. 2007;262(3):273-87.
3084. Thomas DM, Kyle TK, Stanford FC. The gap between expectations and reality of exercise-induced weight loss is associated with discouragement. *Prev Med*. 2015;81:357-60.
3085. Thomas DM, Kyle TK, Stanford FC. The gap between expectations and reality of exercise-induced weight loss is associated with discouragement. *Prev Med*. 2015;81:357-60.
3086. Kelly AS. Debunking the myth: exercise is an effective weight loss treatment. *Exerc Sport Sci Rev*. 2015;43(1):2.
3087. Flatt JP. Issues and misconceptions about obesity. *Obesity (Silver Spring)*. 2011;19(4):676-86.
3088. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine position stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459-71.
3089. Myers A, Gibbons C, Finlayson G, Blundell J. Associations among sedentary and active behaviours, body fat and appetite dysregulation: investigating the myth of physical inactivity and obesity. *Br J Sports Med*. 2017;51(21):1540-4.
3090. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev*. 2006; (4):CD003817.
3091. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. *J Gastroenterol Hepatol*. 2013;28 Suppl 4:59-63.
3092. Bishay RH, Kormas N. Halving your cake and eating it, too: a case-based discussion and review of metabolic rehabilitation for obese adults with diabetes. *Curr Diabetes Rev*. 2018;14(3):246-56.
3093. Bishay RH, Kormas N. Halving your cake and eating it, too: a case-based discussion and review of metabolic rehabilitation for obese adults with diabetes. *Curr Diabetes Rev*. 2018;14(3):246-56.
3094. Williamson PJ, Atkinson G, Batterham AM. Inter-individual differences in weight change following exercise interventions: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2018;19(7):960-75.
3095. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev*. 2006; (4):CD003817.
3096. Williamson PJ, Atkinson G, Batterham AM. Inter-individual differences in weight change following exercise interventions: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev*. 2018;19(7):960-75.
3097. von Loeffelholz C. The role of non-exercise activity thermogenesis in human obesity. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Endotext [Internet]*. South Dartmouth, MA: MDText.com, Inc.; 2000-2018.
3098. Foright RM, Presby DM, Sherk VD, et al. Is regular exercise an effective strategy for weight loss maintenance? *Physiol Behav*. 2018;188:86-93.

3099. Foright RM, Presby DM, Sherk VD, et al. Is regular exercise an effective strategy for weight loss maintenance? *Physiol Behav.* 2018;188:86-93.
3100. Speakman JR, Selman C. Physical activity and resting metabolic rate. *Proc Nutr Soc.* 2003;62(3):621-34.
3101. Kelly AS. Debunking the myth: exercise is an effective weight loss treatment. *Exerc Sport Sci Rev.* 2015;43(1):2.
3102. Shah S, O'Byrne M, Wilson M, Wilson T. Research of a holiday kind: elevators or stairs? *CMAJ.* 2011;183(18):E1353-5.
3103. Dowray S, Swartz JJ, Braxton D, Viera AJ. Potential effect of physical activity based menu labels on the calorie content of selected fast food meals. *Appetite.* 2013;62:173-81.
3104. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *N Engl J Med.* 2013;368(5):446-54.
3105. Bohlen JG, Held JP, Sanderson MO, Patterson RP. Heart rate, rate-pressure product, and oxygen uptake during four sexual activities. *Arch Intern Med.* 1984;144(9):1745-8.
3106. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. *J Gastroenterol Hepatol.* 2013;28 Suppl 4:59-63.
3107. Kelly AS. Debunking the myth: exercise is an effective weight loss treatment. *Exerc Sport Sci Rev.* 2015;43(1):2.
3108. McCaig DC, Hawkins LA, Rogers PJ. Licence to eat: information on energy expended during exercise affects subsequent energy intake. *Appetite.* 2016;107:323-9.
3109. Werle C, Wansink B, Payne C. Is it fun or exercise? The framing of physical activity biases subsequent snacking. *Mark Lett.* 2015;26(4):691-702. *Note:* The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
3110. Werle CO, Wansink B, Payne CR. Just thinking about exercise makes me serve more food. Physical activity and calorie compensation. *Appetite.* 2011;56(2):332-5. *Note:* The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
3111. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol.* 2013;42(6):1831-6.
3112. Fedewa MV, Hathaway ED, Williams TD, Schmidt MD. Effect of exercise training on non-exercise physical activity: a systematic review and meta-analysis of randomized controlled trials. *Sports Med.* 2017;47(6):1171-82.
3113. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol.* 2013;42(6):1831-6.
3114. Stensel D, King J, Thackray A. Role of physical activity in regulating appetite and body fat. *Nutr Bull.* 2016;41(4):314-22.
3115. Blundell J. Physical activity and appetite control: can we close the energy gap? *Nutr Bull.* 2011;36(3):356-66.
3116. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol.* 2013;42(6):1831-6.
3117. Shook R. Obesity and energy balance: what is the role of physical activity? *Expert Rev Endocrinol Metab.* 2016;11(6):511-20.
3118. Flack KD, Ufholz KE, Johnson LK, Fitzgerald JS, Roemmich JN. Energy compensation in response to aerobic exercise training in overweight adults. *Am J Physiol Regul Integr Comp Physiol.* 2018;315(4):R619-26.
3119. Flack KD, Ufholz KE, Johnson LK, Fitzgerald JS, Roemmich JN. Energy compensation in response to aerobic exercise training in overweight adults. *Am J Physiol Regul Integr Comp Physiol.* 2018;315(4):R619-26.
3120. Shook R. Obesity and energy balance: what is the role of physical activity? *Expert Rev Endocrinol Metab.* 2016;11(6):511-20.
3121. Shook R. Obesity and energy balance: what is the role of physical activity? *Expert Rev Endocrinol Metab.* 2016;11(6):511-20.
3122. White LJ, Dressendorfer RH, Holland E, McCoy SC, Ferguson MA. Increased caloric intake soon after exercise in cold water. *Int J Sport Nutr Exerc Metab.* 2005;15(1):38-47.
3123. Gwinup G. Weight loss without dietary restriction: efficacy of different forms of aerobic exercise. *Am J Sports Med.* 1987;15(3):275-9.
3124. Deighton K, Stensel DJ. Creating an acute energy deficit without stimulating compensatory increases in appetite: is there an optimal exercise protocol? *Proc Nutr Soc.* 2014;73(2):352-8.
3125. King NA, Blundell JE. High-fat foods overcome the energy expenditure induced by high-intensity cycling or running. *Eur J Clin Nutr.* 1995;49(2):114-23.
3126. King JA, Wasse LK, Stensel DJ. The acute effects of swimming on appetite, food intake, and plasma acylated ghrelin. *J Obes.* 2011;2011:1-8.
3127. Flynn MG, Costill DL, Kirwan JP, et al. Fat storage in athletes: metabolic and hormonal responses to swimming and running. *Int J Sports Med.* 1990;11(6):433-40.
3128. Gwinup G. Weight loss without dietary restriction: efficacy of different forms of aerobic exercise. *Am J Sports Med.* 1987;15(3):275-9.
3129. Dressendorfer RH. Effect of internal body temperature on energy intake soon after aerobic exercise. *Med Sci Sports Exerc.* 1993;S42:228.
3130. White LJ, Dressendorfer RH, Holland E, McCoy SC, Ferguson MA. Increased caloric intake soon after exercise in cold water. *Int J Sport Nutr Exerc Metab.* 2005;15(1):38-47.
3131. Crabtree DR, Blannin AK. Effects of exercise in the cold on ghrelin, PYY, and food intake in overweight adults. *Med Sci Sports Exerc.* 2015;47(1):49-57.
3132. Fisher G, Hunter GR, Allison DB. Commentary: physical activity does influence obesity risk when it actually occurs in sufficient amount. *Int J Epidemiol.* 2013;42(6):1845-8.
3133. Charlot K, Faure C, Antoine-Jonville S. Influence of hot and cold environments on the regulation of energy balance following a single exercise session: a mini-review. *Nutrients.* 2017;9(6):pii:E592.
3134. Shook R. Obesity and energy balance: what is the role of physical activity? *Expert Rev Endocrinol Metab.* 2016;11(6):511-20.
3135. Lewis SF, Hennekens CH. Regular physical activity: a "magic bullet" for the pandemics of obesity and cardiovascular disease. *Cardiology.* 2016;134(3):360-3.

3136. Paravidino VB, Mediano MF, Hoffman DJ, Sichieri R. Effect of exercise intensity on spontaneous physical activity energy expenditure in overweight boys: a crossover study. *PLoS ONE*. 2016;11(1):e0147141.
3137. Pontzer H, Durazo-Arvizu R, Dugas LR, et al. Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. *Curr Biol*. 2016;26(3):410-7.
3138. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014;99(1):14-23.
3139. Ravussin E, Danforth E. Beyond sloth—physical activity and weight gain. *Science*. 1999;283(5399):184-5.
3140. Shook R. Obesity and energy balance: what is the role of physical activity? *Expert Rev Endocrinol Metab*. 2016;11(6):511-20.
3141. Thomas DM, Bouchard C, Church T, et al. Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. *Obes Rev*. 2012;13(10):835-47.
3142. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. United States Department of Health and Human Services. Published February 2018. Available at: <https://health.gov/paguidelines/second-edition/report>. Accessed April 10, 2019.
3143. Obesity and overweight. World Health Organization. Published February 16, 2018. Available at: <http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed April 10, 2019.
3144. Puterbaugh JS. The emperor's tailors: the failure of the medical weight loss paradigm and its causal role in the obesity of America. *Diabetes Obes Metab*. 2009;11(6):557-70.
3145. Bergouignan A, Rudwill F, Simon C, Blanc S. Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. *J Appl Physiol*. 2011;111(4):1201-10.
3146. Nindl BC, Barnes BR, Alemany JA, Frykman PN, Shippee RL, Friedl KE. Physiological consequences of U.S. Army Ranger training. *Med Sci Sports Exerc*. 2007;39(8):1380-7.
3147. Pulfrey SM, Jones PJ. Energy expenditure and requirement while climbing above 6,000 m. *J Appl Physiol*. 1996;81(3):1306-11.
3148. Bouchard C, Tremblay A, Després JP, et al. The response to exercise with constant energy intake in identical twins. *Obes Res*. 1994;2(5):400-10.
3149. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459-71.
3150. Manore MM, Larson-Meyer DE, Lindsay AR, Hongu N, Houtkooper L. Dynamic energy balance: an integrated framework for discussing diet and physical activity in obesity prevention—is it more than eating less and exercising more? *Nutrients*. 2017;9(8):905.
3151. Manore M. Personal communication. July 2018.
3152. Jakicic JM, Rogers RJ, Davis KK, Collins KA. Role of physical activity and exercise in treating patients with overweight and obesity. *Clin Chem*. 2018;64(1):99-107.
3153. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report, 2008. United States Department of Health and Human Services. Published June 2008. Available at: <https://health.gov/paguidelines/2008/report>. Accessed April 10, 2019.
3154. Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, D.C.: National Academies Press; 2004.
3155. Schoeller DA, Shay K, Kushner RF. How much physical activity is needed to minimize weight gain in previously obese women? *Am J Clin Nutr*. 1997;66(3):551-6.
3156. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014;99(1):14-23.
3157. United States Department of Health and Human Services, United States Department of Agriculture. Dietary Guidelines for Americans, 2005. 6th ed. Washington, D.C.: U.S. Government Printing Office. Published January 2005. Available at: <https://health.gov/dietaryguidelines/dga2005/document/default.htm>. Accessed April 10, 2019.
3158. United States Department of Health and Human Services, United States Department of Agriculture. Appendix 1. 2015-2020 Dietary Guidelines for Americans. 8th ed. Published December 2015. Available at: <http://health.gov/dietaryguidelines/2015/guidelines>. Accessed April 10, 2019.
3159. Luke A, Cooper RS. Authors' response to commentaries on "physical activity does not influence obesity risk." *Int J Epidemiol*. 2013;42(6):1848-51.
3160. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181-8.
3161. Catenacci VA, Ogden LG, Stuht J, et al. Physical activity patterns in the National Weight Control Registry. *Obesity (Silver Spring)*. 2008;16(1):153-61.
3162. Malhotra A, Noakes T, Phinney S. It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. *Br J Sports Med*. 2015;49(15):967-8.
3163. Lewis SF, Hennekens CH. Regular physical activity: a "magic bullet" for the pandemics of obesity and cardiovascular disease. *Cardiology*. 2016;134(3):360-3.
3164. Kelly AS. Debunking the myth: exercise is an effective weight loss treatment. *Exerc Sport Sci Rev*. 2015;43(1):2.
3165. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378(9793):815-25.
3166. Thomas DM, Kyle TK, Stanford FC. The gap between expectations and reality of exercise-induced weight loss is associated with discouragement. *Prev Med*. 2015;81:357-60.
3167. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science*. 1999;283(5399):212-4.

3168. Helmholtz H. On the conservation of force; a physical memoir. In: Tyndall J, Francis W. *Scientific Memoirs, Selected from the Transactions of Foreign Academies of Science, and from Foreign Journals. Natural Philosophy, Volume 1*. London: Taylor and Francis; 1853:114-62.
3169. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science*. 1999;283(5399):212-4.
3170. Kotz CM, Perez-Leighton CE, Teske JA, Billington CJ. Spontaneous physical activity defends against obesity. *Curr Obes Rep*. 2017;6(4):362-70.
3171. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science*. 1999;283(5399):212-4.
3172. Levine JA. Non-exercise activity thermogenesis (NEAT). *Best Pract Res Clin Endocrinol Metab*. 2002;16(4):679-702.
3173. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science*. 1999;283(5399):212-4.
3174. Levine JA, Vander Weg MW, Hill JO, Klesges RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. *Arterioscler Thromb Vasc Biol*. 2006;26(4):729-36.
3175. Levine JA, McCrady SK, Lanningham-Foster LM, Kane PH, Foster RC, Manohar CU. The role of free-living daily walking in human weight gain and obesity. *Diabetes*. 2008;57(3):548-54.
3176. Levine JA. Nonexercise activity thermogenesis—liberating the life-force. *J Intern Med*. 2007;262(3):273-87.
3177. von Loeffelholz C. The role of non-exercise activity thermogenesis in human obesity. In: De Groot LJ, Chrousos G, Dungan JA, et al., eds. *Endotext [Internet]*. South Dartmouth, MA: MDText.com, Inc.; 2000-2018.
3178. Villablanca PA, Alegria JR, Mookadam F, Holmes DR, Wright RS, Levine JA. Nonexercise activity thermogenesis in obesity management. *Mayo Clin Proc*. 2015;90(4):509-19.
3179. Villablanca PA, Alegria JR, Mookadam F, Holmes DR, Wright RS, Levine JA. Nonexercise activity thermogenesis in obesity management. *Mayo Clin Proc*. 2015;90(4):509-19.
3180. McCrady-Spitzer SK, Levine JA. Nonexercise activity thermogenesis: a way forward to treat the worldwide obesity epidemic. *Surg Obes Relat Dis*. 2012;8(5):501-6.
3181. Levine JA. Nonexercise activity thermogenesis—liberating the life-force. *J Intern Med*. 2007;262(3):273-87.
3182. Sun JW, Zhao LG, Yang Y, Ma X, Wang YY, Xiang YB. Association between television viewing time and all-cause mortality: a meta-analysis of cohort studies. *Am J Epidemiol*. 2015;182(11):908-16.
3183. Rezende LFM, Sá TH, Mielke GI, Viscondi JYK, Rey-López JP, Garcia LMT. All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. *Am J Prev Med*. 2016;51(2):253-63.
3184. Rezende LFM, Sá TH, Mielke GI, Viscondi JYK, Rey-López JP, Garcia LMT. All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. *Am J Prev Med*. 2016;51(2):253-63.
3185. von Loeffelholz C. The role of non-exercise activity thermogenesis in human obesity. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Endotext [Internet]*. South Dartmouth, MA: MDText.com, Inc.; 2000-2018.
3186. Saeidifard F, Medina-Inojosa JR, Supervia M, et al. Differences of energy expenditure while sitting versus standing: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018;25(5):522-38.
3187. King PM. A comparison of the effects of floor mats and shoe in-soles on standing fatigue. *Appl Ergon*. 2002;33(5):477-84.
3188. Tüchsen F, Hannerz H, Burr H, Krause N. Prolonged standing at work and hospitalisation due to varicose veins: a 12 year prospective study of the Danish population. *Occup Environ Med*. 2005;62(12):847-50.
3189. Shuval K, Barlow CE, Finley CE, Gabriel KP, Schmidt MD, Defina LF. Standing, obesity, and metabolic syndrome: findings from the cooper center longitudinal study. *Mayo Clin Proc*. 2015;90(11):1524-32.
3190. van der Ploeg HP, Chey T, Ding D, Chau JY, Stamatakis E, Bauman AE. Standing time and all-cause mortality in a large cohort of Australian adults. *Prev Med*. 2014;69:187-91.
3191. Shrestha N, Kukkonen-Harjula KT, Verbeek JH, Ijaz S, Hermans V, Pedisic Z. Workplace interventions for reducing sitting at work. *Cochrane Database Syst Rev*. 2018;6:CD010912.
3192. Mansoubi M, Pearson N, Biddle SJ, Clemes SA. Using sit-to-stand workstations in offices: is there a compensation effect? *Med Sci Sports Exerc*. 2016;48(4):720-5.
3193. Saeidifard F, Medina-Inojosa JR, Supervia M, et al. Differences of energy expenditure while sitting versus standing: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018;25(5):522-38.
3194. Levine JA, Miller JM. The energy expenditure of using a “walk-and-work” desk for office workers with obesity. *Br J Sports Med*. 2007;41(9):558-61.
3195. Koepp GA, Moore G, Levine JA. An under-the-table leg-movement apparatus and changes in energy expenditure. *Front Physiol*. 2017;8:318.
3196. Levine JA. Nonexercise activity thermogenesis—liberating the life-force. *J Intern Med*. 2007;262(3):273-87.
3197. Levine JA, Vander Weg MW, Hill JO, Klesges RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. *Arterioscler Thromb Vasc Biol*. 2006;26(4):729-36.
3198. Commissaris DA, Könemann R, Hiemstra-Van Mastriht S, et al. Effects of a standing and three dynamic workstations on computer task performance and cognitive function tests. *Appl Ergon*. 2014;45(6):1570-8.
3199. Thompson WG, Levine JA. Productivity of transcriptionists using a treadmill desk. *Work*. 2011;40(4):473-7.
3200. McAlpine DA, Manohar CU, McCrady SK, Hensrud D, Levine JA. An office-place stepping device to promote workplace physical activity. *Br J Sports Med*. 2007;41(12):903-7.
3201. Thosar SS, Bielko SL, Mather KJ, Johnston JD, Wallace JP. Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc*. 2015;47(4):843-9.
3202. Pynt J. Rethinking design parameters in the search for optimal dynamic seating. *J Bodyw Mov Ther*. 2015;19(2):291-303.
3203. Morishima T, Restaino RM, Walsh LK, Kanaley JA, Padilla J. Prior exercise and standing as strategies to circumvent sitting-induced leg endothelial dysfunction. *Clin Sci*. 2017;131(11):1045-53.
3204. Thosar SS, Bielko SL, Mather KJ, Johnston JD, Wallace JP. Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc*. 2015;47(4):843-9.
3205. Morishima T, Restaino RM, Walsh LK, Kanaley JA, Padilla J. Prior exercise and standing as strategies to circumvent sitting-induced leg endothelial dysfunction. *Clin Sci*. 2017;131(11):1045-53.

3206. Morishima T, Restaino RM, Walsh LK, Kanaley JA, Padilla J. Prior exercise and standing as strategies to circumvent sitting-induced leg endothelial dysfunction. *Clin Sci*. 2017;131(11):1045–53.
3207. Kruse NT, Hughes WE, Benzo RM, Carr LJ, Casey DP. Workplace strategies to prevent sitting-induced endothelial dysfunction. *Med Sci Sports Exerc*. 2018;50(4):801–8.
3208. O'Sullivan K, O'Sullivan P, O'Keeffe M, O'Sullivan L, Dankaerts W. The effect of dynamic sitting on trunk muscle activation: a systematic review. *Appl Ergon*. 2013;44(4):628–35.
3209. O'Sullivan K, O'Sullivan P, O'Keeffe M, O'Sullivan L, Dankaerts W. The effect of dynamic sitting on trunk muscle activation: a systematic review. *Appl Ergon*. 2013;44(4):628–35.
3210. Koeppe GA, Moore GK, Levine JA. Chair-based fidgeting and energy expenditure. *BMJ Open Sport Exerc Med*. 2016;2(1):e000152.
3211. Koeppe GA, Moore G, Levine JA. An under-the-table leg-movement apparatus and changes in energy expenditure. *Front Physiol*. 2017;8:318.
3212. Koeppe GA, Moore GK, Levine JA. Chair-based fidgeting and energy expenditure. *BMJ Open Sport Exerc Med*. 2016;2(1):e000152.
3213. Morishima T, Restaino RM, Walsh LK, Kanaley JA, Fadel PJ, Padilla J. Prolonged sitting-induced leg endothelial dysfunction is prevented by fidgeting. *Am J Physiol Heart Circ Physiol*. 2016;311(1):H177–82.
3214. Hagger-Johnson G, Gow AJ, Burley V, Greenwood D, Cade JE. Sitting time, fidgeting, and all-cause mortality in the UK women's cohort study. *Am J Prev Med*. 2016;50(2):154–60.
3215. Thomas DM, Kyle TK, Stanford FC. The gap between expectations and reality of exercise-induced weight loss is associated with discouragement. *Prev Med*. 2015;81:357–60.
3216. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS MED*. 2012;9(11):e1001335.
3217. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541–56.
3218. Gerbild H, Larsen CM, Graugaard C, Areskoug Josefsson K. Physical activity to improve erectile function: a systematic review of intervention studies. *Sex Med*. 2018;6(2):75–89.
3219. Hardefeldt PJ, Penninkilampi R, Edirimanne S, Eslick GD. Physical activity and weight loss reduce the risk of breast cancer: a meta-analysis of 139 prospective and retrospective studies. *Clin Breast Cancer*. 2018;18(4):e601–12.
3220. Rezende LFM, Sá TH, Markozannes G, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br J Sports Med*. 2018;52(13):826–33.
3221. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541–56.
3222. Soltani S, Hunter GR, Kazemi A, Shab-Bidar S. The effects of weight loss approaches on bone mineral density in adults: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int*. 2016;27(9):2655–71.
3223. Short KR, Pratt LV, Teague AM. A single exercise session increases insulin sensitivity in normal weight and overweight/obese adolescents. *Pediatr Diabetes*. 2018;19(6):1050–7.
3224. Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ*. 2013;347:f5577.
3225. Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ*. 2013;347:f5577.
3226. Cauza E, Hanusch-Enserer U, Strasser B, et al. The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. *Arch Phys Med Rehabil*. 2005;86(8):1527–33.
3227. Rosenkilde M, Auerbach P, Reichkendler MH, Ploug T, Stallknecht BM, Sjödin A. Body fat loss and compensatory mechanisms in response to different doses of aerobic exercise—a randomized controlled trial in overweight sedentary males. *Am J Physiol Regul Integr Comp Physiol*. 2012;303(6):R571–9.
3228. Ohkawara K, Tanaka S, Miyachi M, Ishikawa-Takata K, Tabata I. A dose-response relation between aerobic exercise and visceral fat reduction: systematic review of clinical trials. *Int J Obes (Lond)*. 2007;31(12):1786–97.
3229. Jakicic JM, Rogers RJ, Davis KK, Collins KA. Role of physical activity and exercise in treating patients with overweight and obesity. *Clin Chem*. 2018;64(1):99–107.
3230. Verheggen RJ, Maessen MF, Green DJ, Hermus AR, Hopman MT, Thijssen DH. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. *Obes Rev*. 2016;17(8):664–90.
3231. Verheggen RJ, Maessen MF, Green DJ, Hermus AR, Hopman MT, Thijssen DH. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. *Obes Rev*. 2016;17(8):664–90.
3232. Vispute SS, Smith JD, LeCheminant JD, Hurley KS. The effect of abdominal exercise on abdominal fat. *J Strength Cond Res*. 2011;25(9):2559–64.
3233. Wewege MA, Thom JM, Rye KA, Parmenter BJ. Aerobic, resistance or combined training: a systematic review and meta-analysis of exercise to reduce cardiovascular risk in adults with metabolic syndrome. *Atherosclerosis*. 2018;274:162–71.
3234. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PLoS ONE*. 2013;8(2):e56415.
3235. Ismail I, Keating SE, Baker MK, Johnson NA. A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. *Obes Rev*. 2012;13(1):68–91.
3236. Roy M, Williams SM, Brown RC, et al. HIIT in the real world: outcomes from a 12-month intervention in overweight adults. *Med Sci Sports Exerc*. 2018;50(9):1818–26.
3237. Maillard F, Pereira B, Boisseau N. Effect of high-intensity interval training on total, abdominal and visceral fat mass: a meta-analysis. *Sports Med*. 2018;48(2):269–88.
3238. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev*. 2017;18(6):635–46.

3239. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev.* 2017;18(6):635-46.
3240. Ross R, Hudson R, Stotz PJ, Lam M. Effect of higher-intensity exercise on weight loss and waist circumference: a randomized trial. *Ann Intern Med.* 2015;162(5):325-34.
3241. Willis WT, Ganley KJ, Herman RM. Fuel oxidation during human walking. *Metab Clin Exp.* 2005;54(6):793-9.
3242. Wilkin LD, Cheryl A, Haddock BL. Energy expenditure comparison between walking and running in average fitness individuals. *J Strength Cond Res.* 2012;26(4):1039-44.
3243. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med.* 2014;48(16):1227-34.
3244. Morris JN, Hardman AE. Walking to health. *Sports Med.* 1997;23(5):306-32.
3245. Stamatakis E, Hamer M, Murphy MH. What Hippocrates called "man's best medicine": walking is humanity's path to a better world. *Br J Sports Med.* 2018;52(12):753-4.
3246. Mabire L, Mani R, Liu L, Mulligan H, Baxter D. The influence of age, sex and body mass index on the effectiveness of brisk walking for obesity management in adults: a systematic review and meta-analysis. *J Phys Act Health.* 2017;14(5):389-407.
3247. Schutz Y, Nguyen DM, Byrne NM, Hills AP. Effectiveness of three different walking prescription durations on total physical activity in normal-and overweight women. *Obes Facts.* 2014;7(4):264-73.
3248. Schutz Y, Nguyen DM, Byrne NM, Hills AP. Effectiveness of three different walking prescription durations on total physical activity in normal-and overweight women. *Obes Facts.* 2014;7(4):264-73.
3249. Betts JA, Chowdhury EA, Gonzalez JT, Richardson JD, Tsintzas K, Thompson D. Is breakfast the most important meal of the day? *Proc Nutr Soc.* 2016;75(4):464-74.
3250. Vieira AF, Costa RR, Macedo RC, Coconcelli L, Krue L. Effects of aerobic exercise performed in fasted v. fed state on fat and carbohydrate metabolism in adults: a systematic review and meta-analysis. *Br J Nutr.* 2016;116(7):1153-64.
3251. Iwayama K, Kawabuchi R, Park I, et al. Transient energy deficit induced by exercise increases 24-h fat oxidation in young trained men. *J Appl Physiol.* 2015;118(1):80-5.
3252. Iwayama K, Kurihara R, Nabekura Y, et al. Exercise increases 24-h fat oxidation only when it is performed before breakfast. *EBioMedicine.* 2015;2(12):2003-9.
3253. Iwayama K, Kawabuchi R, Nabekura Y, et al. Exercise before breakfast increases 24-h fat oxidation in female subjects. *PLoS ONE.* 2017;12(7):e0180472.
3254. Iwayama K, Kawabuchi R, Nabekura Y, et al. Exercise before breakfast increases 24-h fat oxidation in female subjects. *PLoS ONE.* 2017;12(7):e0180472.
3255. Iwayama K, Kawabuchi R, Nabekura Y, et al. Exercise before breakfast increases 24-h fat oxidation in female subjects. *PLoS ONE.* 2017;12(7):e0180472.
3256. Kim HK, Ando K, Tabata H, et al. Effects of different intensities of endurance exercise in morning and evening on the lipid metabolism response. *J Sports Sci Med.* 2016;15(3):467-76.
3257. Farah NM, Gill JM. Effects of exercise before or after meal ingestion on fat balance and postprandial metabolism in overweight men. *Br J Nutr.* 2013;109(12):2297-307.
3258. Farah NM, Gill JM. Effects of exercise before or after meal ingestion on fat balance and postprandial metabolism in overweight men. *Br J Nutr.* 2013;109(12):2297-307.
3259. Philp A, Hargreaves M, Baar K. More than a store: regulatory roles for glycogen in skeletal muscle adaptation to exercise. *Am J Physiol Endocrinol Metab.* 2012;302(11):E1343-51.
3260. Iwayama K, Kurihara R, Nabekura Y, et al. Exercise increases 24-h fat oxidation only when it is performed before breakfast. *EBioMedicine.* 2015;2(12):2003-9.
3261. Montain SJ, Hopper MK, Coggan AR, Coyle EF. Exercise metabolism at different time intervals after a meal. *J Appl Physiol.* 1991;70(2):882-8.
3262. Horowitz JF, Mora-Rodriguez R, Byerley LO, Coyle EF. Lipolytic suppression following carbohydrate ingestion limits fat oxidation during exercise. *Am J Physiol.* 1997;273(4 Pt 1):E768-75.
3263. Stevenson EJ, Astbury NM, Simpson EJ, Taylor MA, MacDonald IA. Fat oxidation during exercise and satiety during recovery are increased following a low-glycemic index breakfast in sedentary women. *J Nutr.* 2009;139(5):890-7.
3264. Thomas DE, Brotherhood JR, Brand JC. Carbohydrate feeding before exercise: effect of glycemic index. *Int J Sports Med.* 1991;12(2):180-6.
3265. Aird TP, Davies RW, Carson BP. Effects of fasted vs fed-state exercise on performance and post-exercise metabolism: a systematic review and meta-analysis. *Scand J Med Sci Sports.* 2018;28(5):1476-93.
3266. Gonzalez JT, Stevenson EJ. New perspectives on nutritional interventions to augment lipid utilisation during exercise. *Br J Nutr.* 2012;107(3):339-49.
3267. Vieira AF, Costa RR, Macedo RC, Coconcelli L, Krue L. Effects of aerobic exercise performed in fasted v. fed state on fat and carbohydrate metabolism in adults: a systematic review and meta-analysis. *Br J Nutr.* 2016;116(7):1153-64.
3268. Iwayama K, Kurihara R, Nabekura Y, et al. Exercise increases 24-h fat oxidation only when it is performed before breakfast. *EBioMedicine.* 2015;2(12):2003-9.
3269. Iwayama K, Kawabuchi R, Nabekura Y, et al. Exercise before breakfast increases 24-h fat oxidation in female subjects. *PLoS ONE.* 2017;12(7):e0180472.
3270. Van Proeyen K, Szlufcik K, Nielens H, et al. Training in the fasted state improves glucose tolerance during fat-rich diet. *J Physiol (Lond).* 2010;588(Pt 21):4289-302.
3271. Schoenfeld BJ, Aragon AA, Wilborn CD, Krieger JW, Sonmez GT. Body composition changes associated with fasted versus non-fasted aerobic exercise. *J Int Soc Sports Nutr.* 2014;11(1):54.
3272. Gillen JB, Percival ME, Ludzki A, Tarnopolsky MA, Gibala MJ. Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women. *Obesity (Silver Spring).* 2013;21(11):2249-55.
3273. Schoenfeld BJ, Aragon AA, Wilborn CD, Krieger JW, Sonmez GT. Body composition changes associated with fasted versus non-fasted aerobic exercise. *J Int Soc Sports Nutr.* 2014;11(1):54.

3274. Segal KR, Gutin B. Thermic effects of food and exercise in lean and obese women. *Metab Clin Exp*. 1983;32(6):581-9.
3275. Goben KW, Sforzo GA, Frye PA. Exercise intensity and the thermic effect of food. *Int J Sport Nutr*. 1992;2(1):87-95.
3276. Davis JM, Sadri S, Sargent RG, Ward D. Weight control and calorie expenditure: thermogenic effects of pre-prandial and post-prandial exercise. *Addict Behav*. 1989;14(3):347-51.
3277. Goben KW, Sforzo GA, Frye PA. Exercise intensity and the thermic effect of food. *Int J Sport Nutr*. 1992;2(1):87-95.
3278. Haxhi J, Scotto di Palumbo A, Sacchetti M. Exercising for metabolic control: is timing important? *Ann Nutr Metab*. 2013;62(1):14-25.
3279. Colberg SR, Zarrabi L, Bennington L, et al. Postprandial walking is better for lowering the glycemic effect of dinner than pre-dinner exercise in type 2 diabetic individuals. *J Am Med Dir Assoc*. 2009;10(6):394-7.
3280. Reynolds AN, Mann JI, Williams S, Venn BJ. Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus than advice that does not specify timing: a randomised crossover study. *Diabetologia*. 2016;59(12):2572-8.
3281. Chacko E. Why exercise before breakfast may not be for diabetes patients. *Conn Med*. 2014;78(9):517-20.
3282. Chacko E. Why exercise before breakfast may not be for diabetes patients. *Conn Med*. 2014;78(9):517-20.
3283. Reynolds AN, Mann JI, Williams S, Venn BJ. Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus than advice that does not specify timing: a randomised crossover study. *Diabetologia*. 2016;59(12):2572-8.
3284. Chacko E. A time for exercise: the exercise window. *J Appl Physiol*. 2017;122(1):206-9.
3285. Ekkekakis P, Vazou S, Bixby WR, Georgiadis E. The mysterious case of the public health guideline that is (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. *Obes Rev*. 2016;17(4):313-29.
3286. Krueger A. Are we having more fun yet? Categorizing and evaluating changes in time allocation. *Brookings Pap Econ Act*. 2007;2007(2):193-215.
3287. Tudor-Locke C, Brashear MM, Johnson WD, Katzmarzyk PT. Accelerometer profiles of physical activity and inactivity in normal weight, overweight, and obese U.S. men and women. *Int J Behav Nutr Phys Act*. 2010;7:60.
3288. Ekkekakis P, Vazou S, Bixby WR, Georgiadis E. The mysterious case of the public health guideline that is (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. *Obes Rev*. 2016;17(4):313-29.
3289. Ekkekakis P, Vazou S, Bixby WR, Georgiadis E. The mysterious case of the public health guideline that is (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. *Obes Rev*. 2016;17(4):313-29.
3290. Lieberman DE. Is exercise really medicine? An evolutionary perspective. *Curr Sports Med Rep*. 2015;14(4):313-9.
3291. Lieberman DE. Is exercise really medicine? An evolutionary perspective. *Curr Sports Med Rep*. 2015;14(4):313-9.
3292. Ekkekakis P, Vazou S, Bixby WR, Georgiadis E. The mysterious case of the public health guideline that is (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. *Obes Rev*. 2016;17(4):313-29.
3293. Lieberman DE. Is exercise really medicine? An evolutionary perspective. *Curr Sports Med Rep*. 2015;14(4):313-9.
3294. Puterbaugh JS. The emperor's tailors: the failure of the medical weight loss paradigm and its causal role in the obesity of America. *Diabetes Obes Metab*. 2009;11(6):557-70.
3295. Jarraya M, Chtourou H, Aloui A, et al. The effects of music on high-intensity short-term exercise in well trained athletes. *Asian J Sports Med*. 2012;3(4):233-8.
3296. Stork MJ, Kwan MY, Gibala MJ, Martin Ginis KA. Music enhances performance and perceived enjoyment of sprint interval exercise. *Med Sci Sports Exerc*. 2015;47(5):1052-60.
3297. Tanaka D, Tsukamoto H, Suga T, et al. Self-selected music-induced reduction of perceived exertion during moderate-intensity exercise does not interfere with post-exercise improvements in inhibitory control. *Physiol Behav*. 2018;194:170-6.
3298. De Bourdeaudhuij I, Crombez G, Deforche B, Vinaimont F, Debode P, Bouckaert J. Effects of distraction on treadmill running time in severely obese children and adolescents. *Int J Obes Relat Metab Disord*. 2002;26(8):1023-9.
3299. Davis JN, Hodges VA, Gillham MB. Physical activity compliance: differences between overweight/obese and normal-weight adults. *Obesity (Silver Spring)*. 2006;14(12):2259-65.
3300. Hill JO, Wyatt HR. Role of physical activity in preventing and treating obesity. *J Appl Physiol*. 2005;99(2):765-70.
3301. Ekkekakis P, Vazou S, Bixby WR, Georgiadis E. The mysterious case of the public health guideline that is (almost) entirely ignored: call for a research agenda on the causes of the extreme avoidance of physical activity in obesity. *Obes Rev*. 2016;17(4):313-29.
3302. Simon M. Best public relations that money can buy: a guide to food industry front groups. Center for Food Safety. Published May 2013. Available at: https://web.archive.org/web/20170822052412/https://www.centerforfoodsafety.org/files/front_groups_final_84531.pdf. Accessed April 10, 2019.
3303. Kirscht JP, Becker MH, Haefner DP, Maiman LA. Effects of threatening communications and mothers health beliefs on weight change in obese children. *J Behav Med*. 1978;1(2):147-57.
3304. Ridberg R, Alper L, Earp J, et al. Big bucks, Big Pharma: marketing disease & pushing drugs: transcript. Media Education Foundation. Published 2006. Available at: <https://www.mediaed.org/transcripts/Big-Bucks-Big-Pharma-Transcript.pdf>. Accessed April 10, 2019.
3305. Segar ML, Richardson CR. Prescribing pleasure and meaning: cultivating walking motivation and maintenance. *Am J Prev Med*. 2014;47(6):838-41.
3306. Segar ML, Guérin E, Phillips E, Fortier M. From a vital sign to vitality: selling exercise so patients want to buy it. *Curr Sports Med Rep*. 2016;15(4):276-81.
3307. Loehr V, Baldwin A. Affective forecasting error in exercise: differences between physically active and inactive individuals. *Sport Exerc Perform Psychol*. 2014;3(3):177-83.
3308. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541-56.

3309. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol*. 2013;42(6):1831-6.
3310. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. *J Gastroenterol Hepatol*. 2013;28 Suppl 4:59-63.
3311. Paley CA, Johnson MI. Physical activity to reduce systemic inflammation associated with chronic pain and obesity: a narrative review. *Clin J Pain*. 2016;32(4):365-70.
3312. Erlanson-Albertsson C, Albertsson PÅ. The use of green leaf membranes to promote appetite control, suppress hedonic hunger and loose [sic] body weight. *Plant Foods Hum Nutr*. 2015;70(3):281-90.
3313. Albertsson PÅ, Köhnke R, Emek SC, et al. Chloroplast membranes retard fat digestion and induce satiety: effect of biological membranes on pancreatic lipase/co-lipase. *Biochem J*. 2007;401(3):727-33.
3314. Östbring K, Rayner M, Sjöholm I, et al. The effect of heat treatment of thylakoids on their ability to inhibit in vitro lipase/co-lipase activity. *Food Funct*. 2014;5(9):2157-65.
3315. Stenblom EL, Weström B, Linninge C, et al. Dietary green-plant thylakoids decrease gastric emptying and gut transit, promote changes in the gut microbial flora, but does not cause steatorrhea. *Nutr Metab (Lond)*. 2016;13:67.
3316. Östbring K, Sjöholm I, Sörenson H, Ekholm A, Erlanson-Albertsson C, Rayner M. Characteristics and functionality of appetite-reducing thylakoid powders produced by three different drying processes. *J Sci Food Agric*. 2018;98(4):1554-65.
3317. Köhnke R, Lindbo A, Larsson T, et al. Thylakoids promote release of the satiety hormone cholecystokinin while reducing insulin in healthy humans. *Scand J Gastroenterol*. 2009;44(6):712-9.
3318. Stenblom EL, Montelius C, Östbring K, et al. Supplementation by thylakoids to a high carbohydrate meal decreases feelings of hunger, elevates CCK levels and prevents postprandial hypoglycaemia in overweight women. *Appetite*. 2013;68:118-23.
3319. Rebello CJ, Chu J, Beyl R, Edwall D, Erlanson-Albertsson C, Greenway FL. Acute effects of a spinach extract rich in thylakoids on satiety: a randomized controlled crossover trial. *J Am Coll Nutr*. 2015;34(6):470-7.
3320. Stenblom EL, Egecioglu E, Landin-Olsson M, Erlanson-Albertsson C. Consumption of thylakoid-rich spinach extract reduces hunger, increases satiety and reduces cravings for palatable food in overweight women. *Appetite*. 2015;91:209-19.
3321. Gustafsson K, Asp NG, Hagander B, Nyman M. Satiety effects of spinach in mixed meals: comparison with other vegetables. *Int J Food Sci Nutr*. 1995;46(4):327-34.
3322. Rebello CJ, O'Neil CE, Greenway FL. Gut fat signaling and appetite control with special emphasis on the effect of thylakoids from spinach on eating behavior. *Int J Obes (Lond)*. 2015;39(12):1679-88.
3323. Montelius C, Erlandsson D, Vitija E, Stenblom EL, Egecioglu E, Erlanson-Albertsson C. Body weight loss, reduced urge for palatable food and increased release of GLP-1 through daily supplementation with green-plant membranes for three months in overweight women. *Appetite*. 2014;81:295-304.
3324. Stenblom E, Montelius C, Erlandsson D, et al. Decreased urge for palatable food after a two-month dietary intervention with green-plant membranes in overweight women. *J Obes Weight Loss Ther*. 2014;4(4).
3325. Östbring K, Sjöholm I, Sörenson H, Ekholm A, Erlanson-Albertsson C, Rayner M. Characteristics and functionality of appetite-reducing thylakoid powders produced by three different drying processes. *J Sci Food Agric*. 2018;98(4):1554-65.
3326. Erlanson-Albertsson C, Albertsson PÅ. The use of green leaf membranes to promote appetite control, suppress hedonic hunger and loose [sic] body weight. *Plant Foods Hum Nutr*. 2015;70(3):281-90.
3327. Östbring K, Rayner M, Sjöholm I, et al. The effect of heat treatment of thylakoids on their ability to inhibit in vitro lipase/co-lipase activity. *Food Funct*. 2014;5(9):2157-65.
3328. Estebaranz F, Galbany J, Martínez L, Turbón D, Pérez-Pérez A. Buccal dental microwear analyses support greater specialization in consumption of hard foodstuffs for *Australopithecus anamensis*. *J Anthropol Sci*. 2012;90:163-85.
3329. Roberts JL, Moreau R. Functional properties of spinach (*Spinacia oleracea* L.) phytochemicals and bioactives. *Food Funct*. 2016;7(8):3337-53.
3330. Gertsch J. The metabolic plant feedback hypothesis: how plant secondary metabolites nonspecifically impact human health. *Planta Med*. 2016;82(11-12):920-9.
3331. Östbring K, Sjöholm I, Sörenson H, Ekholm A, Erlanson-Albertsson C, Rayner M. Characteristics and functionality of appetite-reducing thylakoid powders produced by three different drying processes. *J Sci Food Agric*. 2018;98(4):1554-65.
3332. Sofia NH, Manickavasakam K, Walter TM. Prevalence and risk factors of kidney stone. *GJRA*. 2016;5(3):183-7.
3333. Knoll T, Schubert AB, Fahlenkamp D, Leusmann DB, Wendt-Nordahl G, Schubert G. Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. *J Urol*. 2011;185(4):1304-11.
3334. Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol*. 2007;18(7):2198-204.
3335. Voss S, Hesse A, Zimmermann DJ, Sauerbruch T, von Unruh GE. Intestinal oxalate absorption is higher in idiopathic calcium oxalate stone formers than in healthy controls: measurements with the [(13)C2]oxalate absorption test. *J Urol*. 2006;175(5):1711-5.
3336. Marcason W. Where can I find information on the oxalate content of foods? *J Am Diet Assoc*. 2006;106(4):627-8.
3337. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. *Clin J Am Soc Nephrol*. 2008;3(5):1453-60.
3338. Nouvenne A, Ticinesi A, Morelli I, Guida L, Borghi L, Meschi T. Fad diets and their effect on urinary stone formation. *Transl Androl Urol*. 2014;3(3):303-12.
3339. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. *Kidney Int*. 2001;59(1):270-6.
3340. Sorensen MD, Hsi RS, Chi T, et al. Dietary intake of fiber, fruit and vegetables decreases the risk of incident kidney stones in women: a Women's Health Initiative report. *J Urol*. 2014;192(6):1694-9.
3341. Meschi T, Maggiore U, Fiaccadori E, et al. The effect of fruits and vegetables on urinary stone risk factors. *Kidney Int*. 2004;66(6):2402-10.
3342. Meschi T, Maggiore U, Fiaccadori E, et al. The effect of fruits and vegetables on urinary stone risk factors. *Kidney Int*. 2004;66(6):2402-10.

3343. Turney BW, Appleby PN, Reynard JM, Noble JG, Key TJ, Allen NE. Diet and risk of kidney stones in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Epidemiol.* 2014;29(5):363-9.
3344. Robertson WG, Heyburn PJ, Peacock M, Hanes FA, Swaminathan R. The effect of high animal protein intake on the risk of calcium stone-formation in the urinary tract. *Clin Sci.* 1979;57(3):285-8.
3345. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med.* 2002;346(2):77-84.
3346. Nouvenne A, Ticinesi A, Morelli I, Guida L, Borghi L, Meschi T. Fad diets and their effect on urinary stone formation. *Transl Androl Urol.* 2014;3(3):303-12.
3347. Harvard T. H. Chan School of Public Health Nutrition Department. Directory listing of /health/Oxalate/files. Harvard T. H. Chan School of Public Health Nutrition Department's Oxalate Documentation File Download Site. Published 2007. Available at: <https://regepi.bwh.harvard.edu/health/Oxalate/files>. Accessed April 10, 2019.
3348. Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol.* 2007;18(7):2198-204.
3349. Taylor EN, Curhan GC. Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol.* 2007;18(7):2198-204.
3350. Mosha TC, Gaga HE, Pace RD, Laswai HS, Mtebe K. Effect of blanching on the content of antinutritional factors in selected vegetables. *Plant Foods Hum Nutr.* 1995;47(4):361-7.
3351. Chai W, Liebman M. Effect of different cooking methods on vegetable oxalate content. *J Agric Food Chem.* 2005;53(8):3027-30.
3352. Lien YH. Juicing is not all juicy. *Am J Med.* 2013;126(9):755-6.
3353. Kelly JP, Curhan GC, Cave DR, Anderson TE, Kaufman DW. Factors related to colonization with *Oxalobacter formigenes* in U.S. adults. *J Endourol.* 2011;25(4):673-9.
3354. Makkapati S, D'Agati VD, Balsam L. "Green smoothie cleanse" causing acute oxalate nephropathy. *Am J Kidney Dis.* 2018;71(2):281-6.
3355. Makkapati S, D'Agati VD, Balsam L. "Green smoothie cleanse" causing acute oxalate nephropathy. *Am J Kidney Dis.* 2018;71(2):281-6.
3356. Kikuchi Y, Seta K, Ogawa Y, et al. Chaga mushroom-induced oxalate nephropathy. *Clin Nephrol.* 2014;81(6):440-4.
3357. Albersmeyer M, Hilge R, Schrötte A, Weiss M, Sitter T, Vielhauer V. Acute kidney injury after ingestion of rhubarb: secondary oxalate nephropathy in a patient with type 1 diabetes. *BMC Nephrol.* 2012;13:141.
3358. Haaskjold YL, Drotningvik A, Leh S, Marti HP, Svarstad E. Renal failure due to excessive intake of almonds in the absence of *Oxalobacter formigenes*. *Am J Med.* 2015;128(12):e29-30.
3359. Bernardino M, Parmar MS. Oxalate nephropathy from cashew nut intake. *CMAJ.* 2017;189(10):E405-8.
3360. Neto MM, Silva GE, Costa RS, et al. Star fruit: simultaneous neurotoxic and nephrotoxic effects in people with previously normal renal function. *NDT Plus.* 2009;2(6):485-8.
3361. Barman AK, Goel R, Sharma M, Mahanta PJ. Acute kidney injury associated with ingestion of star fruit: acute oxalate nephropathy. *Indian J Nephrol.* 2016;26(6):446-8.
3362. Brinkley LJ, Gregory J, Pak CY. A further study of oxalate bioavailability in foods. *J Urol.* 1990;144(1):94-6.
3363. Gandhi A, Nasser S, Kassis Akl N, Kotadia S. Quiz page June 2016: rapidly progressive kidney failure. *Am J Kidney Dis.* 2016;67(6):A15-7.
3364. Syed F, Mena-Gutierrez A, Ghaffar U. A case of iced-tea nephropathy. *N Engl J Med.* 2015;372(14):1377-8.
3365. Weaver CM, Plawecki KL. Dietary calcium: adequacy of a vegetarian diet. *Am J Clin Nutr.* 1994;59(5 Suppl):1238S-41S.
3366. Zhao Y, Martin BR, Weaver CM. Calcium bioavailability of calcium carbonate fortified soymilk is equivalent to cow's milk in young women. *J Nutr.* 2005;135(10):2379-82.
3367. Weaver CM, Plawecki KL. Dietary calcium: adequacy of a vegetarian diet. *Am J Clin Nutr.* 1994;59(5 Suppl):1238S-41S.
3368. Weaver CM, Plawecki KL. Dietary calcium: adequacy of a vegetarian diet. *Am J Clin Nutr.* 1994;59(5 Suppl):1238S-41S.
3369. Kumar R, Lieske JC, Collazo-Clavell ML, et al. Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery. *Surgery.* 2011;149(5):654-61.
3370. Kwan TK, Chadban SJ, McKenzie PR, Saunders JR. Acute oxalate nephropathy secondary to orlistat-induced enteric hyperoxaluria. *Nephrology (Carlton).* 2013;18(3):241-2.
3371. Bendtsen NT, Hother AL, Jensen SK, Lorenzen JK, Astrup A. Effect of dairy calcium on fecal fat excretion: a randomized crossover trial. *Int J Obes (Lond).* 2008;32(12):1816-24.
3372. Soerensen KV, Thorning TK, Astrup A, Kristensen M, Lorenzen JK. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. *Am J Clin Nutr.* 2014;99(5):984-91.
3373. Soerensen KV, Thorning TK, Astrup A, Kristensen M, Lorenzen JK. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. *Am J Clin Nutr.* 2014;99(5):984-91.
3374. Christensen R, Lorenzen JK, Svith CR, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes Rev.* 2009;10(4):475-86.
3375. Christensen R, Lorenzen JK, Svith CR, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes Rev.* 2009;10(4):475-86.
3376. Christensen R, Lorenzen JK, Svith CR, et al. Effect of calcium from dairy and dietary supplements on faecal fat excretion: a meta-analysis of randomized controlled trials. *Obes Rev.* 2009;10(4):475-86.
3377. Buchowski MS, Aslam M, Dossett C, Dorminy C, Choi L, Acra S. Effect of dairy and non-dairy calcium on fecal fat excretion in lactose digester and maldigester obese adults. *Int J Obes (Lond).* 2010;34(1):127-35.
3378. Buchowski MS, Aslam M, Dossett C, Dorminy C, Choi L, Acra S. Effect of dairy and non-dairy calcium on fecal fat excretion in lactose digester and maldigester obese adults. *Int J Obes (Lond).* 2010;34(1):127-35.
3379. Onakpoya IJ, Perry R, Zhang J, Ernst E. Efficacy of calcium supplementation for management of overweight and obesity: systematic review of randomized clinical trials. *Nutr Rev.* 2011;69(6):335-43.
3380. Geng T, Qi L, Huang T. Effects of dairy products consumption on body weight and body composition among adults: an updated meta-analysis of 37 randomized control trials. *Mol Nutr Food Res.* 2018;62(1).
3381. Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. *Am J Clin Nutr.* 2006;83(3):559-66.

3382. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2012;96(4):735-47.
3383. Sanders TA. Role of dairy foods in weight management. *Am J Clin Nutr*. 2012;96(4):687-8.
3384. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785-95.
3385. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785-95.
3386. Grossman DC, Curry SJ, Owens DK, et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(15):1592-9.
3387. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336(7638):262-6.
3388. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens*. 1999;12(1 Pt 1):84-92.
3389. Reid IR, Horne A, Mason B, Ames R, Bava U, Gamble GD. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. *J Clin Endocrinol Metab*. 2005;90(7):3824-9.
3390. Denke MA, Fox MM, Schulte MC. Short-term dietary calcium fortification increases fecal saturated fat content and reduces serum lipids in men. *J Nutr*. 1993;123(6):1047-53.
3391. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ*. 2008;336(7638):262-6.
3392. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040.
3393. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. *Ther Adv Drug Saf*. 2013;4(5):199-210.
3394. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. *Ther Adv Drug Saf*. 2013;4(5):199-210.
3395. Reid IR, Bolland MJ. Does widespread calcium supplementation pose cardiovascular risk? Yes: the potential risk is a concern. *Am Fam Physician*. 2013;87(3).
3396. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res*. 2012;27(3):719-22.
3397. Heaney RP, Kopecky S, Maki KC, Hathcock J, Mackay D, Wallace TC. A review of calcium supplements and cardiovascular disease risk. *Adv Nutr*. 2012;3(6):763-71.
3398. Tankeu AT, Ndip Agbor V, Noubiap JJ. Calcium supplementation and cardiovascular risk: a rising concern. *J Clin Hypertens (Greenwich)*. 2017;19(6):640-6.
3399. Rooney MR, Michos ED, Hootman KC, Harnack L, Lutsey PL. Trends in calcium supplementation, National Health and Nutrition Examination Survey (NHANES) 1999-2014. *Bone*. 2018;111:23-7.
3400. Grey A, Bolland M. Web of industry, advocacy, and academia in the management of osteoporosis. *BMJ*. 2015;351:h3170.
3401. Reid IR, Bristow SM, Bolland MJ. Calcium supplements: benefits and risks. *J Intern Med*. 2015;278(4):354-68.
3402. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1-23.
3403. Katan M. Fat under fire: new findings or shaky science? *Nutrition Action Healthletter*. 2014:3-7. Available at: <https://cspinet.org/sites/default/files/attachment/covermay2014.pdf>. Accessed April 10, 2019.
3404. Hughes S. AHA issues "presidential advisory" on harms of saturated fat. *Medscape*. Published June 15, 2017. Available at: <https://www.medscape.com/viewarticle/881689>. Accessed April 10, 2019.
3405. Soleimani AR, Akbari H, Soleimani S, Beladi Mousavi SS, Tamadon MR. Effect of sour tea (*Lipicom*) pill versus captopril on the treatment of hypertension. *J Renal Inj Prev*. 2015;4(3):73-9.
3406. Nwachukwu DC, Aneke EI, Nwachukwu NZ, Azubike N, Obika LF. Does consumption of an aqueous extract of *Hibiscus sabdariffa* affect renal function in subjects with mild to moderate hypertension? *J Physiol Sci*. 2017;67(1):227-34.
3407. Beltrán-Debón R, Rodríguez-Gallego E, Fernández-Arroyo S, et al. The acute impact of polyphenols from *Hibiscus sabdariffa* in metabolic homeostasis: an approach combining metabolomics and gene-expression analyses. *Food Funct*. 2015;6(9):2957-66.
3408. Hopkins AL, Lamm MG, Funk JL, Ritenbaugh C. *Hibiscus sabdariffa* L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. *Fitoterapia*. 2013;85:84-94.
3409. Asgary S, Soltani R, Zolghadr M, Keshvari M, Sarrafzadegan N. Evaluation of the effects of roselle (*Hibiscus sabdariffa* L.) on oxidative stress and serum levels of lipids, insulin and hs-CRP in adult patients with metabolic syndrome: a double-blind placebo-controlled clinical trial. *J Complement Integr Med*. 2016;13(2):175-80.
3410. Alarcon-Aguilar FJ, Zamilpa A, Perez-Garcia MD, et al. Effect of *Hibiscus sabdariffa* on obesity in MSG mice. *J Ethnopharmacol*. 2007;114(1):66-71.
3411. Herranz-López M, Olivares-Vicente M, Encinar JA, et al. Multi-targeted molecular effects of *Hibiscus sabdariffa* polyphenols: an opportunity for a global approach to obesity. *Nutrients*. 2017;9(8):907.
3412. Da Costa Rocha I, Bonnlaender B, Sievers H, Pischel I, Heinrich M. *Hibiscus sabdariffa* L.—a phytochemical and pharmacological review. *Food Chem*. 2014;165:424-43.
3413. Buchholz T, Melzig MF. Medicinal plants traditionally used for treatment of obesity and diabetes mellitus—screening for pancreatic lipase and α -amylase inhibition. *Phytother Res*. 2016;30(2):260-6.
3414. Kao ES, Yang MY, Hung CH, Huang CN, Wang CJ. Polyphenolic extract from *Hibiscus sabdariffa* reduces body fat by inhibiting hepatic lipogenesis and preadipocyte adipogenesis. *Food Funct*. 2016;7(1):171-82.

3415. Alarcon-Aguilar FJ, Zamilpa A, Perez-Garcia MD, et al. Effect of *Hibiscus sabdariffa* on obesity in MSG mice. *J Ethnopharmacol.* 2007;114(1):66-71.
3416. Carvajal-Zarrabal O, Hayward-Jones PM, Orta-Flores Z, et al. Effect of *Hibiscus sabdariffa* L. dried calyx ethanol extract on fat absorption-excretion, and body weight implication in rats. *J Biomed Biotechnol.* 2009;2009:394592.
3417. Chang HC, Peng CH, Yeh DM, Kao ES, Wang CJ. *Hibiscus sabdariffa* extract inhibits obesity and fat accumulation, and improves liver steatosis in humans. *Food Funct.* 2014;5(4):734-9.
3418. McKay DL, Chen CY, Saltzman E, Blumberg JB. *Hibiscus sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. *J Nutr.* 2010;140(2):298-303.
3419. Malik J, Frankova A, Drabek O, Szakova J, Ash C, Kokoska L. Aluminium and other elements in selected herbal tea plant species and their infusions. *Food Chem.* 2013;139(1-4):728-34.
3420. Buchwald-Werner S, Naka I, Wilhelm M, Schütz E, Schoen C, Reule C. Effects of lemon verbena extract (Recoverben®) supplementation on muscle strength and recovery after exhaustive exercise: a randomized, placebo-controlled trial. *J Int Soc Sports Nutr.* 2018;15:5.
3421. Herranz-López M, Barrajón-Catalán E, Segura-Carretero A, Menéndez JA, Joven J, Micol V. Lemon verbena (*Lippia citriodora*) polyphenols alleviate obesity-related disturbances in hypertrophic adipocytes through AMPK-dependent mechanisms. *Phytomedicine.* 2015;22(6):605-14.
3422. McKay DL, Chen CY, Saltzman E, Blumberg JB. *Hibiscus sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. *J Nutr.* 2010;140(2):298-303.
3423. Carnat A, Carnat AP, Fraisse D, Ricoux L, Lamaison JL. The aromatic and polyphenolic composition of Roman camomile tea. *Fitoterapia.* 2004;75(1):32-8.
3424. Boix-Castejón M, Herranz-López M, Pérez Gago A, et al. Hibiscus and lemon verbena polyphenols modulate appetite-related biomarkers in overweight subjects: a randomized controlled trial. *Food Funct.* 2018;9(6):3173-84.
3425. Boix-Castejón M, Herranz-López M, Pérez Gago A, et al. Hibiscus and lemon verbena polyphenols modulate appetite-related biomarkers in overweight subjects: a randomized controlled trial. *Food Funct.* 2018;9(6):3173-84.
3426. Morales-Luna E, Pérez-Ramírez IF, Salgado M, Castaño-Tostado E, Gómez-Aldapa CA, Reynoso-Camacho R. The main beneficial effect of roselle (*Hibiscus sabdariffa*) on obesity is not only related to its anthocyanins content. *J Sci Food Agric.* 2018;99(2):596-605.
3427. Herranz-López M, Fernández-Arroyo S, Pérez-Sánchez A, et al. Synergism of plant-derived polyphenols in adipogenesis: perspectives and implications. *Phytomedicine.* 2012;19(3-4):253-61.
3428. Chu CH, Pang KK, Lo EC. Dietary behavior and knowledge of dental erosion among Chinese adults. *BMC Oral Health.* 2010;10:13.
3429. Ali H, Tahmassebi JF. The effects of smoothies on enamel erosion: an in situ study. *Int J Paediatr Dent.* 2014;24(3):184-91.
3430. Perkins R. A study of the munitions intoxications in France. *Public Health Reports (1896-1970).* 1919;34(43):2335.
3431. Cutting W, Mehrtens H, Tainter M. Actions and uses of dinitrophenol. *J Am Med Assoc.* 1933;101(3):193.
3432. Cutting W, Mehrtens H, Tainter M. Actions and uses of dinitrophenol. *J Am Med Assoc.* 1933;101(3):193.
3433. Rodin FH. Cataracts following the use of dinitrophenol: a summary of thirty-two cases. *Cal West Med.* 1936;44(4):276-9.
3434. Colman E. Dinitrophenol and obesity: an early twentieth-century regulatory dilemma. *Regul Toxicol Pharmacol.* 2007;48(2):115-7.
3435. Grundlingh J, Dargan PI, El-Zanfaly M, Wood DM. 2,4-dinitrophenol (DNP): a weight loss agent with significant acute toxicity and risk of death. *J Med Toxicol.* 2011;7(3):205-12.
3436. Zack F, Blaas V, Goos C, Rentsch D, Büttner A. Death within 44 days of 2,4-dinitrophenol intake. *Int J Legal Med.* 2016;130(5):1237-41.
3437. Chen YC, Cypess AM, Chen YC, et al. Measurement of human brown adipose tissue volume and activity using anatomic MR imaging and functional MR imaging. *J Nucl Med.* 2013;54(9):1584-7.
3438. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-17.
3439. Cohade C, Osman M, Pannu HK, Wahl RL. Uptake in supraclavicular area fat ("USA-Fat"): description on 18F-FDG PET/CT. *J Nucl Med.* 2003;44(2):170-6.
3440. Virtanen KA. The rediscovery of BAT in adult humans using imaging. *Best Pract Res Clin Endocrinol Metab.* 2016;30(4):471-7.
3441. Cohade C, Mourtzikos KA, Wahl RL. "USA-Fat": prevalence is related to ambient outdoor temperature-evaluation with 18F-FDG PET/CT. *J Nucl Med.* 2003;44(8):1267-70.
3442. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-17.
3443. Thyagarajan B, Foster MT. Beiging of white adipose tissue as a therapeutic strategy for weight loss in humans. *Horm Mol Biol Clin Investig.* 2017;31(2).
3444. Chondronikola M, Sidossis LS. Brown and beige fat: from molecules to physiology. *Biochim Biophys Acta.* 2019;864(1):91-103.
3445. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-17.
3446. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-17.
3447. Brendle C, Werner MK, Schmadl M, et al. Correlation of brown adipose tissue with other body fat compartments and patient characteristics: a retrospective analysis in a large patient cohort using PET/CT. *Acad Radiol.* 2018;25(1):102-10.
3448. Lee P, Swarbrick MM, Ho KK. Brown adipose tissue in adult humans: a metabolic renaissance. *Endocr Rev.* 2013;34(3):413-38.
3449. Gadea E, Thivat E, Paulon R, et al. Hibernoma: a clinical model for exploring the role of brown adipose tissue in the regulation of body weight? *J Clin Endocrinol Metab.* 2014;99(1):1-6.

3450. Dong M, Lin J, Lim W, Jin W, Lee HJ. Role of brown adipose tissue in metabolic syndrome, aging, and cancer cachexia. *Front Med*. 2018;12(2):130-8.
3451. Elliott J. Blame it all on brown fat now. *JAMA*. 1980;243(20):1983-5.
3452. Lee P, Swarbrick MM, Ho KK. Brown adipose tissue in adult humans: a metabolic renaissance. *Endocr Rev*. 2013;34(3):413-38.
3453. Ruiz JR, Martinez-Tellez B, Sanchez-Delgado G, Osuna-Prieto FJ, Rensen PCN, Boon MR. Role of human brown fat in obesity, metabolism and cardiovascular disease: strategies to turn up the heat. *Prog Cardiovasc Dis*. 2018;61(2):232-45.
3454. Leitner BP, Huang S, Brychta RJ, et al. Mapping of human brown adipose tissue in lean and obese young men. *Proc Natl Acad Sci USA*. 2017;114(32):8649-54.
3455. Symonds ME. Brown adipose tissue growth and development. *Scientifica (Cairo)*. 2013;2013:305763.
3456. Lee P, Swarbrick MM, Ho KK. Brown adipose tissue in adult humans: a metabolic renaissance. *Endocr Rev*. 2013;34(3):413-38.
3457. Rothwell NJ, Stock MJ. Luxuskonsumption, diet-induced thermogenesis and brown fat: the case in favour. *Clin Sci*. 1983;64(1):19-23.
3458. Moonen MPB, Nascimento EBM, van Marken Lichtenbelt WD. Human brown adipose tissue: underestimated target in metabolic disease? *Biochim Biophys Acta*. 2019;1864(1):104-12.
3459. Ong FJ, Ahmed BA, Oreskovich SM, et al. Recent advances in the detection of brown adipose tissue in adult humans: a review. *Clin Sci*. 2018;132(10):1039-54.
3460. Brychta RJ, Chen KY. Cold-induced thermogenesis in humans. *Eur J Clin Nutr*. 2017;71(3):345-52.
3461. Marlatt KL, Chen KY, Ravussin E. Is activation of human brown adipose tissue a viable target for weight management? *Am J Physiol Regul Integr Comp Physiol*. 2018;315(3):R479-83.
3462. Langeveld M, Tan CY, Soeters MR, et al. Mild cold effects on hunger, food intake, satiety and skin temperature in humans. *Endocr Connect*. 2016;5(2):65-73.
3463. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Invest*. 2013;123(8):3404-8.
3464. Lee P, Swarbrick MM, Ho KK. Brown adipose tissue in adult humans: a metabolic renaissance. *Endocr Rev*. 2013;34(3):413-38.
3465. El Hadi H, Vettor R, Rossato M. Functional imaging of brown adipose tissue in human. *Horm Mol Biol Clin Investig*. 2017;31(1).
3466. Maurizi G, Poloni A, Mattiucci D, et al. Human white adipocytes convert into "rainbow" adipocytes in vitro. *J Cell Physiol*. 2017;232(10):2887-99.
3467. Sandholt CH, Pedersen O. Obesity: beige adipocytes—will they beat obesity? *Nat Rev Endocrinol*. 2015;11(12):694-6.
3468. Tipton MJ, Collier N, Massey H, Corbett J, Harper M. Cold water immersion: kill or cure? *Exp Physiol*. 2017;102(11):1335-55.
3469. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Invest*. 2013;123(8):3404-8.
3470. Leitner BP, Weiner LS, Desir M, et al. Kinetics of human brown adipose tissue activation and deactivation. *Int J Obes (Lond)*. 2019;43(3):633-7.
3471. Moonen MPB, Nascimento EBM, van Marken Lichtenbelt WD. Human brown adipose tissue: underestimated target in metabolic disease? *Biochim Biophys Acta*. 2019;1864(1):104-12.
3472. Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obes (Lond)*. 2006;30(11):1585-94.
3473. Dauncey MJ. Influence of mild cold on 24 h energy expenditure, resting metabolism and diet-induced thermogenesis. *Br J Nutr*. 1981;45(2):257-67.
3474. Huttunen P, Hirvonen J, Kinnula V. The occurrence of brown adipose tissue in outdoor workers. *Eur J Appl Physiol Occup Physiol*. 1981;46(4):339-45.
3475. Harris AM, MacBride LR, Foster RC, McCrady SK, Levine JA. Does non-exercise activity thermogenesis contribute to non-shivering thermogenesis? *J Therm Biol*. 2006;31(8):634-8.
3476. Hansen JC, Gilman AP, Odland JØ. Is thermogenesis a significant causal factor in preventing the "globesity" epidemic? *Med Hypotheses*. 2010;75(2):250-6.
3477. Chen KY, Brychta RJ, Linderman JD, et al. Brown fat activation mediates cold-induced thermogenesis in adult humans in response to a mild decrease in ambient temperature. *J Clin Endocrinol Metab*. 2013;98(7):E1218-23.
3478. Dauncey MJ. Influence of mild cold on 24 h energy expenditure, resting metabolism and diet-induced thermogenesis. *Br J Nutr*. 1981;45(2):257-67.
3479. Jillette P. *Presto!: How I Made Over 100 Pounds Disappear and Other Magical Tales*. New York: Simon & Schuster; 2016.
3480. Tipton MJ, Collier N, Massey H, Corbett J, Harper M. Cold water immersion: kill or cure? *Exp Physiol*. 2017;102(11):1335-55.
3481. Schneeberg NG. The medical history of Thomas Jefferson (1743-1826). *J Med Biogr*. 2008;16(2):118-25.
3482. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med*. 2009;360(15):1518-25.
3483. Iwen KA, Backhaus J, Cassens M, et al. Cold-induced brown adipose tissue activity alters plasma fatty acids and improves glucose metabolism in men. *J Clin Endocrinol Metab*. 2017;102(11):4226-34.
3484. Buijze GA, Siervelt IN, van der Heijden BC, Dijkgraaf MG, Frings-Dresen MH. The effect of cold showering on health and work: a randomized controlled trial. *PLoS ONE*. 2016;11(9):e0161749.
3485. Wijers SL, Saris WH, van Marken Lichtenbelt WD. Individual thermogenic responses to mild cold and overfeeding are closely related. *J Clin Endocrinol Metab*. 2007;92(11):4299-305.
3486. Wijers SL, Saris WH, van Marken Lichtenbelt WD. Cold-induced adaptive thermogenesis in lean and obese. *Obesity (Silver Spring)*. 2010;18(6):1092-9.

3487. Hanssen MJ, van der Lans AA, Brans B, et al. Short-term cold acclimation recruits brown adipose tissue in obese humans. *Diabetes*. 2016;65(5):1179-89.
3488. Hibi M, Oishi S, Matsushita M, et al. Brown adipose tissue is involved in diet-induced thermogenesis and whole-body fat utilization in healthy humans. *Int J Obes (Lond)*. 2016;40(11):1655-61.
3489. Schrauwen P, van Marken Lichtenbelt W. Brown adipose tissue: the magic bullet? *Obesity (Silver Spring)*. 2017;25(3):499.
3490. Ruiz JR, Martinez-Tellez B, Sanchez-Delgado G, Aguilera CM, Gil A. Regulation of energy balance by brown adipose tissue: at least three potential roles for physical activity. *Br J Sports Med*. 2015;49(15):972-3.
3491. Krentz AJ, Fujioka K, Hompesch M. Evolution of pharmacological obesity treatments: focus on adverse side-effect profiles. *Diabetes Obes Metab*. 2016;18(6):558-70.
3492. Boozer CN, Daly PA, Homel P, et al. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes Relat Metab Disord*. 2002;26(5):593-604.
3493. Zell-Kanter M, Quigley MA, Leikin JB. Reduction in ephedra poisonings after FDA ban. *N Engl J Med*. 2015;372(22):2172-4.
3494. Ruiz JR, Martinez-Tellez B, Sanchez-Delgado G, Osuna-Prieto FJ, Rensen PCN, Boon MR. Role of human brown fat in obesity, metabolism and cardiovascular disease: strategies to turn up the heat. *Prog Cardiovasc Dis*. 2018;61(2):232-45.
3495. Roberts LD, Ashmore T, Kotwica AO, et al. Inorganic nitrate promotes the browning of white adipose tissue through the nitrate-nitrite-nitric oxide pathway. *Diabetes*. 2015;64(2):471-84.
3496. Zhang HQ, Chen SY, Wang AS, et al. Sulforaphane induces adipocyte browning and promotes glucose and lipid utilization. *Mol Nutr Food Res*. 2016;60(10):2185-97.
3497. Fernández-Quintela A, Milton-Laskibar I, González M, Portillo MP. Antiobesity effects of resveratrol: which tissues are involved? *Ann NY Acad Sci*. 2017;1403(1):118-31.
3498. Roberts LD, Ashmore T, Kotwica AO, et al. Inorganic nitrate promotes the browning of white adipose tissue through the nitrate-nitrite-nitric oxide pathway. *Diabetes*. 2015;64(2):471-84.
3499. Oi-Kano Y, Kawada T, Watanabe T, et al. Oleuropein, a phenolic compound in extra virgin olive oil, increases uncoupling protein 1 content in brown adipose tissue and enhances noradrenaline and adrenaline secretions in rats. *J Nutr Sci Vitaminol*. 2008;54(5):363-70.
3500. Ghandour RA, Colson C, Giroud M, et al. Impact of dietary ω 3 polyunsaturated fatty acid supplementation on brown and brite adipocyte function. *J Lipid Res*. 2018;59(3):452-61.
3501. Lee SG, Parks JS, Kang HW. Quercetin, a functional compound of onion peel, remodels white adipocytes to brown-like adipocytes. *J Nutr Biochem*. 2017;42:62-71.
3502. Jeong MY, Kim HL, Park J, et al. Rubi Fructus (*Rubus coreanus*) activates the expression of thermogenic genes in vivo and in vitro. *Int J Obes (Lond)*. 2015;39(3):456-64.
3503. Cavalera M, Axling U, Berger K, Holm C. Rose hip supplementation increases energy expenditure and induces browning of white adipose tissue. *Nutr Metab (Lond)*. 2016;13:91.
3504. Aziz SA, Wakeling LA, Miwa S, Alberdi G, Hesketh JE, Ford D. Metabolic programming of a beige adipocyte phenotype by genistein. *Mol Nutr Food Res*. 2017;61(2).
3505. Lone J, Choi JH, Kim SW, Yun JW. Curcumin induces brown fat-like phenotype in 3T3-L1 and primary white adipocytes. *J Nutr Biochem*. 2016;27:193-202.
3506. Baskaran P, Krishnan V, Ren J, Thyagarajan B. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. *Br J Pharmacol*. 2016;173(15):2369-89.
3507. Son HK, Shin HW, Jang ES, Moon BS, Lee CH, Lee JJ. Comparison of antiobesity effects between gochujangs produced using different koji products and tabasco hot sauce in rats fed a high-fat diet. *J Med Food*. 2018;21(3):233-43.
3508. Shi Z, Riley M, Taylor AW, Page A. Chilli consumption and the incidence of overweight and obesity in a Chinese adult population. *Int J Obes (Lond)*. 2017;41(7):1074-9.
3509. Ang QY, Goh HJ, Cao Y, et al. A new method of infrared thermography for quantification of brown adipose tissue activation in healthy adults (TACTICAL): a randomized trial. *J Physiol Sci*. 2017;67(3):395-406.
3510. Alvarez-Parrilla E, de la Rosa LA, Amarowicz R, Shahidi F. Antioxidant activity of fresh and processed jalapeño and serrano peppers. *J Agric Food Chem*. 2011;59(1):163-73.
3511. European Commission Scientific Committee on Food. Opinion of the Scientific Committee on Food on capsaicin. European Commission Health & Consumer Protection Directorate-General. Published February 28, 2002. Available at: https://ec.europa.eu/food/sites/food/files/safety/docs/fs_food-improvement-agents_flavourings-out120.pdf. Accessed April 17, 2019.
3512. Rigamonti AE, Casnici C, Marelli O, et al. Acute administration of capsaicin increases resting energy expenditure in young obese subjects without affecting energy intake, appetite, and circulating levels of orexigenic/anorexigenic peptides. *Nutr Res*. 2018;52:71-9.
3513. Yoneshiro T, Aita S, Kawai Y, Iwanaga T, Saito M. Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. *Am J Clin Nutr*. 2012;95(4):845-50.
3514. Yoneshiro T, Saito M. Transient receptor potential activated brown fat thermogenesis as a target of food ingredients for obesity management. *Curr Opin Clin Nutr Metab Care*. 2013;16(6):625-31.
3515. Nirengi S, Homma T, Inoue N, et al. Assessment of human brown adipose tissue density during daily ingestion of thermogenic capsinoids using near-infrared time-resolved spectroscopy. *J Biomed Opt*. 2016;21(9):091305.
3516. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Invest*. 2013;123(8):3404-8.
3517. Yoneshiro T, Aita S, Matsushita M, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *J Clin Invest*. 2013;123(8):3404-8.
3518. Yoshioka M, Lim K, Kikuzato S, et al. Effects of red-pepper diet on the energy metabolism in men. *J Nutr Sci Vitaminol*. 1995;41(6):647-56.
3519. Yoshioka M, Lim K, Kikuzato S, et al. Effects of red-pepper diet on the energy metabolism in men. *J Nutr Sci Vitaminol*. 1995;41(6):647-56.

3520. Yoshioka M, St-Pierre S, Suzuki M, Tremblay A. Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. *Br J Nutr*. 1998;80(6):503-10.
3521. Ludy MJ, Mattes RD. The effects of hedonically acceptable red pepper doses on thermogenesis and appetite. *Physiol Behav*. 2011;102(3-4):251-8.
3522. López-Carrillo L, López-Cervantes M, Robles-Díaz G, et al. Capsaicin consumption, *Helicobacter pylori* positivity and gastric cancer in Mexico. *Int J Cancer*. 2003;106(2):277-82.
3523. Smiciklas-Wright H, Mitchell D, Mickle S, Cook A, Goldman J. Foods commonly eaten in the United States quantities consumed per eating occasion and in a day, 1994-96. United States Department of Agriculture NFS Report No. 96-5. Published January 2002. Available at: <https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/Portion.pdf>. Accessed April 17, 2019.
3524. Ludy MJ, Mattes RD. The effects of hedonically acceptable red pepper doses on thermogenesis and appetite. *Physiol Behav*. 2011;102(3-4):251-8.
3525. Smeets AJ, Janssens PL, Westerterp-Plantenga MS. Addition of capsaicin and exchange of carbohydrate with protein counteract energy intake restriction effects on fullness and energy expenditure. *J Nutr*. 2013;143(4):442-7.
3526. Smeets AJ, Janssens PL, Westerterp-Plantenga MS. Addition of capsaicin and exchange of carbohydrate with protein counteract energy intake restriction effects on fullness and energy expenditure. *J Nutr*. 2013;143(4):442-7.
3527. Janssens PL, Hursel R, Martens EA, Westerterp-Plantenga MS. Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. *PLoS ONE*. 2013;8(7):e67786.
3528. Zsiborás C, Mátics R, Hegyi P, et al. Capsaicin and capsiate could be appropriate agents for treatment of obesity: a meta-analysis of human studies. *Crit Rev Food Sci Nutr*. 2018;58(9):1419-27.
3529. Whiting S, Derbyshire EJ, Tiwari B. Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. *Appetite*. 2014;73:183-8.
3530. Leung FW. Capsaicin as an anti-obesity drug. *Prog Drug Res*. 2014;68:171-9.
3531. Tremblay A, Arguin H, Panahi S. Capsaicinoids: a spicy solution to the management of obesity? *Int J Obes (Lond)*. 2016;40(8):1198-204.
3532. Snitker S, Fujishima Y, Shen H, et al. Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. *Am J Clin Nutr*. 2009;89(1):45-50.
3533. Lejeune MP, Kovacs EM, Westerterp-Plantenga MS. Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. *Br J Nutr*. 2003;90(3):651-9.
3534. Belza A, Jessen AB. Bioactive food stimulants of sympathetic activity: effect on 24-h energy expenditure and fat oxidation. *Eur J Clin Nutr*. 2005;59(6):733-41.
3535. Belza A, Jessen AB. Bioactive food stimulants of sympathetic activity: effect on 24-h energy expenditure and fat oxidation. *Eur J Clin Nutr*. 2005;59(6):733-41.
3536. Ahuja KD, Robertson IK, Geraghty DP, Ball MJ. The effect of 4-week chilli supplementation on metabolic and arterial function in humans. *Eur J Clin Nutr*. 2007;61(3):326-33.
3537. Cha YS, Kim SR, Yang JA, et al. Kochujang, fermented soybean-based red pepper paste, decreases visceral fat and improves blood lipid profiles in overweight adults. *Nutr Metab (Lond)*. 2013;10(1):24.
3538. de Freitas MC, Cholewa JM, Gobbo LA, de Oliveira JVN, Lira FS, Rossi FE. Acute capsaicin supplementation improves 1,500-m running time-trial performance and rate of perceived exertion in physically active adults. *J Strength Cond Res*. 2018;32(2):572-7.
3539. de Freitas MC, Cholewa JM, Freire RV, et al. Acute capsaicin supplementation improves resistance training performance in trained men. *J Strength Cond Res*. 2018;32(8):2227-32.
3540. Chopan M, Littenberg B. The association of hot red chili pepper consumption and mortality: a large population-based cohort study. *PLoS ONE*. 2017;12(1):e0169876.
3541. Ruiz JM, Steffen P, Smith TB. Hispanic mortality paradox: a systematic review and meta-analysis of the longitudinal literature. *Am J Public Health*. 2013;103(3):e52-60.
3542. Schneiderman N, Chirinos DA, Avilés-Santa ML, Heiss G. Challenges in preventing heart disease in Hispanics: early lessons learned from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prog Cardiovasc Dis*. 2014;57(3):253-61.
3543. The Hispanic paradox. *Lancet*. 2015;385(9981):1918.
3544. Miniño AM. Death in the United States, 2011. *NCHS Data Brief*. 2013;(115):1-8.
3545. Young RP, Hopkins RJ. A review of the Hispanic paradox: time to spill the beans? *Eur Respir Rev*. 2014;23(134):439-49.
3546. Buettner D. *The Blue Zones, 9 Lessons for Living Longer from the People Who've Lived the Longest*. Washington, D.C.: National Geographic Society; 2012.
3547. Darmadi-Blackberry I, Wahlqvist ML, Kouris-Blazos A, et al. Legumes: the most important dietary predictor of survival in older people of different ethnicities. *Asia Pac J Clin Nutr*. 2004;13(2):217-20.
3548. Chopan M, Littenberg B. The association of hot red chili pepper consumption and mortality: a large population-based cohort study. *PLoS ONE*. 2017;12(1):e0169876.
3549. Lv J, Qi L, Yu C, et al. Consumption of spicy foods and total and cause specific mortality: population based cohort study. *BMJ*. 2015;351:h3942.
3550. Mohd Yusof YA. Gingerol and its role in chronic diseases. *Adv Exp Med Biol*. 2016;929:177-207.
3551. Liu J, Shi JZ, Yu LM, Goyer RA, Waalkes MP. Mercury in traditional medicines: is cinnabar toxicologically similar to common mercurials? *Exp Biol Med (Maywood)*. 2008;233(7):810-7.
3552. Vijoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13:20.
3553. Martins LB, Rodrigues AMDS, Rodrigues DF, dos Santos LC, Teixeira AL, Ferreira AVM. Double-blind placebo-controlled randomized clinical trial of ginger (*Zingiber officinale* Rosc.) addition in migraine acute treatment. *Cephalgia*. 2019;39(1):68-76.
3554. Pourmasoumi M, Hadi A, Rafie N, Najafgholizadeh A, Mohammadi H, Rouhani MH. The effect of ginger supplementation on lipid profile: a systematic review and meta-analysis of clinical trials. *Phytomedicine*. 2018;43:28-36.

3555. Makhdoomi Arzati M, Mohammadzadeh Honarvar N, Saedisomeolia A, et al. The effects of ginger on fasting blood sugar, hemoglobin A1c, and lipid profiles in patients with type 2 diabetes. *Int J Endocrinol Metab.* 2017;15(4):e57927.
3556. Mazidi M, Gao HK, Rezaie P, Ferns GA. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. *Food Nutr Res.* 2016;60:32613.
3557. Wang J, Ke W, Bao R, Hu X, Chen F. Beneficial effects of ginger *Zingiber officinale Roscoe* on obesity and metabolic syndrome: a review. *Ann NY Acad Sci.* 2017;1398(1):83-98.
3558. Wang Y, Yu H, Zhang X, et al. Evaluation of daily ginger consumption for the prevention of chronic diseases in adults: a cross-sectional study. *Nutrition.* 2017;36:79-84.
3559. Mansour MS, Ni YM, Roberts AL, Kelleman M, Roychoudhury A, St-Onge MP. Ginger consumption enhances the thermic effect of food and promotes feelings of satiety without affecting metabolic and hormonal parameters in overweight men: a pilot study. *Metab Clin Exp.* 2012;61(10):1347-52.
3560. Mansour MS, Ni YM, Roberts AL, Kelleman M, Roychoudhury A, St-Onge MP. Ginger consumption enhances the thermic effect of food and promotes feelings of satiety without affecting metabolic and hormonal parameters in overweight men: a pilot study. *Metab Clin Exp.* 2012;61(10):1347-52.
3561. Miyamoto M, Matsuzaki K, Katakura M, Hara T, Tanabe Y, Shido O. Oral intake of encapsulated dried ginger root powder hardly affects human thermoregulatory function, but appears to facilitate fat utilization. *Int J Biometeorol.* 2015;59(10):1461-74.
3562. Mansour MS, Ni YM, Roberts AL, Kelleman M, Roychoudhury A, St-Onge MP. Ginger consumption enhances the thermic effect of food and promotes feelings of satiety without affecting metabolic and hormonal parameters in overweight men: a pilot study. *Metab Clin Exp.* 2012;61(10):1347-52.
3563. Iwasaki Y, Morita A, Iwasawa T, et al. A nonpungent component of steamed ginger—[10]-shogaol—increases adrenaline secretion via the activation of TRPV1. *Nutr Neurosci.* 2006;9(3-4):169-78.
3564. Henry CJ, Piggott SM. Effect of ginger on metabolic rate. *Hum Nutr Clin Nutr.* 1987;41(1):89-92.
3565. Sugita J, Yoneshiro T, Hatano T, et al. Grains of paradise (*Aframomum melegueta*) extract activates brown adipose tissue and increases whole-body energy expenditure in men. *Br J Nutr.* 2013;110(4):733-8.
3566. Sugita J, Yoneshiro T, Sugishima Y, et al. Daily ingestion of grains of paradise (*Aframomum melegueta*) extract increases whole-body energy expenditure and decreases visceral fat in humans. *J Nutr Sci Vitaminol.* 2014;60(1):22-7.
3567. Maharlouei N, Tabrizi R, Lankarani KB, et al. The effects of ginger intake on weight loss and metabolic profiles among overweight and obese subjects: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr.* 2018:1-14.
3568. Morgan JP, Penovich P. Jamaica ginger paralysis. Forty-seven-year follow-up. *Arch Neurol.* 1978;35(8):530-2.
3569. Crandall FG. Paralysis—from spurious Jamaica ginger extract: report on Los Angeles county outbreak. *Cal West Med.* 1931;35(3):180-2.
3570. Kwan HY, Wu J, Su T, et al. Cinnamon induces browning in subcutaneous adipocytes. *Sci Rep.* 2017;7(1):2447.
3571. Borzoei A, Rafraf M, Asghari-Jafarabadi M. Cinnamon improves metabolic factors without detectable effects on adiponectin in women with polycystic ovary syndrome. *Asia Pac J Clin Nutr.* 2018;27(3):556-63.
3572. Zare R, Nadjarzadeh A, Zarshenas MM, Shams V, Heydari M. Efficacy of cinnamon in patients with type II diabetes mellitus: a randomized controlled clinical trial. *Clin Nutr.* 2019;38(2):549-56.
3573. Vafa M, Mohammadi F, Shidfar F, et al. Effects of cinnamon consumption on glycemic status, lipid profile and body composition in type 2 diabetic patients. *Int J Prev Med.* 2012;3(8):531-6.
3574. Gupta Jain S, Puri S, Misra A, Gulati S, Mani K. Effect of oral cinnamon intervention on metabolic profile and body composition of Asian Indians with metabolic syndrome: a randomized double-blind control trial. *Lipids Health Dis.* 2017;16(1):113.
3575. Wainstein J, Stern N, Heller S, Boaz M. Dietary cinnamon supplementation and changes in systolic blood pressure in subjects with type 2 diabetes. *J Med Food.* 2011;14(12):1505-10.
3576. Kort DH, Lobo RA. Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial. *Am J Obstet Gynecol.* 2014;211(5):487.e1-6.
3577. Mang B, Wolters M, Schmitt B, et al. Effects of a cinnamon extract on plasma glucose, HbA_{1c}, and serum lipids in diabetes mellitus type 2. *Eur J Clin Invest.* 2006;36(5):340-4.
3578. Shishehbor F, Rezaeyan Safar M, Rajaei E, Haghighizadeh MH. Cinnamon consumption improves clinical symptoms and inflammatory markers in women with rheumatoid arthritis. *J Am Coll Nutr.* 2018:1-6.
3579. Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raee MJ, Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: a randomized double-blind placebo controlled clinical trial. *Phytother Res.* 2018;32(2):276-83.
3580. Askari F, Rashidkhani B, Hekmatdoost A. Cinnamon may have therapeutic benefits on lipid profile, liver enzymes, insulin resistance, and high-sensitivity C-reactive protein in nonalcoholic fatty liver disease patients. *Nutr Res.* 2014;34(2):143-8.
3581. Oketch-Rabah HA, Marles RJ, Brinckmann JA. Cinnamon and cassia nomenclature confusion: a challenge to the applicability of clinical data. *Clin Pharmacol Ther.* 2018;104(3):435-45.
3582. Bautista DM, Siemens J, Glazer JM, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature.* 2007;448(7150):204-8.
3583. Rossato M, Granzotto M, Macchi V, et al. Human white adipocytes express the cold receptor TRPM8 which activation induces UCP1 expression, mitochondrial activation and heat production. *Mol Cell Endocrinol.* 2014;383(1-2):137-46.
3584. Sakellariou P, Valente A, Carrillo AE, et al. Chronic L-menthol-induced browning of white adipose tissue hypothesis: a putative therapeutic regime for combating obesity and improving metabolic health. *Med Hypotheses.* 2016;93:21-6.
3585. Ma S, Yu H, Zhao Z, et al. Activation of the cold-sensing TRPM8 channel triggers UCP1-dependent thermogenesis and prevents obesity. *J Mol Cell Biol.* 2012;4(2):88-96.

3586. Valente A, Carrillo AE, Tzatzarakis MN, et al. The absorption and metabolism of a single L-menthol oral versus skin administration: effects on thermogenesis and metabolic rate. *Food Chem Toxicol.* 2015;86:262-73.
3587. Gonseth S, Jacot-Sadowski I, Diethelm PA, Barras V, Cornuz J. The tobacco industry's past role in weight control related to smoking. *Eur J Public Health.* 2012;22(2):234-7.
3588. Valente A, Carrillo AE, Tzatzarakis MN, et al. The absorption and metabolism of a single L-menthol oral versus skin administration: effects on thermogenesis and metabolic rate. *Food Chem Toxicol.* 2015;86:262-73.
3589. Patel T, Ishiujji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol.* 2007;57(5):873-8.
3590. Topp R, Ledford ER, Jacks DE. Topical menthol, ice, peripheral blood flow, and perceived discomfort. *J Athl Train.* 2013;48(2):220-5.
3591. Johar P, Grover V, Topp R, Behm DG. A comparison of topical menthol to ice on pain, evoked tetanic and voluntary force during delayed onset muscle soreness. *Int J Sports Phys Ther.* 2012;7(3):314-22.
3592. Sundstrup E, Jakobsen MD, Brandt M, et al. Acute effect of topical menthol on chronic pain in slaughterhouse workers with carpal tunnel syndrome: triple-blind, randomized placebo-controlled trial. *Rehabil Res Pract.* 2014;2014:310913.
3593. Borhani Haghighi A, Motazedian S, Rezaii R, et al. Cutaneous application of menthol 10% solution as an abortive treatment of migraine without aura: a randomised, double-blind, placebo-controlled, crossed-over study. *Int J Clin Pract.* 2010;64(4):451-6.
3594. Vizin RCL, Motzko-Soares ACP, Armentano GM, et al. Short-term menthol treatment promotes persistent thermogenesis without induction of compensatory food consumption in Wistar rats: implications for obesity control. *J Appl Physiol.* 2018;124(3):672-83.
3595. Patel T, Ishiujji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol.* 2007;57(5):873-8.
3596. Nair B. Final report on the safety assessment of *Mentha piperita* (peppermint) oil, *Mentha piperita* (peppermint) leaf extract, *Mentha piperita* (peppermint) leaf, and *Mentha piperita* (peppermint) leaf water. *Int J Toxicol.* 2001;20 Suppl 3:61-73.
3597. Kanerva L, Rantanen T, Aalto-Korte K, et al. A multicenter study of patch test reactions with dental screening series. *Am J Contact Dermatitis.* 2001;12(2):83-7.
3598. Patel T, Ishiujji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. *J Am Acad Dermatol.* 2007;57(5):873-8.
3599. Chan TY. Potential dangers from topical preparations containing methyl salicylate. *Hum Exp Toxicol.* 1996;15(9):747-50.
3600. Beulaygue IC, French MT. Got munchies? Estimating the relationship between marijuana use and body mass index. *J Ment Health Policy Econ.* 2016;19(3):123-40.
3601. Jin LZ, Rangan A, Mehlsen J, Andersen LB, Larsen SC, Heitmann BL. Association between use of cannabis in adolescence and weight change into midlife. *PLoS ONE.* 2017;12(1):e0168897.
3602. Mohs ME, Watson RR, Leonard-Green T. Nutritional effects of marijuana, heroin, cocaine, and nicotine. *J Am Diet Assoc.* 1990;90(9):1261-7.
3603. Simon V, Cota D. Endocannabinoids and metabolism: past, present and future. *Eur J Endocrinol.* 2017;176(6):R309-24.
3604. Badowski ME, Perez SE. Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS. *HIV AIDS (Auckl).* 2016;8:37-45.
3605. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite.* 1988;11(1):1-14.
3606. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. *Science.* 1973;179(4077):1011-4.
3607. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci USA.* 1990;87(5):1932-6.
3608. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet.* 2007;370(9600):1706-13.
3609. Richey JM, Woolcott O. Re-visiting the endocannabinoid system and its therapeutic potential in obesity and associated diseases. *Curr Diab Rep.* 2017;17(10):99.
3610. Le Foll B, Trigo JM, Sharkey KA, Le Strat Y. Cannabis and Δ^9 -tetrahydrocannabinol (THC) for weight loss? *Med Hypotheses.* 2013;80(5):564-7.
3611. Jin LZ, Rangan A, Mehlsen J, Andersen LB, Larsen SC, Heitmann BL. Association between use of cannabis in adolescence and weight change into midlife. *PLoS ONE.* 2017;12(1):e0168897.
3612. Zwillich CW, Doekel R, Hammill S, Weil JV. The effects of smoked marijuana on metabolism and respiratory control. *Am Rev Respir Dis.* 1978;118(5):885-91.
3613. Lahesmaa M, Eriksson O, Gnad T, et al. Cannabinoid type 1 receptors are upregulated during acute activation of brown adipose tissue. *Diabetes.* 2018;67(7):1226-36.
3614. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, D.C.: National Academies Press; 2017. Available at: <https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>. Accessed April 17, 2019.
3615. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, D.C.: National Academies Press; 2017. Available at: <https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>. Accessed April 17, 2019.
3616. Kim HS, Anderson JD, Saghafi O, Heard KJ, Monte AA. Cyclic vomiting presentations following marijuana liberalization in Colorado. *Acad Emerg Med.* 2015;22(6):694-9.
3617. Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. *Clin Toxicol (Phila).* 2018;56(1):15-24.

3618. Moon AM, Buckley SA, Mark NM. Successful treatment of cannabinoid hyperemesis syndrome with topical capsaicin. *ACG Case Rep J*. 2018;5:e3.
3619. Komatsu T, Nakamori M, Komatsu K, et al. Oolong tea increases energy metabolism in Japanese females. *J Med Invest*. 2003;50(3-4):170-5.
3620. Willems MET, Şahin MA, Cook MD. Matcha green tea drinks enhance fat oxidation during brisk walking in females. *Int J Sport Nutr Exerc Metab*. 2018;28(5):536-41.
3621. Venables MC, Hulston CJ, Cox HR, Jeukendrup AE. Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. *Am J Clin Nutr*. 2008;87(3):778-84.
3622. Dulloo AG, Duret C, Rohrer D, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr*. 1999;70(6):1040-5.
3623. Hursel R, Viechtbauer W, Dulloo AG, et al. The effects of catechin rich teas and caffeine on energy expenditure and fat oxidation: a meta-analysis. *Obes Rev*. 2011;12(7):e573-81.
3624. Dulloo AG, Duret C, Rohrer D, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr*. 1999;70(6):1040-5.
3625. Palamar J. How ephedrine escaped regulation in the United States: a historical review of misuse and associated policy. *Health Policy*. 2011;99(1):1-9.
3626. Shixian Q, Vancrey B, Shi J, Kakuda Y, Jiang Y. Green tea extract thermogenesis-induced weight loss by epigallocatechin gallate inhibition of catechol-O-methyltransferase. *J Med Food*. 2006;9(4):451-8.
3627. Shixian Q, Vancrey B, Shi J, Kakuda Y, Jiang Y. Green tea extract thermogenesis-induced weight loss by epigallocatechin gallate inhibition of catechol-O-methyltransferase. *J Med Food*. 2006;9(4):451-8.
3628. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the flavonoid content of selected foods, release 3.0. Nutrient Data Laboratory, Agricultural Research Service, United States Department of Agriculture. Published September 2011. Available at: https://www.ars.usda.gov/ARSUserFiles/80400525/Data/Flav/Flav_R03.pdf. Accessed April 17, 2019.
3629. Rains TM, Agarwal S, Maki KC. Antiobesity effects of green tea catechins: a mechanistic review. *J Nutr Biochem*. 2011;22(1):1-7.
3630. Kadowaki M, Ootani E, Sugihara N, Furuno K. Inhibitory effects of catechin gallates on o-methyltranslation of protocatechuic acid in rat liver cytosolic preparations and cultured hepatocytes. *Biol Pharm Bull*. 2005;28(8):1509-13.
3631. Dulloo AG, Duret C, Rohrer D, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr*. 1999;70(6):1040-5.
3632. Li G, Zhang Y, Thabane L, et al. Effect of green tea supplementation on blood pressure among overweight and obese adults: a systematic review and meta-analysis. *J Hypertens*. 2015;33(2):243-54.
3633. Lorenz M, Paul F, Moobed M, et al. The activity of catechol-O-methyltransferase (COMT) is not impaired by high doses of epigallocatechin-3-gallate (EGCG) in vivo. *Eur J Pharmacol*. 2014;740:645-51.
3634. Hodgson AB, Randell RK, Boon N, et al. Metabolic response to green tea extract during rest and moderate-intensity exercise. *J Nutr Biochem*. 2013;24(1):325-34.
3635. Cardoso GA, Salgado JM, de Castro César M, Donado-Pestana CM. The effects of green tea consumption and resistance training on body composition and resting metabolic rate in overweight or obese women. *J Med Food*. 2013;16(2):120-7.
3636. Mi Y, Liu X, Tian H, et al. EGCG stimulates the recruitment of brite adipocytes, suppresses adipogenesis and counteracts TNF- α -triggered insulin resistance in adipocytes. *Food Funct*. 2018;9(6):3374-36.
3637. Gosselin C, Haman F. Effects of green tea extracts on non-shivering thermogenesis during mild cold exposure in young men. *Br J Nutr*. 2013;110(2):282-8.
3638. Yoneshiro T, Matsushita M, Hibi M, et al. Tea catechin and caffeine activate brown adipose tissue and increase cold-induced thermogenic capacity in humans. *Am J Clin Nutr*. 2017;105(4):873-81.
3639. Nirengi S, Amagasa S, Homma T, et al. Daily ingestion of catechin-rich beverage increases brown adipose tissue density and decreases extramyocellular lipids in healthy young women. *Springerplus*. 2016;5(1):1363.
3640. Yoneshiro T, Matsushita M, Hibi M, et al. Tea catechin and caffeine activate brown adipose tissue and increase cold-induced thermogenic capacity in humans. *Am J Clin Nutr*. 2017;105(4):873-81.
3641. Nirengi S, Amagasa S, Homma T, et al. Daily ingestion of catechin-rich beverage increases brown adipose tissue density and decreases extramyocellular lipids in healthy young women. *Springerplus*. 2016;5(1):1363.
3642. Tang D, Li TY, Liu JJ, et al. Effects of prenatal exposure to coal-burning pollutants on children's development in China. *Environ Health Perspect*. 2008;116(5):674-9.
3643. Han WY, Zhao FJ, Shi YZ, Ma LF, Ruan JY. Scale and causes of lead contamination in Chinese tea. *Environ Pollut*. 2006;139(1):125-32.
3644. Han WY, Zhao FJ, Shi YZ, Ma LF, Ruan JY. Scale and causes of lead contamination in Chinese tea. *Environ Pollut*. 2006;139(1):125-32.
3645. Chen Y, Xu J, Yu M, Chen X, Shi J. Lead contamination in different varieties of tea plant (*Camellia sinensis* L.) and factors affecting lead bioavailability. *J Sci Food Agric*. 2010;90(9):1501-7.
3646. Shen FM, Chen HW. Element composition of tea leaves and tea infusions and its impact on health. *Bull Environ Contam Toxicol*. 2008;80(3):300-4.
3647. Karak T, Bhagat R. Trace elements in tea leaves, made tea and tea infusion: a review. *Food Res Int*. 2010;43(9):2234-52.
3648. Schwalfenberg G, Genuis SJ, Rodushkin I. The benefits and risks of consuming brewed tea: beware of toxic element contamination. *J Toxicol*. 2013;2013:370460.
3649. Shen FM, Chen HW. Element composition of tea leaves and tea infusions and its impact on health. *Bull Environ Contam Toxicol*. 2008;80(3):300-4.
3650. Karak T, Bhagat R. Trace elements in tea leaves, made tea and tea infusion: a review. *Food Res Int*. 2010;43(9):2234-52.
3651. American College of Obstetricians and Gynecologists. Committee Opinion No. 462: moderate caffeine consumption during pregnancy. *Obstet Gynecol*. 2010;116(2, Part 1):467-8.

3652. Chen IJ, Liu CY, Chiu JP, Hsu CH. Therapeutic effect of high-dose green tea extract on weight reduction: a randomized, double-blind, placebo-controlled clinical trial. *Clin Nutr*. 2016;35(3):592-9.
3653. Hoofnagle JH, Wright EC. Weight loss from green tea extracts. *Clin Nutr*. 2016;35(1):238.
3654. Hussain M, Habib-Ur-Rehman M, Akhtar L. Therapeutic benefits of green tea extract on various parameters in non-alcoholic fatty liver disease patients. *Pak J Med Sci*. 2017;33(4):931-6.
3655. Josic J, Olsson AT, Wickeberg J, Lindstedt S, Hlebowicz J. Does green tea affect postprandial glucose, insulin and satiety in healthy subjects: a randomized controlled trial. *Nutr J*. 2010;9:63.
3656. Auvichayapat P, PrapoChanung M, Tunkammerdthai O, et al. Effectiveness of green tea on weight reduction in obese Thais: a randomized, controlled trial. *Physiol Behav*. 2008;93(3):486-91.
3657. Jurgens TM, Whelan AM, Killian L, Doucette S, Kirk S, Foy E. Green tea for weight loss and weight maintenance in overweight or obese adults. *Cochrane Database Syst Rev*. 2012;12:CD008650.
3658. Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. *Am J Clin Nutr*. 2010;91(1):73-81.
3659. Hayat K, Iqbal H, Malik U, Bilal U, Mushtaq S. Tea and its consumption: benefits and risks. *Crit Rev Food Sci Nutr*. 2015;55(7):939-54.
3660. Yuan F, Dong H, Fang K, Gong J, Lu F. Effects of green tea on lipid metabolism in overweight or obese people: a meta-analysis of randomized controlled trials. *Mol Nutr Food Res*. 2018;62(1).
3661. Shin CM, Lee DH, Seo AY, et al. Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: a randomized clinical trial. *Clin Nutr*. 2018;37(2):452-8.
3662. Ide K, Yamada H, Kawasaki Y. Effect of gargling with tea and ingredients of tea on the prevention of influenza infection: a meta-analysis. *BMC Public Health*. 2016;16:396.
3663. Tang J, Zheng JS, Fang L, Jin Y, Cai W, Li D. Tea consumption and mortality of all cancers, CVD and all causes: a meta-analysis of eighteen prospective cohort studies. *Br J Nutr*. 2015;114(5):673-83.
3664. Basu A, Sanchez K, Leyva MJ, et al. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *J Am Coll Nutr*. 2010;29(1):31-40.
3665. Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. *Dig Dis Sci*. 2013;58(9):2682-90.
3666. Phan AD, Netzel G, Wang D, Flanagan BM, D'Arcy BR, Gidley MJ. Binding of dietary polyphenols to cellulose: structural and nutritional aspects. *Food Chem*. 2015;171:388-96.
3667. Glube N, von Moos L, Duchateau G. Capsule shell material impacts the in vitro disintegration and dissolution behaviour of a green tea extract. *Results Pharma Sci*. 2013;3:1-6.
3668. Kim A, Chiu A, Barone MK, et al. Green tea catechins decrease total and low-density lipoprotein cholesterol: a systematic review and meta-analysis. *J Am Diet Assoc*. 2011;111(11):1720-9.
3669. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf*. 2008;31(6):469-84.
3670. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults—results of a systematic review. *Regul Toxicol Pharmacol*. 2018;95:412-33.
3671. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf*. 2008;31(6):469-84.
3672. Dekant W, Fujii K, Shibata E, Morita O, Shimotoyodome A. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. *Toxicol Lett*. 2017;277:104-8.
3673. Chang K. World tea production and trade current and future development. Food and Agriculture Organization of the United Nations. Published 2015. Available at: <http://www.fao.org/3/a-i4480e.pdf>. Accessed April 17, 2019.
3674. Grove KA, Lambert JD. Laboratory, epidemiological, and human intervention studies show that tea (*Camellia sinensis*) may be useful in the prevention of obesity. *J Nutr*. 2010;140(3):446-53.
3675. Shanafelt TD, Call TG, Zent CS, et al. Phase 2 trial of daily, oral Polyphenon E in patients with asymptomatic, Rai stage 0 to II chronic lymphocytic leukemia. *Cancer*. 2013;119(2):363-70.
3676. Dekant W, Fujii K, Shibata E, Morita O, Shimotoyodome A. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. *Toxicol Lett*. 2017;277:104-8.
3677. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf*. 2008;31(6):469-84.
3678. Jochmann N, Lorenz M, Krosigk Av, et al. The efficacy of black tea in ameliorating endothelial function is equivalent to that of green tea. *Br J Nutr*. 2008;99(4):863-8.
3679. Wang ZM, Zhou B, Wang YS, et al. Black and green tea consumption and the risk of coronary artery disease: a meta-analysis. *Am J Clin Nutr*. 2011;93(3):506-15.
3680. Woodward M, Tunstall-Pedoe H. Coffee and tea consumption in the Scottish Heart Health Study follow up: conflicting relations with coronary risk factors, coronary disease, and all cause mortality. *J Epidemiol Community Health*. 1999;53(8):481-7.
3681. Hertog MG, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. *Am J Clin Nutr*. 1997;65(5):1489-94.
3682. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. 1993;342(8878):1007-11.
3683. Geleijnse JM, Launer LJ, Van der Kuip DA, Hofman A, Witteman JC. Inverse association of tea and flavonoid intakes with incident myocardial infarction: the Rotterdam Study. *Am J Clin Nutr*. 2002;75(5):880-6.
3684. Lorenz M, Jochmann N, von Krosigk A, et al. Addition of milk prevents vascular protective effects of tea. *Eur Heart J*. 2007;28(2):219-23.
3685. Hursel R, Westerterp-Plantenga MS. Consumption of milk-protein combined with green tea modulates diet-induced thermogenesis. *Nutrients*. 2011;3(8):725-33.
3686. Lee RJ, Bayne A, Tiangco M, Garen G, Chow AK. Prevention of tea-induced extrinsic tooth stain. *Int J Dent Hyg*. 2014;12(4):267-72.

3687. Serafini M, Testa MF, Villaño D, et al. Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med*. 2009;46(6):769–74.
3688. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature*. 2003;424(6952):1013.
3689. Duarte GS, Farah A. Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem*. 2011;59(14):7925–31.
3690. Budryn G, Patecz B, Rachwał-Rosiak D, et al. Effect of inclusion of hydroxycinnamic and chlorogenic acids from green coffee bean in β -cyclodextrin on their interactions with whey, egg white and soy protein isolates. *Food Chem*. 2015;168:276–87.
3691. Felberg I, Farah A, Monteiro M, et al. Effect of simultaneous consumption of soymilk and coffee on the urinary excretion of isoflavones, chlorogenic acids and metabolites in healthy adults. *J Funct Foods*. 2015;19:688–99.
3692. Felberg I, Farah A, Monteiro M, et al. Effect of simultaneous consumption of soymilk and coffee on the urinary excretion of isoflavones, chlorogenic acids and metabolites in healthy adults. *J Funct Foods*. 2015;19:688–99.
3693. European Society of Cardiology. Milk eliminates cardiovascular health benefits of tea, researchers warn. *ScienceDaily*. Published January 9, 2007. Available at: <https://www.sciencedaily.com/releases/2007/01/070108191523.htm>. Accessed April 17, 2019.
3694. von Elm E, Antes G. Tea without milk: lifestyle advice based on a small lab study. *Eur Heart J*. 2007;28(11):1398.
3695. Lorenz M, Stangl K, Stangl V. Milk casein and its benefits on cardiovascular risk: reply. *Eur Heart J*. 2007;28(11):1397–8.
3696. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200–5.
3697. Marcason W. What is green coffee extract? *J Acad Nutr Diet*. 2013;113(2):364.
3698. Mullin GE. Supplements for weight loss: hype or help for obesity? Part II. The inside scoop on green coffee bean extract. *Nutr Clin Pract*. 2015;30(2):311–2.
3699. Vinson JA, Burnham BR, Nagendran MV. Randomized, double-blind, placebo-controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects. *Diabetes Metab Syndr Obes*. 2012;5:21–7.
3700. *Federal Trade Commission v. Applied Food Sciences, Inc*, 1:14-CV- 00851 (U.S. District Court, Western District of TX, Austin, 2014).
3701. Mullin GE. Supplements for weight loss: hype or help for obesity? Part II. The inside scoop on green coffee bean extract. *Nutr Clin Pract*. 2015;30(2):311–2.
3702. Vinson JA, Burnham BR, Nagendran MV. Randomized, double-blind, placebo-controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects [Retraction]. *Diabetes Metab Syndr Obes*. 2014;7:467.
3703. Dellalibera O, Lemaire B, Lafay S. Svetol®, green coffee extract, induces weight loss and increases the lean to fat mass ratio in volunteers with overweight problem. *Phytotherapie*. 2006;4(4):194–7.
3704. Thom E. The effect of chlorogenic acid enriched coffee on glucose absorption in healthy volunteers and its effect on body mass when used long-term in overweight and obese people. *J Int Med Res*. 2007;35(6):900–8.
3705. Roshan H, Nikpayam O, Sedaghat M, Sohrab G. Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance and appetite in patients with the metabolic syndrome: a randomised clinical trial. *Br J Nutr*. 2018;119(3):250–8.
3706. Haggins H, Means J. The effect of certain drugs on the respiration and gaseous metabolism in normal human subjects. *J Pharmacol Exp Ther*. 1915:1–29.
3707. Kole J, Barnhill A. Caffeine content labeling: a missed opportunity for promoting personal and public health. *J Caffeine Res*. 2013;3(3):108–13.
3708. Dulloo AG, Duret C, Rohrer D, et al. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr*. 1999;70(6):1040–5.
3709. Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev*. 2017;31:70–8.
3710. Schubert MM, Hall S, Leveritt M, Grant G, Sabapathy S, Desbrow B. Caffeine consumption around an exercise bout: effects on energy expenditure, energy intake, and exercise enjoyment. *J Appl Physiol*. 2014;117(7):745–54.
3711. Schubert MM, Hall S, Leveritt M, Grant G, Sabapathy S, Desbrow B. Caffeine consumption around an exercise bout: effects on energy expenditure, energy intake, and exercise enjoyment. *J Appl Physiol*. 2014;117(7):745–54.
3712. Clarke ND, Richardson DL, Thie J, Taylor R. Coffee ingestion enhances 1-mile running race performance. *Int J Sports Physiol Perform*. 2018;13(6):789–94.
3713. Richardson DL, Clarke ND. Effect of coffee and caffeine ingestion on resistance exercise performance. *J Strength Cond Res*. 2016;30(10):2892–900.
3714. Schubert MM, Hall S, Leveritt M, Grant G, Sabapathy S, Desbrow B. Caffeine consumption around an exercise bout: effects on energy expenditure, energy intake, and exercise enjoyment. *J Appl Physiol*. 2014;117(7):745–54.
3715. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. *Am J Clin Nutr*. 1989;49(1):44–50.
3716. Tagliabue A, Terracina D, Cena H, Turconi G, Lanzola E, Montomoli C. Coffee induced thermogenesis and skin temperature. *Int J Obes Relat Metab Disord*. 1994;18(8):537–41.
3717. Bracco D, Ferrarra JM, Arnaud MJ, Jéquier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. *Am J Physiol*. 1995;269(4 Pt 1):E671–8.
3718. Agricultural Research Service, United States Department of Agriculture. Basic report: 14209, beverages, coffee, brewed, prepared with tap water. National Nutrient Database for Standard Reference 1. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/14209>. Accessed April 17, 2019.
3719. Lenne RL, Mann T. Reducing sugar use in coffee while maintaining enjoyment: a randomized controlled trial. *J Health Psychol*. 2017;1359105317723452.
3720. An R, Shi Y. Consumption of coffee and tea with add-ins in relation to daily energy, sugar, and fat intake in US adults, 2001–2012. *Public Health*. 2017;146:1–3.

3721. Dunkin Donuts. Nutrition guide. Updated March 26, 2019. Available at: <https://www.dunkindonuts.com/content/dam/dd/pdf/nutrition.pdf>. Accessed April 17, 2019.
3722. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. *Am J Clin Nutr*. 1989;49(1):44-50.
3723. Gavrieli A, Karfopoulou E, Kardatou E, et al. Effect of different amounts of coffee on dietary intake and appetite of normal-weight and overweight/obese individuals. *Obesity (Silver Spring)*. 2013;21(6):1127-32.
3724. Schubert MM, Irwin C, Seay RF, Clarke HE, Allegro D, Desbrow B. Caffeine, coffee, and appetite control: a review. *Int J Food Sci Nutr*. 2017;68(8):901-12.
3725. Ohnaka K, Ikeda M, Maki T, et al. Effects of 16-week consumption of caffeinated and decaffeinated instant coffee on glucose metabolism in a randomized controlled trial. *J Nutr Metab*. 2012;2012:207426.
3726. Yoshioka M, Doucet E, Drapeau V, Dionne I, Tremblay A. Combined effects of red pepper and caffeine consumption on 24 h energy balance in subjects given free access to foods. *Br J Nutr*. 2001;85(2):203-11.
3727. Harpaz E, Tamir S, Weinstein A, Weinstein Y. The effect of caffeine on energy balance. *J Basic Clin Physiol Pharmacol*. 2017;28(1):1-10.
3728. Heath RD, Brahmabhatt M, Tahan AC, Ibdah JA, Tahan V. Coffee: the magical bean for liver diseases. *World J Hepatol*. 2017;9(15):689-96.
3729. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.
3730. Surdea-Blaga T, Negrutiu DE, Palage M, Dumitrascu DL. Food and gastroesophageal reflux disease. *Curr Med Chem*. 2017;5.
3731. Liu H, Yao K, Zhang W, Zhou J, Wu T, He C. Coffee consumption and risk of fractures: a meta-analysis. *Arch Med Sci*. 2012;8(5):776-83.
3732. Chandrasekaran S, Rochtchina E, Mitchell P. Effects of caffeine on intraocular pressure: the Blue Mountains Eye Study. *J Glaucoma*. 2005;14(6):504-7.
3733. Bryant CM, Dowell CJ, Fairbrother G. Caffeine reduction education to improve urinary symptoms. *Br J Nurs*. 2002;11(8):560-5.
3734. Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev*. 2017;31:70-8.
3735. Drake C, Roehrs T, Shambroom J, Roth T. Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med*. 2013;9(11):1195-200.
3736. Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res*. 1995;675(1-2):67-74.
3737. Clark I, Landolt HP. Coffee, caffeine, and sleep: a systematic review of epidemiological studies and randomized controlled trials. *Sleep Med Rev*. 2017;31:70-8.
3738. Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res*. 1995;675(1-2):67-74.
3739. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.
3740. Manchester J, Eshel I, Marion DW. The benefits and risks of energy drinks in young adults and military service members. *Mil Med*. 2017;182(7):e1726-33.
3741. Thornton J, Colby DA, Devine P. Proposed actions for the US Food and Drug Administration to implement to minimize adverse effects associated with energy drink consumption. *Am J Public Health*. 2014;104(7):1175-80.
3742. Manchester J, Eshel I, Marion DW. The benefits and risks of energy drinks in young adults and military service members. *Mil Med*. 2017;182(7):e1726-33.
3743. Mattson ME. Update on emergency department visits involving energy drinks: a continuing public health concern. The CBHSQ Report. Published January 10, 2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK384664/pdf/Bookshelf_NBK384664.pdf. Accessed April 17, 2019.
3744. Ali F, Rehman H, Babayan Z, Stapleton D, Joshi DD. Energy drinks and their adverse health effects: a systematic review of the current evidence. *Postgrad Med*. 2015;127(3):308-22.
3745. Al-Shaar L, Vercammen K, Lu C, Richardson S, Tamez M, Mattei J. Health effects and public health concerns of energy drink consumption in the United States: a mini-review. *Front Public Health*. 2017;5:225.
3746. Al-Shaar L, Vercammen K, Lu C, Richardson S, Tamez M, Mattei J. Health effects and public health concerns of energy drink consumption in the United States: a mini-review. *Front Public Health*. 2017;5:225.
3747. Alford C, Cox H, Wescott R. The effects of Red Bull Energy Drink on human performance and mood. *Amino Acids*. 2001;21(2):139-50.
3748. Baum M, Weiss M. The influence of a taurine containing drink on cardiac parameters before and after exercise measured by echocardiography. *Amino Acids*. 2001;20(1):75-82.
3749. Grasser EK, Yepuri G, Dulloo AG, Montani JP. Cardio-and cerebrovascular responses to the energy drink Red Bull in young adults: a randomized cross-over study. *Eur J Nutr*. 2014;53(7):1561-71.
3750. Phillips MD, Rola KS, Christensen KV, Ross JW, Mitchell JB. Preexercise energy drink consumption does not improve endurance cycling performance but increases lactate, monocyte, and interleukin-6 response. *J Strength Cond Res*. 2014;28(5):1443-53.
3751. Svatikova A, Covassin N, Somers KR, et al. A randomized trial of cardiovascular responses to energy drink consumption in healthy adults. *JAMA*. 2015;314(19):2079-82.
3752. Higgins JP, Yang B, Herrin NE, et al. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. *World J Cardiol*. 2017;9(2):162-6.
3753. Fletcher EA, Lacey CS, Aaron M, Kolasa M, Occiano A, Shah SA. Randomized controlled trial of high-volume energy drink versus caffeine consumption on ECG and hemodynamic parameters. *J Am Heart Assoc*. 2017;6(5).
3754. Fletcher EA, Lacey CS, Aaron M, Kolasa M, Occiano A, Shah SA. Randomized controlled trial of high-volume energy drink versus caffeine consumption on ECG and hemodynamic parameters. *J Am Heart Assoc*. 2017;6(5).
3755. Seifert SM, Schaechter JL, Hershoin ER, Lipshultz SE. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics*. 2011;127(3):511-28.

3756. Ahmad Fuzi SF, Koller D, Bruggraber S, Pereira DI, Dainty JR, Mushtaq S. A 1-h time interval between a meal containing iron and consumption of tea attenuates the inhibitory effects on iron absorption: a controlled trial in a cohort of healthy UK women using a stable iron isotope. *Am J Clin Nutr*. 2017;106(6):1413-21.
3757. Wansink B, Sobal J. Mindless eating: the 200 daily food decisions we overlook. *Environ Behav*. 2007;39:106-23. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
3758. Cleo G, Isenring E, Thomas R, Glasziou P. Could habits hold the key to weight loss maintenance? A narrative review. *J Hum Nutr Diet*. 2017;30(5):655-64.
3759. Townsend D, Bever T. *Sentence Comprehension: The Integration of Habits and Rules*. Cambridge, MA: MIT Press; 2001.
3760. Rothman AJ, Sheeran P, Wood W. Reflective and automatic processes in the initiation and maintenance of dietary change. *Ann Behav Med*. 2009;38 Suppl 1:S4-17.
3761. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of "habit-formation" and general practice. *Br J Gen Pract*. 2012;62(605):664-6.
3762. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of "habit-formation" and general practice. *Br J Gen Pract*. 2012;62(605):664-6.
3763. Orbell S, Verplanken B. The automatic component of habit in health behavior: habit as cue-contingent automaticity. *Health Psychol*. 2010;29(4):374-83.
3764. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing*. 2006;25:90-103.
3765. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of "habit-formation" and general practice. *Br J Gen Pract*. 2012;62(605):664-6.
3766. Orbell S, Verplanken B. The automatic component of habit in health behavior: habit as cue-contingent automaticity. *Health Psychol*. 2010;29(4):374-83.
3767. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of "habit-formation" and general practice. *Br J Gen Pract*. 2012;62(605):664-6.
3768. Lally P, van Jaarsveld CHM, Potts HWW, Wardle J. How are habits formed: modelling habit formation in the real world. *Euro J Soc Psychol*. 2010;40:998-1009.
3769. Orbell S, Verplanken B. The automatic component of habit in health behavior: habit as cue-contingent automaticity. *Health Psychol*. 2010;29(4):374-83.
3770. Neal DT, Wood W, Wu M, Kurlander D. The pull of the past: when do habits persist despite conflict with motives? *Pers Soc Psychol Bull*. 2011;37(11):1428-37.
3771. Neal DT, Wood W, Wu M, Kurlander D. The pull of the past: when do habits persist despite conflict with motives? *Pers Soc Psychol Bull*. 2011;37(11):1428-37.
3772. van't Riet J, Sijtsema SJ, Dagevos H, De Bruijn GJ. The importance of habits in eating behaviour. An overview and recommendations for future research. *Appetite*. 2011;57(3):585-96.
3773. Lally P, Gardner B. Promoting habit formation. *Health Psychol Rev*. 2011;7:sup1:S137-58.
3774. Wood W, Tam L, Witt MG. Changing circumstances, disrupting habits. *J Pers Soc Psychol*. 2005;88(6):918-33.
3775. Lally P, Gardner B. Promoting habit formation. *Health Psychol Rev*. 2011;7:sup1:S137-58.
3776. Neal DT, Wood W, Wu M, Kurlander D. The pull of the past: when do habits persist despite conflict with motives? *Pers Soc Psychol Bull*. 2011;37(11):1428-37.
3777. Neal DT, Wood W, Wu M, Kurlander D. The pull of the past: when do habits persist despite conflict with motives? *Pers Soc Psychol Bull*. 2011;37(11):1428-37.
3778. Neal DT, Wood W, Wu M, Kurlander D. The pull of the past: when do habits persist despite conflict with motives? *Pers Soc Psychol Bull*. 2011;37(11):1428-37.
3779. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing*. 2006;25:90-103.
3780. Wood W, Tam L, Witt MG. Changing circumstances, disrupting habits. *J Pers Soc Psychol*. 2005;88(6):918-33.
3781. Derzon JH, Lipsey MW. A meta-analysis of the effectiveness of mass communication for changing substance-use knowledge, attitudes, and behavior. In: Crano WD, Burgoon M, eds. *Mass Media and Drug Prevention: Classic and Contemporary Theories and Research*. Mahwah, NJ: Lawrence Erlbaum Associates; 2002:231-58.
3782. Wood W, Tam L, Witt MG. Changing circumstances, disrupting habits. *J Pers Soc Psychol*. 2005;88(6):918-33.
3783. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing*. 2006;25:90-103.
3784. van't Riet J, Sijtsema SJ, Dagevos H, De Bruijn GJ. The importance of habits in eating behaviour. An overview and recommendations for future research. *Appetite*. 2011;57(3):585-96.
3785. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing*. 2006;25:90-103.
3786. Heatherton TF, Nichols PA. Personal accounts of successful versus failed attempts at life change. *PSPB*. 1994;20(6):664-75.
3787. Riskind J. [DARE's] program's cost soars past \$1 billion with little accounting. Center for Educational Research + Development. Published June 30, 2002. Available at: <http://www.cerd.org/d-a-r-e-s-programs-cost-soars-past-1-billion-with-little-accounting>. Accessed April 17, 2019.
3788. Kanof ME. Youth illicit drug use prevention: DARE long-term evaluations and federal efforts to identify effective programs. GAO-03-172R, United States General Accounting Office. Published January 15, 2003. Available at: <https://www.gao.gov/new.items/d03172r.pdf>. Accessed April 17, 2019.
3789. Steinberg L. How to improve the health of American adolescents. *Perspect Psychol Sci*. 2015;10(6):711-5.
3790. Bryan CJ, Yeager DS, Hinojosa CP, et al. Harnessing adolescent values to motivate healthier eating. *Proc Natl Acad Sci USA*. 2016;113(39):10830-5.
3791. Bryan CJ, Yeager DS, Hinojosa CP, et al. Harnessing adolescent values to motivate healthier eating. *Proc Natl Acad Sci USA*. 2016;113(39):10830-5.
3792. Bryan CJ, Yeager DS, Hinojosa CP, et al. Harnessing adolescent values to motivate healthier eating. *Proc Natl Acad Sci USA*. 2016;113(39):10830-5.
3793. Wilde O. *The Picture of Dorian Gray*. Brooklyn, NY: Millennium Publications; 1890.
3794. Gollwitzer PM. Implementation intentions: strong effects of simple plans. *Am Psychol*. 1999;54:493-503.
3795. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing*. 2006;25:90-103.

3796. Verplanken B, Faes S. Good intentions, bad habits, and effects of forming implementation intentions on healthy eating. *Eur J Soc Psychol.* 1999;29(5-6):591-604.
3797. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing.* 2006;25:90-103.
3798. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of “habit-formation” and general practice. *Br J Gen Pract.* 2012;62(605):664-6.
3799. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of “habit-formation” and general practice. *Br J Gen Pract.* 2012;62(605):664-6.
3800. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of “habit-formation” and general practice. *Br J Gen Pract.* 2012;62(605):664-6.
3801. Greger M. Does coffee affect cholesterol? NutritionFacts.org. Published August 27, 2018. Available at: <https://nutritionfacts.org/video/does-coffee-affect-cholesterol>. Accessed April 17, 2019.
3802. Liu H, Wang C, Qi X, Zou J, Sun Z. Antiglycation and antioxidant activities of mogroside extract from *Siraitia grosvenorii* (swingle) fruits. *J Food Sci Technol.* 2018;55(5):1880-8.
3803. den Hartog GJ, Boots AW, Adam-Perrot A, et al. Erythritol is a sweet antioxidant. *Nutrition.* 2010;26(4):449-58.
3804. Kimura T, Kanasaki A, Hayashi N, et al. d-Allulose enhances postprandial fat oxidation in healthy humans. *Nutrition.* 2017;43-44:16-20.
3805. Verplanken B, Wood W. Interventions to break and create consumer habits. *J Pub Policy Marketing.* 2006;25:90-103.
3806. Orbell S, Verplanken B. The automatic component of habit in health behavior: habit as cue-contingent automaticity. *Health Psychol.* 2010;29(4):374-83.
3807. Mazhari F, Boskabady M, Moeintaghavi A, Habibi A. The effect of toothbrushing and flossing sequence on interdental plaque reduction and fluoride retention: a randomized controlled clinical trial. *J Periodontol.* 2018;89(7):824-32.
3808. Torkzaban P, Arabi SR, Sabounchi SS, Roshanaei G. The efficacy of brushing and flossing sequence on control of plaque and gingival inflammation. *Oral Health Prev Dent.* 2015;13(3):267-73.
3809. Pedersen S, Sniehotta FF, Sainsbury K, et al. The complexity of self-regulating food intake in weight loss maintenance. A qualitative study among short- and long-term weight loss maintainers. *Soc Sci Med.* 2018;208:18-24.
3810. Stadler G, Oettingen G, Gollwitzer PM. Intervention effects of information and self-regulation on eating fruits and vegetables over two years. *Health Psychol.* 2010;29(3):274-83.
3811. Stadler G, Oettingen G, Gollwitzer PM. Intervention effects of information and self-regulation on eating fruits and vegetables over two years. *Health Psychol.* 2010;29(3):274-83.
3812. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol.* 2009;28(6):690-701.
3813. Cleo G, Isenring E, Thomas R, Glasziou P. Could habits hold the key to weight loss maintenance? A narrative review. *J Hum Nutr Diet.* 2017;30(5):655-64.
3814. 10 top tips for a healthy weight. Cancer Research UK. Published July 2017. Available at: <https://publications.cancerresearchuk.org/publication/ten-top-tips-healthy-weight>. Accessed April 17, 2019.
3815. Cleo G, Glasziou P, Beller E, Isenring E, Thomas R. Habit-based interventions for weight loss maintenance in adults with overweight and obesity: a randomized controlled trial. *Int J Obes (Lond).* 2019;43:374-83.
3816. Lally P, Wardle J, Gardner B. Experiences of habit formation: a qualitative study. *Psychol Health Med.* 2011;16(4):484-9.
3817. Lally P, Wardle J, Gardner B. Experiences of habit formation: a qualitative study. *Psychol Health Med.* 2011;16(4):484-9.
3818. Lally P, van Jaarsveld CHM, Potts HWW, Wardle J. How are habits formed: modelling habit formation in the real world. *Euro J Soc Psychol.* 2010;40:998-1009.
3819. Spencer JA, Fremouw WJ. Binge eating as a function of restraint and weight classification. *J Abnorm Psychol.* 1979;88(3):262-7.
3820. Cochran W, Tesser A. The “what the hell” effect: some effects of goal proximity and goal framing on performance. In: Martin LL, Tesser A, eds. *Striving and Feeling: Interactions Among Goals, Affect, and Self-Regulation*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1996:99-120.
3821. Chandon P, Wansink B. The biasing health halos of fast food restaurant health claims: lower calorie estimates and higher side-disk consumption intentions. *J Consumer Res.* 2007;34:301-14. Note: The legitimacy of Brian Wansink’s research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
3822. Soman D, Cheema A. When goals are counterproductive: the effects of violation of a behavioral goal on subsequent performance. *J Consumer Res.* 2004;31(1):52-62.
3823. Cochran W, Tesser A. The “what the hell” effect: some effects of goal proximity and goal framing on performance. In: Martin LL, Tesser A, eds. *Striving and Feeling: Interactions Among Goals, Affect, and Self-Regulation*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1996:99-120.
3824. Cochran W, Tesser A. The “what the hell” effect: some effects of goal proximity and goal framing on performance. In: Martin LL, Tesser A, eds. *Striving and Feeling: Interactions Among Goals, Affect, and Self-Regulation*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1996:99-120.
3825. Prinsen S, Evers C, de Ridder D. Oops I did it again: examining self-licensing effects in a subsequent self-regulation dilemma. *Appl Psychol Health Well Being.* 2016;8(1):104-26.
3826. Lee JM, Chen SH, Hsieh CJ. Does perceived safety of light cigarette encourage smokers to smoke more or to inhale more deeply? *Int J Public Health.* 2008;53(5):236-44.
3827. Hennecke M, Freund AM. Identifying success on the process level reduces negative effects of prior weight loss on subsequent weight loss during a low-calorie diet. *Appl Psychol Health Well Being.* 2014;6(1):48-66.
3828. Blanken I, van de Ven N, Zeelenberg M. A meta-analytic review of moral licensing. *Pers Soc Psychol Bull.* 2015;41(4):540-58.
3829. Mazar N, Zhong CB. Do green products make us better people? *Psychol Sci.* 2010;21(4):494-8.
3830. Effron DA, Conway P. When virtue leads to villainy: advances in research on moral self-licensing. *Curr Opin Psychol.* 2015;6:32-5.

3831. Effron DA, Monin B, Miller DT. The unhealthy road not taken: licensing indulgence by exaggerating counterfactual sins. *J Exp Soc Psychol*. 2013;49(3):573–8.
3832. Khan U, Dhar R. Where there is a way, is there a will? The effect of future choices on self-control. *J Exp Psychol Gen*. 2007;136(2):277–88.
3833. Khan U, Dhar R. Where there is a way, is there a will? The effect of future choices on self-control. *J Exp Psychol Gen*. 2007;136(2):277–88.
3834. Prinsen S, Dohle S, Evers C, de Ridder DTD, Hofmann W. Introducing functional and dysfunctional self-licensing: associations with indices of (un)successful dietary regulation. *J Pers*. 2019;87(5):934–47.
3835. Pogue D. Technology's friction problem. Make buying, voting and losing weight easier by blasting away unnecessary steps. *Sci Am*. 2012;306(4):28.
3836. Sciamanna CN, Kiernan M, Rolls BJ, et al. Practices associated with weight loss versus weight-loss maintenance results of a national survey. *Am J Prev Med*. 2011;41(2):159–66.
3837. Chang T, Ravi N, Plegue MA, Sonnevile KR, Davis MM. Inadequate hydration, BMI, and obesity among US adults: NHANES 2009–2012. *Ann Fam Med*. 2016;14(4):320–4.
3838. Muckelbauer R, Barbosa CL, Mittag T, Burkhardt K, Mikelaishvili N, Müller-Nordhorn J. Association between water consumption and body weight outcomes in children and adolescents: a systematic review. *Obesity (Silver Spring)*. 2014;22(12):2462–75.
3839. Joiner BL. Lurking variables: some examples. *Am Stat*. 1981;35(4):227–33.
3840. An R, McCaffrey J. Plain water consumption in relation to energy intake and diet quality among US adults, 2005–2012. *J Hum Nutr Diet*. 2016;29(5):624–32.
3841. Stookey JJD. Negative, null and beneficial effects of drinking water on energy intake, energy expenditure, fat oxidation and weight change in randomized trials: a qualitative review. *Nutrients*. 2016;8(1):19.
3842. Fresán U, Gea A, Bes-Rastrollo M, Ruiz-Canela M, Martínez-González MA. Substitution models of water for other beverages, and the incidence of obesity and weight gain in the SUN cohort. *Nutrients*. 2016;8(11):688.
3843. Wang YC, Ludwig DS, Sonnevile K, Gortmaker SL. Impact of change in sweetened caloric beverage consumption on energy intake among children and adolescents. *Arch Pediatr Adolesc Med*. 2009;163(4):336–43.
3844. Pan A, Malik VS, Hao T, Willett WC, Mozaffarian D, Hu FB. Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. *Int J Obes (Lond)*. 2013;37(10):1378–85.
3845. Stookey JD, Constant F, Popkin BM, Gardner CD. Drinking water is associated with weight loss in overweight dieting women independent of diet and activity. *Obesity (Silver Spring)*. 2008;16(11):2481–8.
3846. Leung CW, DiMatteo SG, Gosliner WA, Ritchie LD. Sugar-sweetened beverage and water intake in relation to diet quality in U.S. children. *Am J Prev Med*. 2018;54(3):394–402.
3847. Goodman AB, Blanck HM, Sherry B, Park S, Nebeling L, Yaroch AL. Behaviors and attitudes associated with low drinking water intake among US adults, Food Attitudes and Behaviors Survey, 2007. *Prev Chronic Dis*. 2013;10:E51.
3848. Kant AK, Graubard BI. Contributors of water intake in US children and adolescents: associations with dietary and meal characteristics—National Health and Nutrition Examination Survey 2005–2006. *Am J Clin Nutr*. 2010;92(4):887–96.
3849. Pan A, Malik VS, Hao T, Willett WC, Mozaffarian D, Hu FB. Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. *Int J Obes (Lond)*. 2013;37(10):1378–85.
3850. Maffeis C, Tommasi M, Tomasselli F, et al. Fluid intake and hydration status in obese vs normal weight children. *Eur J Clin Nutr*. 2016;70(5):560–5.
3851. Carretero-Gómez J, Arévalo Lorigo JC, Gómez Huelgas R, et al. Hydration and obesity among outpatient-based population: H2Ob study. *J Investig Med*. 2018;66(4):780–3.
3852. Rosinger AY, Lawman HG, Akinbami LJ, Ogden CL. The role of obesity in the relation between total water intake and urine osmolality in US adults, 2009–2012. *Am J Clin Nutr*. 2016;104(6):1554–61.
3853. Chang T, Ravi N, Plegue MA, Sonnevile KR, Davis MM. Inadequate hydration, BMI, and obesity among US adults: NHANES 2009–2012. *Ann Fam Med*. 2016;14(4):320–4.
3854. Stookey JD, Constant F, Popkin BM, Gardner CD. Drinking water is associated with weight loss in overweight dieting women independent of diet and activity. *Obesity (Silver Spring)*. 2008;16(11):2481–8.
3855. Wong JMW, Ebbeling CB, Robinson L, Feldman HA, Ludwig DS. Effects of advice to drink 8 cups of water per day in adolescents with overweight or obesity: a randomized clinical trial. *JAMA Pediatr*. 2017;171(5):e170012.
3856. Stookey JD, Del Toro R, Hamer J, et al. Qualitative and/or quantitative drinking water recommendations for pediatric obesity treatment. *J Obes Weight Loss Ther*. 2014;4(4):232.
3857. Muckelbauer R, Libuda L, Clausen K, Toschke AM, Reinehr T, Kersting M. Promotion and provision of drinking water in schools for overweight prevention: randomized, controlled cluster trial. *Pediatrics*. 2009;123(4):e661–7.
3858. Schwartz AE, Leardo M, Aneja S, Elbel B. Effect of a school-based water intervention on child body mass index and obesity. *JAMA Pediatr*. 2016;170(3):220–6.
3859. Turner L, Hager E. The power of a simple intervention to improve student health: just add water. *JAMA Pediatr*. 2016;170(3):199–200.
3860. Schwartz AE, Leardo M, Aneja S, Elbel B. Effect of a school-based water intervention on child body mass index and obesity. *JAMA Pediatr*. 2016;170(3):220–6.
3861. Stookey JD. Under what conditions do water-intervention studies significantly improve child body weight? *Ann Nutr Metab*. 2017;70 Suppl 1:62–7.
3862. Larnkjaer A, Arnberg K, Michaelsen KF, Jensen SM, Mølgaard C. Effect of increased intake of skimmed milk, casein, whey or water on body composition and leptin in overweight adolescents: a randomized trial. *Pediatr Obes*. 2015;10(6):461–7.
3863. Larnkjaer A, Arnberg K, Michaelsen KF, Jensen SM, Mølgaard C. Effect of increased intake of skimmed milk, casein, whey or water on body composition and leptin in overweight adolescents: a randomized trial. *Pediatr Obes*. 2015;10(6):461–7.
3864. Arnberg K, Mølgaard C, Michaelsen KF, Jensen SM, Trolle E, Larnkjær A. Skim milk, whey, and casein increase body weight and whey and casein increase the plasma C-peptide concentration in overweight adolescents. *J Nutr*. 2012;142(12):2083–90.

3865. Liljeberg Elmståhl H, Björck I. Milk as a supplement to mixed meals may elevate postprandial insulinaemia. *Eur J Clin Nutr.* 2001;55(11):994-9.
3866. Stookey JJ. Negative, null and beneficial effects of drinking water on energy intake, energy expenditure, fat oxidation and weight change in randomized trials: a qualitative review. *Nutrients.* 2016;8(1):19.
3867. Keller U, Szinnai G, Bilz S, Berneis K. Effects of changes in hydration on protein, glucose and lipid metabolism in man: impact on health. *Eur J Clin Nutr.* 2003;57 Suppl 2:S69-74.
3868. Jones BH, Standridge MK, Moustaid N. Angiotensin II increases lipogenesis in 3T3-L1 and human adipose cells. *Endocrinology.* 1997;138(4):1512-9.
3869. Saiki A, Ohira M, Endo K, et al. Circulating angiotensin II is associated with body fat accumulation and insulin resistance in obese subjects with type 2 diabetes mellitus. *Metab Clin Exp.* 2009;58(5):708-13.
3870. Thornton SN. Increased hydration can be associated with weight loss. *Front Nutr.* 2016;3:18.
3871. Mao S, Huang S. A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and the risk of overweight/obesity. *J Renin Angiotensin Aldosterone Syst.* 2015;16(3):687-94.
3872. Onufrak SJ, Park S, Sharkey JR, Sherry B. The relationship of perceptions of tap water safety with intake of sugar-sweetened beverages and plain water among US adults. *Public Health Nutr.* 2014;17(1):179-85.
3873. Saleh MA, Abdel-Rahman FH, Woodard BB, et al. Chemical, microbial and physical evaluation of commercial bottled waters in greater Houston area of Texas. *J Environ Sci Health A Tox Hazard Subst Environ Eng.* 2008;43(4):335-47.
3874. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res.* 2009;43(8):2057-92.
3875. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res.* 2009;43(8):2057-92.
3876. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res.* 2009;43(8):2057-92.
3877. Villanueva CM, Fernández F, Malats N, Grimalt JO, Kogevinas M. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. *J Epidemiol Community Health.* 2003;57(3):166-73.
3878. Hwang BF, Jaakkola JJ. Water chlorination and birth defects: a systematic review and meta-analysis. *Arch Environ Health.* 2003;58(2):83-91.
3879. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. *Water Res.* 2009;43(8):2057-92.
3880. Villanueva CM, Fernández F, Malats N, Grimalt JO, Kogevinas M. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. *J Epidemiol Community Health.* 2003;57(3):166-73.
3881. Odom R, Regli S, Messner M, Cromwell J, Javdan M. Benefit-cost analysis of the Stage 1 D/DBP Rule. *J Am Water Works Assoc.* 1999;91(4):137-47.
3882. Grellier J, Rushton L, Briggs DJ, Nieuwenhuijsen MJ. Assessing the human health impacts of exposure to disinfection by-products—a critical review of concepts and methods. *Environ Int.* 2015;78:61-81.
3883. Villanueva CM, Fernández F, Malats N, Grimalt JO, Kogevinas M. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. *J Epidemiol Community Health.* 2003;57(3):166-73.
3884. Stalter D, O'Malley E, von Gunten U, Escher B. Point-of-use water filters can effectively remove disinfection by-products and toxicity from chlorinated and chloraminated tap water. *Environ Sci Water Res Technol.* 2016;2(5):875-83.
3885. Anumol T, Clarke BO, Merel S, Snyder SA. Point-of-use devices for attenuation of trace organic compounds in water. *J Am Water Works Assoc.* 2015;107(9):E474-85.
3886. Anumol T, Clarke BO, Merel S, Snyder SA. Point-of-use devices for attenuation of trace organic compounds in water. *J Am Water Works Assoc.* 2015;107(9):E474-85.
3887. Weinberg HS, Pereira VRPJ, Singer PC, Savitz DA. Considerations for improving the accuracy of exposure to disinfection by-products by ingestion in epidemiologic studies. *Sci Total Environ.* 2006;354(1):35-42.
3888. Stalter D, O'Malley E, von Gunten U, Escher B. Point-of-use water filters can effectively remove disinfection by-products and toxicity from chlorinated and chloraminated tap water. *Environ Sci Water Res Technol.* 2016;2(5):875-83.
3889. Anumol T, Clarke BO, Merel S, Snyder SA. Point-of-use devices for attenuation of trace organic compounds in water. *J Am Water Works Assoc.* 2015;107(9):E474-85.
3890. Stalter D, O'Malley E, von Gunten U, Escher B. Point-of-use water filters can effectively remove disinfection by-products and toxicity from chlorinated and chloraminated tap water. *Environ Sci Water Res Technol.* 2016;2(5):875-83.
3891. McKenzie AL, Muñoz CX, Armstrong LE. Accuracy of urine color to detect equal to or greater than 2% body mass loss in men. *J Athl Train.* 2015;50(12):1306-9.
3892. Perrier ET, Johnson EC, McKenzie AL, Ellis LA, Armstrong LE. Urine colour change as an indicator of change in daily water intake: a quantitative analysis. *Eur J Nutr.* 2016;55(5):1943-9.
3893. McKenzie AL, Armstrong LE. Monitoring body water balance in pregnant and nursing women: the validity of urine color. *Ann Nutr Metab.* 2017;70 Suppl 1:18-22.
3894. Ellis LA, Yates BA, McKenzie AL, Muñoz CX, Casa DJ, Armstrong LE. Effects of three oral nutritional supplements on human hydration indices. *Int J Sport Nutr Exerc Metab.* 2016;26(4):356-62.
3895. Kenefick RW, Heavens KR, Dennis WE, et al. Quantification of chromatographic effects of vitamin B supplementation in urine and implications for hydration assessment. *J Appl Physiol.* 2015;119(2):110-5.
3896. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, D.C.: National Academies Press; 2006.
3897. Rosner MH. Preventing deaths due to exercise-associated hyponatremia: the 2015 Consensus Guidelines. *Clin J Sport Med.* 2015;25(4):301-2.
3898. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, D.C.: National Academies Press; 2006.
3899. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2014;17(8):1689-96.

3900. Barbaresko J, Koch M, Schulze MB, Nöthlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. *Nutr Rev*. 2013;71(8):511-27.
3901. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials. *Obes Rev*. 2016;17(11):1067-79.
3902. Agricultural Research Service, United States Department of Agriculture. Nutrients: 22:6 n-3 (DHA)(g) ; 20:5 n-3 (EPA)(g) Food groups: finfish and shellfish products. USDA Food Composition Databases. Published 2018. Available at: <https://ndb.nal.usda.gov/ndb/nutrients/report/nutrientsfrm?max=25&offset=0&totalCount=0&nutrient1=621&nutrient2=629&nutrient3=&fg=15&subset=0&sort=c&measureby=g>. Accessed August 24, 2018.
3903. Buoite Stella A, Gortan Cappellari G, Barazzoni R, Zanetti M. Update on the impact of omega 3 fatty acids on inflammation, insulin resistance and sarcopenia: a review. *Int J Mol Sci*. 2018;19(1):218.
3904. Du S, Jin J, Fang W, Su Q. Does fish oil have an anti-obesity effect in overweight/obese adults? A meta-analysis of randomized controlled trials. *PLoS ONE*. 2015;10(11):e0142652.
3905. Sutcliffe JT, Wilson LD, de Heer HD, Foster RL, Carnot MJ. C-reactive protein response to a vegan lifestyle intervention. *Complement Ther Med*. 2015;23(1):32-7.
3906. Macknin M, Kong T, Weier A, et al. Plant-based, non-added-fat or American Heart Association diets: impact on cardiovascular risk in obese children with hypercholesterolemia and their parents. *J Pediatr*. 2015;166(4):953-9.e1-3.
3907. Turner-McGrievy GM, Wirth MD, Shivappa N, et al. Randomization to plant-based dietary approaches leads to larger short-term improvements in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat. *Nutr Res*. 2015;35(2):97-106.
3908. Hosseinpour-Niazi S, Mirmiran P, Fallah-Ghohroudi A, Azizi F. Non-soya legume-based therapeutic lifestyle change diet reduces inflammatory status in diabetic patients: a randomised cross-over clinical trial. *Br J Nutr*. 2015;114(2):213-9.
3909. Watzl B, Kulling SE, Möseneder J, Barth SW, Bub A. A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. *Am J Clin Nutr*. 2005;82(5):1052-8.
3910. Lee-Kwan SH, Moore LV, Blanck HM, Harris DM, Galuska D. Disparities in state-specific adult fruit and vegetable consumption—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:1241-7.
3911. Kopf JC, Suhr MJ, Clarke J, et al. Role of whole grains versus fruits and vegetables in reducing subclinical inflammation and promoting gastrointestinal health in individuals affected by overweight and obesity: a randomized controlled trial. *Nutr J*. 2018;17(1):72.
3912. Vincent HK, Innes KE, Vincent KR. Oxidative stress and potential interventions to reduce oxidative stress in overweight and obesity. *Diabetes Obes Metab*. 2007;9(6):813-39.
3913. Ryan BJ, Nissim A, Winyard PG. Oxidative post-translational modifications and their involvement in the pathogenesis of autoimmune diseases. *Redox Biol*. 2014;2:715-24.
3914. Jeszka-Skowron M, Zgoła-Grześkowiak A, Stanisz E, Waśkiewicz A. Potential health benefits and quality of dried fruits: goji fruits, cranberries and raisins. *Food Chem*. 2017;221:228-36.
3915. Wang S, Suh JH, Zheng X, Wang Y, Ho CT. Identification and quantification of potential anti-inflammatory hydroxycinnamic acid amides from wolfberry. *J Agric Food Chem*. 2017;65(2):364-72.
3916. Wu WB, Hung DK, Chang FW, Ong ET, Chen BH. Anti-inflammatory and anti-angiogenic effects of flavonoids isolated from *Lycium barbarum* Linnaeus on human umbilical vein endothelial cells. *Food Funct*. 2012;3(10):1068-81.
3917. Oh YC, Cho WK, Im GY, et al. Anti-inflammatory effect of Lycium Fruit water extract in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. *Int Immunopharmacol*. 2012;13(2):181-9.
3918. Lee YJ, Ahn Y, Kwon O, et al. Dietary wolfberry extract modifies oxidative stress by controlling the expression of inflammatory mRNAs in overweight and hypercholesterolemic subjects: a randomized, double-blind, placebo-controlled trial. *J Agric Food Chem*. 2017;65(2):309-16.
3919. Vidal K, Bucheli P, Gao Q, et al. Immunomodulatory effects of dietary supplementation with a milk-based wolfberry formulation in healthy elderly: a randomized, double-blind, placebo-controlled trial. *Rejuvenation Res*. 2012;15(1):89-97.
3920. Hsu CH, Nance DM, Amagase H. A meta-analysis of clinical improvements of general well-being by a standardized *Lycium barbarum*. *J Med Food*. 2012;15(11):1006-14.
3921. *Burge v. Freeliffe International, Inc*, CV 09-1159 (D. Ariz. 2009).
3922. de Souza Zanchet MZ, Nardi GM, de Oliveira Souza Bratti L, Filippin-Monteiro FB, Locatelli C. *Lycium barbarum* reduces abdominal fat and improves lipid profile and antioxidant status in patients with metabolic syndrome. *Oxid Med Cell Longev*. 2017;2017:9763210.
3923. Agricultural Research Service, United States Department of Agriculture. Full report (all nutrients): 45243476, goji berries, UPC: 760286615304. USDA Branded Food Products Database. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/45243476>. Accessed April 17, 2019.
3924. de Souza Zanchet MZ, Nardi GM, de Oliveira Souza Bratti L, Filippin-Monteiro FB, Locatelli C. *Lycium barbarum* reduces abdominal fat and improves lipid profile and antioxidant status in patients with metabolic syndrome. *Oxid Med Cell Longev*. 2017;2017:9763210.
3925. Bays H, Weiter K, Anderson J. A randomized study of raisins versus alternative snacks on glycemic control and other cardiovascular risk factors in patients with type 2 diabetes mellitus. *Phys Sportsmed*. 2015;43(1):37-43.
3926. Bentley J. Potatoes and tomatoes account for over half of U.S. vegetable availability. Economic Research Service, United States Department of Agriculture. Published September 8, 2015. Available at: <https://www.ers.usda.gov/amber-waves/2015/september/potatoes-and-tomatoes-account-for-over-half-of-us-vegetable-availability>. Accessed April 17, 2019.
3927. Kim YI, Mohri S, Hirai S, et al. Tomato extract suppresses the production of proinflammatory mediators induced by interaction between adipocytes and macrophages. *Biosci Biotechnol Biochem*. 2015;79(1):82-7.
3928. Colmán-Martínez M, Martínez-Huélamo M, Valderas-Martínez P, et al. *trans*-Lycopene from tomato juice attenuates inflammatory biomarkers in human plasma samples: an intervention trial. *Mol Nutr Food Res*. 2017;61(11).

3929. Ghavipour M, Saedisomeolia A, Djalali M, et al. Tomato juice consumption reduces systemic inflammation in overweight and obese females. *Br J Nutr*. 2013;109(11):2031-5.
3930. Biddle MJ, Lennie TA, Bricker GV, Kopec RE, Schwartz SJ, Moser DK. Lycopene dietary intervention: a pilot study in patients with heart failure. *J Cardiovasc Nurs*. 2015;30(3):205-12.
3931. Xaplanteris P, Vlachopoulos C, Pietri P, et al. Tomato paste supplementation improves endothelial dynamics and reduces plasma total oxidative status in healthy subjects. *Nutr Res*. 2012;32(5):390-4.
3932. Burton-Freeman B, Talbot J, Park E, Krishnankutty S, Edirisinghe I. Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weight men and women. *Mol Nutr Food Res*. 2012;56(4):622-31.
3933. Krasinska B, Osińska A, Osinski M, et al. Standardised tomato extract as an alternative to acetylsalicylic acid in patients with primary hypertension and high cardiovascular risk—a randomised, controlled trial. *Arch Med Sci*. 2018;14(4):773-80.
3934. Ghavipour M, Saedisomeolia A, Djalali M, et al. Tomato juice consumption reduces systemic inflammation in overweight and obese females. *Br J Nutr*. 2013;109(11):2031-5.
3935. Mohri S, Takahashi H, Sakai M, et al. Wide-range screening of anti-inflammatory compounds in tomato using LC-MS and elucidating the mechanism of their functions. *PLoS ONE*. 2018;13(1):e0191203.
3936. Markovits N, Ben Amotz A, Levy Y. The effect of tomato-derived lycopene on low carotenoids and enhanced systemic inflammation and oxidation in severe obesity. *Isr Med Assoc J*. 2009;11(10):598-601.
3937. Hirose A, Terauchi M, Tamura M, et al. Tomato juice intake increases resting energy expenditure and improves hypertriglyceridemia in middle-aged women: an open-label, single-arm study. *Nutr J*. 2015;14:34.
3938. Li YF, Chang YY, Huang HC, Wu YC, Yang MD, Chao PM. Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. *Nutrition*. 2015;31(5):691-6.
3939. George T, Sharma V, Methven L, Lovegrove J. The effects of enriching white bread with vegetables on measures of hunger in young women. *Proc Nutr Soc*. 2010;69(OCE1).
3940. Vinha AF, Barreira SV, Costa AS, Alves RC, Oliveira MB. Pre-meal tomato (*Lycopersicon esculentum*) intake can have anti-obesity effects in young women? *Int J Food Sci Nutr*. 2014;65(8):1019-26.
3941. United States Department of Agriculture. Tomatoes, fresh. Household USDA Foods Fact Sheet. Published October 2012. Available at: https://whatscooking.fns.usda.gov/sites/default/files/factsheets/HHFS_TOMATOES_FRESH_Oct2012.pdf. Accessed April 17, 2019.
3942. Conceição de Oliveira M, Sichieri R, Sanchez Moura A. Weight loss associated with a daily intake of three apples or three pears among overweight women. *Nutrition*. 2003;19(3):253-6.
3943. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689-96.
3944. Allijn IE, Vaessen SF, Quarles van Ufford LC, et al. Head-to-head comparison of anti-inflammatory performance of known natural products in vitro. *PLoS ONE*. 2016;11(5):e0155325.
3945. Daily JW, Yang M, Park S. Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *J Med Food*. 2016;19(8):717-29.
3946. Abidi A, Gupta S, Agarwal M, Bhalla HL, Saluja M. Evaluation of efficacy of curcumin as an add-on therapy in patients of bronchial asthma. *J Clin Diagn Res*. 2014;8(8):HC19-24.
3947. Panahi Y, Sahebkar A, Parvin S, Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. *Ann Clin Biochem*. 2012;49(Pt 6):580-8.
3948. Garg SK, Ahuja V, Sankar MJ, Kumar A, Moss AC. Curcumin for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:CD008424.
3949. Khajehdehi P, Zanjaninejad B, Aflaki E, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *J Ren Nutr*. 2012;22(1):50-7.
3950. Vors C, Couillard C, Paradis ME, et al. Supplementation with resveratrol and curcumin does not affect the inflammatory response to a high-fat meal in older adults with abdominal obesity: a randomized, placebo-controlled crossover trial. *J Nutr*. 2018;148(3):379-88.
3951. Derosa G, Maffioli P, Simental-Mendía LE, Bo S, Sahebkar A. Effect of curcumin on circulating interleukin-6 concentrations: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2016;111:394-404.
3952. Sahebkar A, Cicero AFG, Simental-Mendía LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor- α levels: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2016;107:234-42.
3953. Halder S, Lim J, Chia SC, Ponnalagu S, Henry CJ. Effects of two doses of curry prepared with mixed spices on postprandial ghrelin and subjective appetite responses—a randomized controlled crossover trial. *Foods*. 2018;7(4):47.
3954. Shao W, Yu Z, Chiang Y, et al. Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. *PLoS ONE*. 2012;7(1):e28784.
3955. Hariri M, Haghghatdoost F. Effect of curcumin on anthropometric measures: a systematic review on randomized clinical trials. *J Am Coll Nutr*. 2018;37(3):215-22.
3956. Kohl A, Gögebakan O, Möhlig M, et al. Increased interleukin-10 but unchanged insulin sensitivity after 4 weeks of (1, 3)(1, 6)- β -glucan consumption in overweight humans. *Nutr Res*. 2009;29(4):248-54.
3957. Yenidogan E, Akgul GG, Gulcelik MA, Dinc S, Colakoglu MK, Kayaoglu HA. Effect of β -glucan on drain fluid and amount of drainage following modified radical mastectomy. *Adv Ther*. 2014;31(1):130-9.
3958. Talbott SM, Talbott JA, Talbott TL, Dingler E. β -glucan supplementation, allergy symptoms, and quality of life in self-described ragweed allergy sufferers. *Food Sci Nutr*. 2013;1(1):90-101.
3959. Mosikanon K, Arthan D, Kettawan A, Tungtrongchitr R, Prangthip P. Yeast β -glucan modulates inflammation and waist circumference in overweight and obese subjects. *J Diet Suppl*. 2017;14(2):173-85.

3960. Santas J, Lázaro E, Cuñé J. Effect of a polysaccharide-rich hydrolysate from *Saccharomyces cerevisiae* (LipiGo®) in body weight loss: randomised, double-blind, placebo-controlled clinical trial in overweight and obese adults. *J Sci Food Agric*. 2017;97(12):4250-7.
3961. Barclay GR, McKenzie H, Pennington J, Parratt D, Pennington CR. The effect of dietary yeast on the activity of stable chronic Crohn's disease. *Scand J Gastroenterol*. 1992;27(3):196-200.
3962. Cannistrà C, Finocchi V, Trivisonno A, Tambasco D. New perspectives in the treatment of hidradenitis suppurativa: surgery and brewer's yeast-exclusion diet. *Surgery*. 2013;154(5):1126-30.
3963. Ruder K. The Biggest Loser. Erik Chopin fought diabetes—and his demons—to win big on the hit television show. *Diabetes Forecast*. 2007:48-52.
3964. Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health*. 2007;121(7):492-6.
3965. Marzocchi R, Cappellari D, Dalle Grave R, Marchesini G. Massive weight loss without surgery in a super obese patient. *Obes Surg*. 2011;21(4):540-5.
3966. Applebaum M. Why diets fail—expert diet advice as a cause of diet failure. *Am Psychol*. 2008;63(3):200-2.
3967. Wadden TA, Van Itallie TB, Blackburn GL. Responsible and irresponsible use of very-low-calorie diets in the treatment of obesity. *JAMA*. 1990;263(1):83-5.
3968. Thomas DM, Gonzalez MC, Pereira AZ, Redman LM, Heymsfield SB. Time to correctly predict the amount of weight loss with dieting. *J Acad Nutr Diet*. 2014;114(6):857-61.
3969. Guth E. Counting calories as an approach to achieve weight control. *JAMA*. 2018;319(3):225-6.
3970. The best ways to cut calories from your diet. Mayo Clinic. Published March 28, 2018. Available at: <https://www.mayoclinic.org/healthy-lifestyle/weight-loss/in-depth/calories/art-20048065>. Accessed April 17, 2019.
3971. United States Department of Health and Human Services. Overweight and obesity: what you can do. SurgeonGeneral.gov. Available at: https://web.archive.org/web/20121014023446/http://www.surgeongeneral.gov/library/calls/obesity/fact_whatcanyou.do.html. Accessed April 17, 2019.
3972. Guth E. JAMA patient page. Healthy weight loss. *JAMA*. 2014;312(9):974.
3973. Wishnofsky M. Caloric equivalents of gained or lost weight. *Am J Clin Nutr*. 1958;6(5):542-6.
3974. Guo J, Brager DC, Hall KD. Simulating long-term human weight-loss dynamics in response to calorie restriction. *Am J Clin Nutr*. 2018;107(4):558-65.
3975. National Institute of Diabetes and Digestive and Kidney Diseases. Body weight planner. National Institutes of Health. Available at: <https://www.niddk.nih.gov/bwp>. Accessed April 17, 2019.
3976. Dulloo AG. Explaining the failures of obesity therapy: willpower attenuation, target miscalculation or metabolic compensation? *Int J Obes (Lond)*. 2012;36(11):1418-20.
3977. University of Texas M. D. Anderson Cancer Center. Obesity reversed in mice by destroying blood vessels that service fat cells. *ScienceDaily*. Published May 10, 2004. Available at: <https://www.sciencedaily.com/releases/2004/05/040510012211.htm>. Accessed April 17, 2019.
3978. National Institute of Diabetes and Digestive and Kidney Diseases. Body weight planner. National Institutes of Health. Available at: <https://www.niddk.nih.gov/bwp>. Accessed April 17, 2019.
3979. Thomas DM, Martin CK, Lettieri S, et al. Can a weight loss of one pound a week be achieved with a 3500-kcal deficit? Commentary on a commonly accepted rule. *Int J Obes (Lond)*. 2013;37(12):1611-3.
3980. Moyer VA. What we don't know can hurt our patients: physician innumeracy and overuse of screening tests. *Ann Intern Med*. 2012;156(5):392-3.
3981. Counting calories in kids' meals. Fast Food Facts. Available at: http://www.fastfoodmarketing.org/media/fastfoodfacts_kidsmealcalories.pdf. Accessed August 9, 2018.
3982. Freij MY, Sell RL, Bozack AK, Weiss LJ, Garcia AC. Modeling potential effects of reduced calories in kids' meals with toy giveaways. *Child Obes*. 2014;10(1):58-63.
3983. Brown AW, Hall KD, Thomas D, Dhurandhar NV, Heymsfield SB, Allison DB. Order of magnitude misestimation of weight effects of children's meal policy proposals. *Child Obes*. 2014;10(6):542-4.
3984. Retraction of "modeling potential effects of reduced calories in kids' meals with toy giveaways." *Child Obes*. 2014;10(6):546.
3985. Dulloo AG. Explaining the failures of obesity therapy: willpower attenuation, target miscalculation or metabolic compensation? *Int J Obes (Lond)*. 2012;36(11):1418-20.
3986. Redman LM, Heilbronn LK, Martin CK, et al. Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. *PLoS ONE*. 2009;4(2):e4377.
3987. Hall KD. Metabolic adaptations to weight loss. *Obesity (Silver Spring)*. 2018;26(5):790-1.
3988. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. *Obes Rev*. 2010;11(7):531-47.
3989. Astrup A, Gøtzsche PC, Van de Werken K, et al. Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr*. 1999;69(6):1117-22.
3990. Johannsen DL, Knuth ND, Huizenga R, Rood JC, Ravussin E, Hall KD. Metabolic slowing with massive weight loss despite preservation of fat-free mass. *J Clin Endocrinol Metab*. 2012;97(7):2489-96.
3991. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. *Obesity (Silver Spring)*. 2016;24(8):1612-9.
3992. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
3993. Klos LA, Greenleaf C, Paly N, Kessler MM, Shoemaker CG, Suchla EA. Losing weight on reality TV: a content analysis of the weight loss behaviors and practices portrayed on *The Biggest Loser*. *J Health Commun*. 2015;20(6):639-46.
3994. Hall KD. Diet versus exercise in "The Biggest Loser" weight loss competition. *Obesity (Silver Spring)*. 2013;21(5):957-9.
3995. Hall KD. Diet versus exercise in "The Biggest Loser" weight loss competition. *Obesity (Silver Spring)*. 2013;21(5):957-9.
3996. Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011;378(9793):826-37.

3997. Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011;378(9793):826-37.
3998. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am*. 2018;102(1):183-97.
3999. Guo J, Brager DC, Hall KD. Simulating long-term human weight-loss dynamics in response to calorie restriction. *Am J Clin Nutr*. 2018;107(4):558-65.
4000. Hall KD, Sacks G, Chandramohan D, et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet*. 2011;378(9793):826-37.
4001. Hall KD, Schoeller DA, Brown AW. Reducing calories to lose weight. *JAMA*. 2018;319(22):2336-7.
4002. Hall KD, Schoeller DA, Brown AW. Reducing calories to lose weight. *JAMA*. 2018;319(22):2336-7.
4003. Osborne TB, Mendel LB, Ferry EL. The effect of retardation of growth upon the breeding period and duration of life of rats. *Science*. 1917;45(1160):294-5.
4004. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805-15.e4.
4005. European hare (*Lepus europaeus*) longevity, ageing, and life history. Human Ageing Genomic Resources. Published October 14, 2017. Available at: http://genomics.senescence.info/species/entry.php?species=Lepus_europaeus. Accessed April 17, 2019.
4006. Galapagos tortoise (*Chelonoidis nigra*) longevity, ageing, and life history. Human Ageing Genomic Resources. Published 2018. Available at: http://genomics.senescence.info/species/entry.php?species=Chelonoidis_nigra. Accessed August 10, 2018.
4007. Civitarese AE, Carling S, Heilbronn LK, et al. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS MED*. 2007;4(3):e76.
4008. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805-15.e4.
4009. Bourzac K. Interventions: live long and prosper. *Nature*. 2012;492(7427):S18-20.
4010. Rebrin I, Forster MJ, Sohal RS. Association between life-span extension by caloric restriction and thiol redox state in two different strains of mice. *Free Radic Biol Med*. 2011;51(1):225-33.
4011. Le Bourg E, Redman LM. Do-it-yourself calorie restriction: the risks of simplistically translating findings in animal models to humans. *Bioessays*. 2018;40(9):e1800087.
4012. Dai DF, Chiao YA, Marcinek DJ, Szeto HH, Rabinovitch PS. Mitochondrial oxidative stress in aging and healthspan. *Longev Healthspan*. 2014;3:6.
4013. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab*. 2018;314(4):E396-405.
4014. Anderson RM, Le Couteur DG, de Cabo R. Caloric restriction research: new perspectives on the biology of aging. *J Gerontol A Biol Sci Med Sci*. 2017;73(1):1-3.
4015. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab*. 2018;314(4):E396-405.
4016. Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. *J Gerontol A Biol Sci Med Sci*. 2015;70(9):1097-104.
4017. Das SK, Roberts SB, Bhapkar MV, et al. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: a 2-y randomized controlled trial of calorie restriction in nonobese humans. *Am J Clin Nutr*. 2017;105(4):913-27.
4018. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev*. 2006;127(1):1-7.
4019. Martin CK, Bhapkar M, Pittas AG, et al. Effect of calorie restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: the CALERIE 2 randomized clinical trial. *JAMA Intern Med*. 2016;176(6):743-52.
4020. Das SK, Roberts SB, Bhapkar MV, et al. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: a 2-y randomized controlled trial of calorie restriction in nonobese humans. *Am J Clin Nutr*. 2017;105(4):913-27.
4021. Franklin JC, Scheile BC. Observations on human behavior in experimental semi-starvation and rehabilitation. *J Clin Psychol*. 1948;4(1):28-45.
4022. Dulloo AG, Jacquet J, Montani JP. How dieting makes some fatter: from a perspective of human body composition autoregulation. *Proc Nutr Soc*. 2012;71(3):379-89.
4023. Dulloo AG, Jacquet J, Montani JP. How dieting makes some fatter: from a perspective of human body composition autoregulation. *Proc Nutr Soc*. 2012;71(3):379-89.
4024. Marlatt KL, Redman LM, Burton JH, Martin CK, Ravussin E. Persistence of weight loss and acquired behaviors 2 y after stopping a 2-y calorie restriction intervention. *Am J Clin Nutr*. 2017;105(4):928-35.
4025. Kahathuduwa CN, Binks M, Martin CK, Dawson JA. Extended calorie restriction suppresses overall and specific food cravings: a systematic review and a meta-analysis. *Obes Rev*. 2017;18(10):1122-35.
4026. Nicoll R, Henein MY. Caloric restriction and its effect on blood pressure, heart rate variability and arterial stiffness and dilatation: a review of the evidence. *Int J Mol Sci*. 2018;19(3):751.
4027. Florian JP, Baisch FJ, Heer M, Pawelczyk JA. Caloric restriction decreases orthostatic tolerance independently from 6° head-down bedrest. *PLoS ONE*. 2015;10(4):e0118812.
4028. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003;108(21):2660-5.
4029. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab*. 2018;314(4):E396-405.

4030. Das SK, Roberts SB, Bhapkar MV, et al. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: a 2-y randomized controlled trial of calorie restriction in nonobese humans. *Am J Clin Nutr*. 2017;105(4):913-27.
4031. Racette SB, Rochon J, Uhrich ML, et al. Effects of two years of calorie restriction on aerobic capacity and muscle strength. *Med Sci Sports Exerc*. 2017;49(11):2240-9.
4032. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511-9.
4033. Backx EM, Tieland M, Borgonjen-van den Berg KJ, Claessen PR, van Loon LJ, de Groot LC. Protein intake and lean body mass preservation during energy intake restriction in overweight older adults. *Int J Obes (Lond)*. 2016;40(2):299-304.
4034. Kim JE, O'Connor LE, Sands LP, Slebodnik MB, Campbell WW. Effects of dietary protein intake on body composition changes after weight loss in older adults: a systematic review and meta-analysis. *Nutr Rev*. 2016;74(3):210-24.
4035. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511-9.
4036. Smith GI, Yoshino J, Kelly SC, et al. High-protein intake during weight loss therapy eliminates the weight-loss-induced improvement in insulin action in obese postmenopausal women. *Cell Rep*. 2016;17(3):849-61.
4037. Knuth ND, Johannsen DL, Tamboli RA, et al. Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. *Obesity (Silver Spring)*. 2014;22(12):2563-9.
4038. Sardeli AV, Komatsu TR, Mori MA, Gáspari AF, Chacon-Mikahil MPT. Resistance training prevents muscle loss induced by caloric restriction in obese elderly individuals: a systematic review and meta-analysis. *Nutrients*. 2018;10(4):423.
4039. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. *Arch Intern Med*. 2006;166(22):2502-10.
4040. Romashkan SV, Das SK, Villareal DT, et al. Safety of two-year caloric restriction in non-obese healthy individuals. *Oncotarget*. 2016;7(15):19124-33.
4041. Tufan F, Soyluk O, Karan MA. Healthy behaviors potentially due to calorie restriction. *JAMA Intern Med*. 2016;176(11):1724.
4042. Collier R. Intermittent fasting: the next big weight loss fad. *CMAJ*. 2013;185(8):E321-2.
4043. Stewart WK, Fleming LW, Robertson PC. Massive obesity treated by intermittent fasting. A metabolic and clinical study. *Am J Med*. 1966;40(6):967-86.
4044. Johnstone AM. Fasting—the ultimate diet? *Obes Rev*. 2007;8(3):211-22.
4045. Follin O, Denis W. On starvation and obesity, with special reference to acidosis. *J Biol Chem*. 1915;21:181-92.
4046. Stewart WK, Fleming LW. Features of a successful therapeutic fast of 382 days' duration. *Postgrad Med J*. 1973;49(569):203-9.
4047. Stewart WK, Fleming LW. Features of a successful therapeutic fast of 382 days' duration. *Postgrad Med J*. 1973;49(569):203-9.
4048. Karns R. "Dramatic" treatment for obesity: diseased patients test starvation diet. *JAMA*. 1966;197(1):22,31.
4049. Thomson TJ, Runcie J, Miller V. Treatment of obesity by total fasting for up to 249 days. *Lancet*. 1966;2(7471):992-6.
4050. Duncan GG, Jenson WK, Fraser RI, Cristofori FC. Correction and control of intractable obesity. Practicable application of intermittent periods of total fasting. *JAMA*. 1962;181:309-12.
4051. Harrison M. The long-term value of fasting in the treatment of obesity. *Lancet*. 1966;288(7477):1340-2.
4052. Spencer IO. Death during therapeutic starvation for obesity. *Lancet*. 1968;1(7555):1288-90.
4053. Duncan GG, Jenson WK, Fraser RI, Cristofori FC. Correction and control of intractable obesity. Practicable application of intermittent periods of total fasting. *JAMA*. 1962;181:309-12.
4054. Silverstone JT, Stark JE, Buckle RM. Hunger during total starvation. *Lancet*. 1966;1(7451):1343-4.
4055. Karns R. "Dramatic" treatment for obesity: diseased patients test starvation diet. *JAMA*. 1966;197(1):22,31.
4056. Duncan GG, Jenson WK, Fraser RI, Cristofori FC. Correction and control of intractable obesity. Practicable application of intermittent periods of total fasting. *JAMA*. 1962;181:309-12.
4057. Thomson TJ, Runcie J, Miller V. Treatment of obesity by total fasting for up to 249 days. *Lancet*. 1966;2(7471):992-6.
4058. Watkins E, Serpell L. The psychological effects of short-term fasting in healthy women. *Front Nutr*. 2016;3:27.
4059. Appleton KM, Baker S. Distraction, not hunger, is associated with lower mood and lower perceived work performance on fast compared to non-fast days during intermittent fasting. *J Health Psychol*. 2015;20(6):702-11.
4060. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444-53.
4061. Komaki G, Tamai H, Sumioki H, et al. Plasma beta-endorphin during fasting in man. *Horm Res*. 1990;33(6):239-43.
4062. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444-53.
4063. MacCuish AC, Munro JF, Duncan LJ. Follow-up study of refractory obesity treated by fasting. *Br Med J*. 1968;1(5584):91-2.
4064. Swanson DW, Dinello FA. Follow-up of patients starved for obesity. *Psychosom Med*. 1970;32(2):209-14.
4065. Maagoe H, Mogensen EF. The effect of treatment on obesity. A follow-up investigation of a material treated with complete starvation. *Dan Med Bull*. 1970;17(7):206-9.
4066. Duncan GG. Intermittent fasts in the correction and control of intractable obesity. *Trans Am Clin Climatol Assoc*. 1962;74:121-9.
4067. Mayer J. Reducing by total fasting. *Postgrad Med*. 1964;35:279-82.
4068. Harrison M. The long-term value of fasting in the treatment of obesity. *Lancet*. 1966;2(7477):1340-2.
4069. Drenick EJ, Johnson D. Weight reduction by fasting and semistarvation in morbid obesity: long-term follow-up. *Int J Obes*. 1978;2(2):123-32.
4070. Stunkard A, McLaren-Hume M. The results of treatment for obesity: a review of the literature and report of a series. *AMA Arch Intern Med*. 1959;103(1):79-85.
4071. Innes J, Campbell I, Campbell C, Needle A, Munro J. Long-term follow-up of therapeutic starvation. *BMJ*. 1974;2(5915):356-9.

4072. Innes J, Campbell I, Campbell C, Needle A, Munro J. Long-term follow-up of therapeutic starvation. *BMJ*. 1974;2(5915):356-9.
4073. Sievers ML, Hendriks ME. Two weight-reduction programs among southwestern Indians. *Health Serv Rep*. 1972;87(6):530-6.
4074. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *N Engl J Med*. 2013;368(5):446-54.
4075. Johnstone AM. Fasting—the ultimate diet? *Obes Rev*. 2007;8(3):211-22.
4076. Johnson D. Therapeutic fasting in morbid obesity. *Arch Intern Med*. 1977;137(10):1381-2.
4077. Munro JF, MacCuish AC, Goodall JA, Fraser J, Duncan LJ. Further experience with prolonged therapeutic starvation in gross refractory obesity. *Br Med J*. 1970;4(5737):712-4.
4078. Beer AM, Ismar LE, Wessely DK, Pötschke T, Weidner B, Wiebelitz KR. Retrospective long-term comparison of naturopathic fasting therapy and weight reduction diet in overweight patients. *Evid Based Complement Alternat Med*. 2014;2014:453407.
4079. Boschmann M, Michalsen A. Fasting therapy—old and new perspectives. *Forsch Komplementmed*. 2013;20(6):410-1.
4080. Cahill GF. Survival in starvation. *Am J Clin Nutr*. 1998;68(1):1-2.
4081. Owen OE, Smalley KJ, D'Alessio DA, Mozzoli MA, Dawson EK. Protein, fat, and carbohydrate requirements during starvation: anaplerosis and cataplerosis. *Am J Clin Nutr*. 1998;68(1):12-34.
4082. Boschmann M, Michalsen A. Fasting therapy—old and new perspectives. *Forsch Komplementmed*. 2013;20(6):410-1.
4083. Goldhamer A, Helms S, Salloum TK. Chapter 37: Fasting. In: Pizzorno J, Murray M, eds. *Textbook of Natural Medicine*. 4th ed. St. Louis, MO: Churchill Livingstone; 2013. Available at: <https://brightlineeating.com/wp-content/uploads/2017/08/Textbook-of-Natural-Medicine-4th-Edition-Chapter-37.pdf>. Accessed April 17, 2019.
4084. Hall KD. Quantitative physiology of human starvation: adaptations of energy expenditure, macronutrient metabolism and body composition. In: McCue MD, ed. *Comparative Physiology of Fasting, Starvation, and Food Limitation*. Berlin: Springer-Verlag Berlin Heidelberg; 2012:379-93.
4085. Ball MF, Canary JJ, Kyle LH. Comparative effects of caloric restriction and total starvation on body composition in obesity. *Ann Intern Med*. 1967;67(1):60-7.
4086. Mayer J. Should you starve yourself thin? *Family Health/Today's Health*. 1977.
4087. Hodges RE, Hood J, Canham JE, Sauberlich HE, Baker EM. Clinical manifestations of ascorbic acid deficiency in man. *Am J Clin Nutr*. 1971;24(4):432-43.
4088. Drenick EJ, Joven CB, Swendseid ME. Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. *N Engl J Med*. 1966;274(17):937-9.
4089. Hutcheon DA. Malnutrition-induced Wernicke's encephalopathy following a water-only fasting diet. *Nutr Clin Pract*. 2015;30(1):92-9.
4090. Başoğlu M, Yetimlar Y, Gürgör N, et al. Neurological complications of prolonged hunger strike. *Eur J Neurol*. 2006;13(10):1089-97.
4091. Goldhamer A, Helms S, Salloum TK. Chapter 37: Fasting. In: Pizzorno J, Murray M, eds. *Textbook of Natural Medicine*. 4th ed. St. Louis, MO: Churchill Livingstone; 2013. Available at: <https://brightlineeating.com/wp-content/uploads/2017/08/Textbook-of-Natural-Medicine-4th-Edition-Chapter-37.pdf>. Accessed April 17, 2019.
4092. Sotaniemi KA, Kaarela K. Dry beriberi in a slimmer. *Br Med J*. 1977;2(6103):1634-5.
4093. Devathanan G, Koh C. Wernicke's encephalopathy in prolonged fasting. *Lancet*. 1982;2(8307):1108-9.
4094. Lana-Peixoto MA, Dos Santos EC, Pittella JE. Coma and death in unrecognized Wernicke's encephalopathy. An autopsy study. *Arq Neuropsiquiatr*. 1992;50(3):329-33.
4095. Spencer IO. Death during therapeutic starvation for obesity. *Lancet*. 1968;1(7555):1288-90.
4096. Drenick EJ. Death during therapeutic starvation. *Lancet*. 1968;292(7567):573.
4097. Spencer IO. Death during therapeutic starvation for obesity. *Lancet*. 1968;1(7555):1288-90.
4098. Kahan A, Porter AMW. Death during therapeutic starvation. *Lancet*. 1968;291(7556):1378-9.
4099. Keys A. Caloric undernutrition and starvation, with notes on protein deficiency. *J Am Med Assoc*. 1948;138(7):500-11.
4100. Leitner ZA. Fragmentation of cardiac myofibrils after therapeutic starvation. *Lancet*. 1969;1(7605):1101.
4101. Garnett ES, Barnard DL, Ford J, Goodbody RA, Woodehouse MA. Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. *Lancet*. 1969;1(7601):914-6.
4102. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444-53.
4103. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. *Ann Intern Med*. 1951;35(1):69-96.
4104. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. *Nutrition*. 2010;26(2):156-67.
4105. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. *Nutr Clin Pract*. 2012;27(1):34-40.
4106. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. *Nutrition*. 2010;26(2):156-67.
4107. Hopmann RFW, Brugnoni GP. Decomposition of the yellow form of thiamine. *Angew Chem*. 1981;20(11):961-2.
4108. van Zanten AR. How relevant is refeeding syndrome? *Neth J Med*. 2016;74(3):102-3.
4109. Finnell JS, Saul BC, Goldhamer AC, Myers TR. Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. *BMC Complement Altern Med*. 2018;18(1):67.
4110. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444-53.
4111. Finnell JS, Saul BC, Goldhamer AC, Myers TR. Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. *BMC Complement Altern Med*. 2018;18(1):67.
4112. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metab*. 2014;19(2):181-92.

4113. Runcie J, Thomson TJ. Prolonged starvation—a dangerous procedure? *Br Med J*. 1970;3(5720):432-5.
4114. Liu G, Slater N, Perkins A. Epilepsy: treatment options. *Am Fam Physician*. 2017;96(2):87-96.
4115. Johnstone AM. Fasting—the ultimate diet? *Obes Rev*. 2007;8(3):211-22.
4116. Duncan GG, Jensen WK, Fraser RJ, Cristofori FC. Correction and control of intractable obesity. Practicable application of intermittent periods of total fasting. *JAMA*. 1962;181:309-12.
4117. Brosnan JT. Comments on metabolic needs for glucose and the role of gluconeogenesis. *Eur J Clin Nutr*. 1999;53 Suppl 1:S107-11.
4118. Kamel SK, Lin SH, Cheema-Dhadli S, Marliss EB, Halperin ML. Prolonged total fasting: a feast for the integrative physiologist. *Kidney Int*. 1998;53(3):531-9.
4119. Saudek CD, Felig P. The metabolic events of starvation. *Am J Med*. 1976;60(1):117-26.
4120. Cahill GF. Survival in starvation. *Am J Clin Nutr*. 1998;68(1):1-2.
4121. VanItallie TB, Nufert TH. Ketones: metabolism's ugly duckling. *Nutr Rev*. 2003;61(10):327-41.
4122. Owen OE, Morgan AP, Kemp HG, Sullivan JM, Herrera MG, Cahill GF. Brain metabolism during fasting. *J Clin Invest*. 1967;46(10):1589-95.
4123. Gibson AA, Seimon RV, Lee CM, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev*. 2015;16(1):64-76.
4124. Duncan G, Cristofori F, Yue J, Murthy M. The control of obesity by intermittent fasts. *Med Clin North Am*. 1964;48(5):1359-72.
4125. Wheless JW. History of the ketogenic diet. *Epilepsia*. 2008;49 Suppl 8:3-5.
4126. Turner RP. Letter to the editor. *Lancet*. 2003;4(5):592-3.
4127. Rho JM. How does the ketogenic diet induce anti-seizure effects? *Neurosci Lett*. 2017;637:4-10.
4128. Wilder RM. The effect of ketonemia on the course of epilepsy. *Mayo Clin Bull*. 1921;2:307-8.
4129. Peterman M. The ketogenic diet in the treatment of epilepsy. *Am J Dis Child*. 1924:28-33.
4130. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev*. 2012;(3):CD001903.
4131. Wheless JW. History of the ketogenic diet. *Epilepsia*. 2008;49 Suppl 8:3-5.
4132. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open*. 2018;3(2):175-92.
4133. What is ketosis? Learn about the benefits and how to achieve ketosis. Charlie Foundation. Available at: <https://charlifoundation.org/learn-about-ketosis>. Accessed April 17, 2019.
4134. Martin-McGill KJ, Srikandarajah N, Marson AG, Tudur Smith C, Jenkinson MD. The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: a systematic review. *CNS Oncol*. 2018;7(2):CNS17.
4135. Klement RJ, Feinman RD, Gross EC, et al. Need for new review of article on ketogenic dietary regimes for cancer patients. *Med Oncol*. 2017;34(6):108.
4136. Gonder U. Article on ketogenic dietary regimes for cancer highly misleading. *Med Oncol*. 2017;34(6):109.
4137. Klement RJ, Feinman RD, Gross EC, et al. Need for new review of article on ketogenic dietary regimes for cancer patients. *Med Oncol*. 2017;34(6):108.
4138. Erickson N, Boscheri A, Linke B, Huebner J. Systematic review: isocaloric ketogenic dietary regimes for cancer patients. *Med Oncol*. 2017;34(5):72.
4139. Deng G, Cassileth B. Complementary or alternative medicine in cancer care—myths and realities. *Nat Rev Clin Oncol*. 2013;10(11):656-64.
4140. Bonuccelli G, Tsirigos A, Whitaker-Menezes D, et al. Ketones and lactate “fuel” tumor growth and metastasis: evidence that epithelial cancer cells use oxidative mitochondrial metabolism. *Cell Cycle*. 2010;9(17):3506-14.
4141. Martinez-Outschoorn UE, Prisco M, Ertel A, et al. Ketones and lactate increase cancer cell “stemness,” driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via metabologenomics. *Cell Cycle*. 2011;10(8):1271-86.
4142. Martinez-Outschoorn UE, Prisco M, Ertel A, et al. Ketones and lactate increase cancer cell “stemness,” driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via metabologenomics. *Cell Cycle*. 2011;10(8):1271-86.
4143. Martinez-Outschoorn UE, Lin Z, Whitaker-Menezes D, Howell A, Sotgia F, Lisanti MP. Ketone body utilization drives tumor growth and metastasis. *Cell Cycle*. 2012;11(21):3964-71.
4144. Brenner DR, Brockton NT, Kotsopoulos J, et al. Breast cancer survival among young women: a review of the role of modifiable lifestyle factors. *Cancer Causes Control*. 2016;27(4):459-72.
4145. Fradet Y, Meyer F, Bairati I, Shadmani R, Moore L. Dietary fat and prostate cancer progression and survival. *Eur Urol*. 1999;35(5-6):388-91.
4146. Brennan SF, Woodside JV, Lunny PM, Cardwell CR, Cantwell MM. Dietary fat and breast cancer mortality: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2017;57(10):1999-2008.
4147. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society / American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol*. 2016;34(6):611-35.
4148. Mayer A, Vaupel P, Struss HG, Giese A, Stockinger M, Schmidberger H. Response to commentary by Champ and Klement: is a ketogenic diet the solution for the hyperglycemia problem in glioblastoma therapy? *Strahlenther Onkol*. 2015;191(3):283-4.
4149. Martin-McGill KJ, Srikandarajah N, Marson AG, Tudur Smith C, Jenkinson MD. The role of ketogenic diets in the therapeutic management of adult and paediatric gliomas: a systematic review. *CNS Oncol*. 2018;7(2):CNS17.
4150. Aragon AA, Schoenfeld BJ, Wildman R, et al. International Society of Sports Nutrition position stand: diets and body composition. *J Int Soc Sports Nutr*. 2017;14:16.
4151. Hall KD, Bemis T, Brychta R, et al. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. *Cell Metab*. 2015;22(3):427-36.
4152. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr*. 2016;104(2):324-33.

4153. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. *Am J Physiol Endocrinol Metab.* 2017;313(5):E608-12.
4154. Taubes G. What if it's all been a big fat lie? *New York Times.* Published July 7, 2002. Available at: <https://www.nytimes.com/2002/07/07/magazine/what-if-it-s-all-been-a-big-fat-lie.html>. Accessed April 17, 2019.
4155. Yoder S. The Big Fat Surprise: a critical review; part 1. *The Science of Nutrition.* Published August 10, 2014. <https://thescienceofnutrition.wordpress.com/2014/08/10/the-big-fat-surprise-a-critical-review-part-1>. Accessed August 14, 2018.
4156. Fumento M. Big fat fake. *Reason.* Published March 2003. Available at: <https://reason.com/2003/03/01/big-fat-fake-2/>. Accessed August 14, 2018.
4157. Liebman B. The truth about the Atkins diet. *Nutrition Action Healthletter.* 2002;29(9):3-7.
4158. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr.* 2016;104(2):324-33.
4159. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr.* 2016;104(2):324-33.
4160. Kephart WC, Pledge CD, Roberson PA, et al. The three-month effects of a ketogenic diet on body composition, blood parameters, and performance metrics in crossfit trainees: a pilot study. *Sports (Basel).* 2018;6(1):1.
4161. Hall KD. A review of the carbohydrate-insulin model of obesity. *Eur J Clin Nutr.* 2017;71(3):323-6.
4162. Hall KD. A review of the carbohydrate-insulin model of obesity. *Eur J Clin Nutr.* 2017;71(3):323-6.
4163. Hall KD, Bemis T, Brychta R, et al. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. *Cell Metab.* 2015;22(3):427-36.
4164. Bray GA. Low-carbohydrate diets and realities of weight loss. *JAMA.* 2003;289(14):1853-5.
4165. Banting W. *Letter on Corpulence.* New York: Mohun, Ebbs & Hough; 1864.
4166. Fumento M. *The Fat of the Land: The Obesity Epidemic and How Overweight Americans Can Help Themselves.* New York: Viking Penguin; 1997.
4167. Hall KD, Bemis T, Brychta R, et al. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. *Cell Metab.* 2015;22(3):427-36.
4168. Hall KD, Guo J. Obesity energetics: body weight regulation and the effects of diet composition. *Gastroenterology.* 2017;152(7):1718-27.e3.
4169. Hall KD. A review of the carbohydrate-insulin model of obesity. *Eur J Clin Nutr.* 2017;71(3):323-6.
4170. Molteni M, Simon M, Niiler E, Thompson A. The struggles of a \$40 million nutrition science crusade. *Wired.* Published June 18, 2018. Available at: <https://www.wired.com/story/how-a-dollar40-million-nutrition-science-crusade-fell-apart>. Accessed April 17, 2019.
4171. Internal Revenue Service. 2012-2016. Nutrition Science Initiative Form 990 Section A.1a(D) Reportable compensation from the organization (W-2/1099-MISC).
4172. Roberts SB, Das SK. One strike against low-carbohydrate diets. *Cell Metab.* 2015;22(3):357-8.
4173. Hall KD, Bemis T, Brychta R, et al. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. *Cell Metab.* 2015;22(3):427-36.
4174. Freedhoff Y, Hall K. Weight loss diet studies: we need help not hype. *Lancet.* 2016;388(10047):849-51.
4175. Gibson AA, Seimon RV, Lee CM, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev.* 2015;16(1):64-76.
4176. Hall KD, Chung ST. Low-carbohydrate diets for the treatment of obesity and type 2 diabetes. *Curr Opin Clin Nutr Metab Care.* 2018;21(4):308-12.
4177. Ye F, Li XJ, Jiang WL, Sun HB, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. *J Clin Neurol.* 2015;11(1):26-31.
4178. Vaccarezza MM, Silva WH. Dietary therapy is not the best option for refractory nonsurgical epilepsy. *Epilepsia.* 2015;56(9):1330-4.
4179. Willmott NS, Bryan RA. Case report: scurvy in an epileptic child on a ketogenic diet with oral complications. *Eur Arch Paediatr Dent.* 2008;9(3):148-52.
4180. Bank IM, Shemie SD, Rosenblatt B, Bernard C, Mackie AS. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol.* 2008;39(6):429-31.
4181. United States Food and Drug Administration. The declaration of certain isolated or synthetic non-digestible carbohydrates as dietary fiber on nutrition and supplement facts labels: guidance for industry. FDA.gov. Published June 2018. Available at: <https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM610144.pdf>. Accessed April 17, 2019.
4182. Wibisono C, Rowe N, Beavis E, et al. Ten-year single-center experience of the ketogenic diet: factors influencing efficacy, tolerability, and compliance. *J Pediatr.* 2015;166(4):1030-6.e1.
4183. Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. *Epilepsy Res.* 2018;145:163-8.
4184. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-8.
4185. Gabert L, Vors C, Louche-Pélissier C, et al. 13C tracer recovery in human stools after digestion of a fat-rich meal labelled with [1,1,1-13C]tripalmitin and [1,1,1-13C]triolein. *Rapid Commun Mass Spectrom.* 2011;25(19):2697-703.
4186. Tremblay F, Krebs M, Dombrowski L, et al. Overactivation of S6 kinase 1 as a cause of human insulin resistance during increased amino acid availability. *Diabetes.* 2005;54(9):2674-84.
4187. Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br J Nutr.* 2009;101(10):1493-502.
4188. Noto H, Goto A, Tsujimoto T, Noda M. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS ONE.* 2013;8(1):e55030.

4189. Li S, Flint A, Pai JK, et al. Low carbohydrate diet from plant or animal sources and mortality among myocardial infarction survivors. *J Am Heart Assoc.* 2014;3(5):e001169.
4190. Nestel PJ, Whyte HM, Goodman DS. Distribution and turnover of cholesterol in humans. *J Clin Invest.* 1969;48(6):982-91.
4191. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr.* 1992;56(2):320-8.
4192. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr.* 2013;110(7):1178-87.
4193. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation.* 2017;136(3):e1-23.
4194. Nicholls SJ, Lundman P, Harmer JA, et al. Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function. *J Am Coll Cardiol.* 2006;48(4):715-20.
4195. Phillips SA, Jurva JW, Syed AQ, et al. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. *Hypertension.* 2008;51(2):376-82.
4196. Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br J Nutr.* 2013;110(5):969-70.
4197. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition.* 2012;28(10):1016-21.
4198. Henry K. Published study reports use of nutritional ketosis with mobile app intervention could reverse type 2 diabetes. *Purdue University Research Foundation News.* Published February 7, 2018. Available at: <https://www.purdue.edu/newsroom/releases/2018/Q1/published-study-reports-use-of-nutritional-ketosis-with-mobile-app-intervention-could-reverse-type-2-diabetes.html>. Accessed April 17, 2019.
4199. Sweeney JS. Dietary factors that influence the dextrose tolerance test. *Arch Intern Med.* 1927;40(6):818.
4200. Himsworth HP. The dietetic factor determining the glucose tolerance and sensitivity to insulin in healthy men. *Clin Sci.* 1935;2:67-94.
4201. Parry SA, Woods RM, Hodson L, Hulston CJ. A single day of excessive dietary fat intake reduces whole-body insulin sensitivity: the metabolic consequence of binge eating. *Nutrients.* 2017;9(8):818.
4202. Robertson MD, Henderson RA, Vist GE, Rumsey RD. Extended effects of evening meal carbohydrate-to-fat ratio on fasting and postprandial substrate metabolism. *Am J Clin Nutr.* 2002;75(3):505-10.
4203. Hernández EÁ, Kahl S, Seelig A, et al. Acute dietary fat intake initiates alterations in energy metabolism and insulin resistance. *J Clin Invest.* 2017;127(2):695-708.
4204. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther.* 2018;9(2):583-612.
4205. Anderson JW, Ward K. High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus. *Am J Clin Nutr.* 1979;32(11):2312-21.
4206. Anderson JW, Ward K. High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus. *Am J Clin Nutr.* 1979;32(11):2312-21.
4207. Angeloni C, Zambonin L, Hrelia S. Role of methylglyoxal in Alzheimer's disease. *Biomed Res Int.* 2014;2014:238485.
4208. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci.* 2010;65(9):963-75.
4209. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc.* 2010;110(6):911-16.e12.
4210. Beisswenger BG, Delucia EM, Lapoint N, Sanford RJ, Beisswenger PJ. Ketosis leads to increased methylglyoxal production on the Atkins diet. *Ann NY Acad Sci.* 2005;1043:201-10.
4211. Jones AW, Rössner S. False-positive breath-alcohol test after a ketogenic diet. *Int J Obes (Lond).* 2007;31(3):559-61.
4212. Franz MJ. Protein and diabetes: much advice, little research. *Curr Diab Rep.* 2002;2(5):457-64.
4213. Beisswenger BG, Delucia EM, Lapoint N, Sanford RJ, Beisswenger PJ. Ketosis leads to increased methylglyoxal production on the Atkins diet. *Ann NY Acad Sci.* 2005;1043:201-10.
4214. Beisswenger BG, Delucia EM, Lapoint N, Sanford RJ, Beisswenger PJ. Ketosis leads to increased methylglyoxal production on the Atkins diet. *Ann NY Acad Sci.* 2005;1043:201-10.
4215. Sheikh M, Chahal M, Rock-Willoughby J, Grubb BP. Carbohydrate-restricted diet and acute coronary syndrome: a case report and review of this conflicting and yet unknown association. *Am J Ther.* 2014;21(2):e41-4.
4216. Aragon AA, Schoenfeld BJ, Wildman R, et al. International Society of Sports Nutrition position stand: diets and body composition. *J Int Soc Sports Nutr.* 2017;14:16.
4217. White AM, Johnston CS, Swan PD, Tjonn SL, Sears B. Blood ketones are directly related to fatigue and perceived effort during exercise in overweight adults adhering to low-carbohydrate diets for weight loss: a pilot study. *J Am Diet Assoc.* 2007;107(10):1792-6.
4218. Kephart WC, Pledge CD, Roberson PA, et al. The three-month effects of a ketogenic diet on body composition, blood parameters, and performance metrics in crossfit trainees: a pilot study. *Sports (Basel).* 2018;6(1):1.
4219. Burke LM, Ross ML, Garvican-Lewis LA, et al. Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J Physiol (Lond).* 2016;595(9):2785-807.
4220. Vargas S, Romance R, Petro JL, et al. Efficacy of ketogenic diet on body composition during resistance training in trained men: a randomized controlled trial. *J Int Soc Sports Nutr.* 2018;15(1):31.
4221. Paoli A, Bianco A, Grimaldi KA. The ketogenic diet and sport: a possible marriage? *Exerc Sport Sci Rev.* 2015;43(3):153-62.
4222. Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol.* 2006;48(12):978-81.
4223. Simm PJ, Bicknell-Royle J, Lawrie J, et al. The effect of the ketogenic diet on the developing skeleton. *Epilepsy Res.* 2017;136:62-6.
4224. Nordli D. The ketogenic diet: uses and abuses. *Neurology.* 2002;58(12 Suppl 7):S21-4.

4225. Bergqvist AG, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr.* 2008;88(6):1678-84.
4226. Yancy WS, Olsen MK, Dudley T, Westman EC. Acid-base analysis of individuals following two weight loss diets. *Eur J Clin Nutr.* 2007;61(12):1416-22.
4227. Wijnen BFM, de Kinderen RJA, Lambrechts DAJE, et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. *Epilepsy Res.* 2017;132:91-9.
4228. Liu G, Slater N, Perkins A. Epilepsy: treatment options. *Am Fam Physician.* 2017;96(2):87-96.
4229. Kouda K, Iki M. Beneficial effects of mild stress (hormetic effects): dietary restriction and health. *J Physiol Anthropol.* 2010;29(4):127-32.
4230. Collier R. Intermittent fasting: the science of going without. *CMAJ.* 2013;185(9):E363-4.
4231. Twain M. *My Debut as a Literary Person: With Other Essays and Stories.* Hartford, CT: American Pub Co; 1903.
4232. Twain M. *A Connecticut Yankee in King Arthur's Court.* New York: Charles L. Webster and Co; 1889.
4233. Collier R. Intermittent fasting: the science of going without. *CMAJ.* 2013;185(9):E363-4.
4234. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutr Rev.* 2015;73(10):661-74.
4235. Johnstone AM. Fasting—the ultimate diet? *Obes Rev.* 2007;8(3):211-22.
4236. Awada A, Al Jumah M. The first-of-Ramadan headache. *Headache.* 1999;39(7):490-3.
4237. Mosek A, Korczyn AD. Yom Kippur headache. *Neurology.* 1995;45(11):1953-5.
4238. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutr Rev.* 2015;73(10):661-74.
4239. Cronise RJ, Sinclair DA, Bremer AA. Oxidative priority, meal frequency, and the energy economy of food and activity: implications for longevity, obesity, and cardiometabolic disease. *Metab Syndr Relat Disord.* 2017;15(1):6-17.
4240. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4241. Klein S, Sakurai Y, Romijn JA, Carroll RM. Progressive alterations in lipid and glucose metabolism during short-term fasting in young adult men. *Am J Physiol.* 1993;265(5 Pt 1):E801-6.
4242. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4243. Anson RM, Guo Z, De Cabo R, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. *Proc Natl Acad Sci USA.* 2003;100(10):6216-20.
4244. Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. *Am J Clin Nutr.* 2015;102(2):464-70.
4245. Johnstone AM, Faber P, Gibney ER, et al. Effect of an acute fast on energy compensation and feeding behaviour in lean men and women. *Int J Obes Relat Metab Disord.* 2002;26(12):1623-8.
4246. Harvey J, Howell A, Morris J, Harvie M. Intermittent energy restriction for weight loss: spontaneous reduction of energy intake on unrestricted days. *Food Sci Nutr.* 2018;6(3):674-80.
4247. Antoni R, Johnston KL, Collins AL, Robertson MD. Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants. *Br J Nutr.* 2016;115(6):951-9.
4248. Clayton DJ, Creese M, Skidmore N, Stensel DJ, James LJ. No effect of 24 h severe energy restriction on appetite regulation and ad libitum energy intake in overweight and obese males. *Int J Obes (Lond).* 2016;40(11):1662-70.
4249. Harvey J, Howell A, Morris J, Harvie M. Intermittent energy restriction for weight loss: spontaneous reduction of energy intake on unrestricted days. *Food Sci Nutr.* 2018;6(3):674-80.
4250. Levitsky DA, Derosimo L. One day of food restriction does not result in an increase in subsequent daily food intake in humans. *Physiol Behav.* 2010;99(4):495-9.
4251. Tinsley GM, Moore ML, Graybeal AJ. Reliability of hunger-related assessments during 24-hour fasts and their relationship to body composition and subsequent energy compensation. *Physiol Behav.* 2018;188:221-6.
4252. Klempel MC, Bhutani S, Fitzgibbon M, Freels S, Varady KA. Dietary and physical activity adaptations to alternate day modified fasting: implications for optimal weight loss. *Nutr J.* 2010;9:35.
4253. Varady KA, Bhutani S, Klempel MC, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. *Nutr J.* 2013;12(1):146.
4254. Hoddy KK, Kroeger CM, Trepanowski JF, Barnosky A, Bhutani S, Varady KA. Meal timing during alternate day fasting: impact on body weight and cardiovascular disease risk in obese adults. *Obesity (Silver Spring).* 2014;22(12):2524-31.
4255. Eshghinia S, Mohammadzadeh F. The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women. *J Diabetes Metab Disord.* 2013;12(1):4.
4256. Kroeger CM, Trepanowski JF, Klempel MC, et al. Eating behavior traits of successful weight losers during 12 months of alternate-day fasting: an exploratory analysis of a randomized controlled trial. *Nutr Health.* 2018;24(1):5-10.
4257. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4258. Varady KA. Alternate day fasting: effects on body weight and chronic disease risk in humans and animals. In: McCue MD, ed. *Comparative Physiology of Fasting, Starvation, and Food Limitation.* Berlin: Springer-Verlag Berlin Heidelberg; 2012.
4259. Catenacci VA, Pan Z, Ostendorf D, et al. A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity. *Obesity (Silver Spring).* 2016;24(9):1874-83.
4260. Coutinho SR, Halset EH, Gåsbakk S, et al. Compensatory mechanisms activated with intermittent energy restriction: a randomized control trial. *Clin Nutr.* 2018;37(3):815-23.
4261. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med.* 2017;177(7):930-8.

4262. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med.* 2017;177(7):930-8.
4263. Benau EM, Orloff NC, Janke EA, Serpell L, Timko CA. A systematic review of the effects of experimental fasting on cognition. *Appetite.* 2014;77:52-61.
4264. Hoddy KK, Kroeger CM, Trepanowski JF, Barnosky AR, Bhutani S, Varady KA. Safety of alternate day fasting and effect on disordered eating behaviors. *Nutr J.* 2015;14:44.
4265. Schaumberg K, Anderson DA, Reilly EE, Anderson LM. Does short-term fasting promote pathological eating patterns? *Eat Behav.* 2015;19:168-72.
4266. Barnosky A, Kroeger CM, Trepanowski JF, et al. Effect of alternate day fasting on markers of bone metabolism: an exploratory analysis of a 6-month randomized controlled trial. *Nutr Healthy Aging.* 2017;4(3):255-63.
4267. Golbidi S, Daiber A, Korac B, Li H, Essop MF, Laher I. Health benefits of fasting and caloric restriction. *Curr Diab Rep.* 2017;17(12):123.
4268. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev.* 2011;12(7):e593-601.
4269. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4270. St-Onge MP, Ard J, Baskin ML, et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. *Circulation.* 2017;135(9):e96-121.
4271. Bhutani S, Klempel M, Kroeger C, et al. Alternate day fasting with or without exercise: effects on endothelial function and adipokines in obese humans. *e-SPEN Journal.* 2013;8(5):e205-9.
4272. Klempel MC, Kroeger CM, Norkeviciute E, Goslawski M, Phillips SA, Varady KA. Benefit of a low-fat over high-fat diet on vascular health during alternate day fasting. *Nutr Diabetes.* 2013;3:e71.
4273. Horne BD, Muhlestein JB, Butler AR, Brown H, Anderson JL. Effects of water-only fasting among pre-diabetic patients. *Behavioral Medicine, Clinical Nutrition, Education, and Exercise.* 2014;63 (Suppl 1):A590 (abstr). Available at: http://hw-f5-diabetes.highwire.org/content/diabetes/63/Supplement_1/A582.full.pdf. Accessed August 6, 2018.
4274. Antoni R, Johnston KL, Collins AL, Robertson MD. Investigation into the acute effects of total and partial energy restriction on postprandial metabolism among overweight/obese participants. *Br J Nutr.* 2016;115(6):951-9.
4275. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4276. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med.* 2017;177(7):930-8.
4277. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2017;38(32):2459-72.
4278. Roberts WC. It's the cholesterol, stupid! *Am J Cardiol.* 2010;106(9):1364-6.
4279. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabet Med.* 2018;35(5):588-94.
4280. Lammers LA, Achterbergh R, de Vries EM, et al. Short-term fasting alters cytochrome P450-mediated drug metabolism in humans. *Drug Metab Dispos.* 2015;43(6):819-28.
4281. Johnson JB, Laub DR, John S. The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life. *Med Hypotheses.* 2006;67(2):209-11.
4282. Johnstone A. Fasting for weight loss: an effective strategy or latest dieting trend? *Int J Obes (Lond).* 2015;39(5):727-33.
4283. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic Biol Med.* 2007;42(5):665-74.
4284. Vallejo EA. La dieta de hambre a dias alternos en la alimentacion de los viejos. *Rev Clin Esp.* 1956;63:25-7.
4285. Johnson JB, Laub DR, John S. The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life. *Med Hypotheses.* 2006;67(2):209-11.
4286. Vallejo EA. La dieta de hambre a dias alternos en la alimentacion de los viejos. *Rev Clin Esp.* 1956;63:25-7.
4287. Stunkard AJ. Nutrition, aging and obesity: a critical review of a complex relationship. *Int J Obes.* 1983;7(3):201-20.
4288. Conley M, Le Fevre L, Haywood C, Proietto J. Is two days of intermittent energy restriction per week a feasible weight loss approach in obese males? A randomised pilot study. *Nutr Diet.* 2018;75(1):65-72.
4289. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond).* 2011;35(5):714-27.
4290. SundfØr TM, Svendsen M, Tønstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr Metab Cardiovasc Dis.* 2018;28(7):698-706.
4291. SundfØr TM, Svendsen M, Tønstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr Metab Cardiovasc Dis.* 2018;28(7):698-706.
4292. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond).* 2011;35(5):714-27.
4293. Solianik R, Sujeta A. Two-day fasting evokes stress, but does not affect mood, brain activity, cognitive, psychomotor, and motor performance in overweight women. *Behav Brain Res.* 2018;338:166-72.
4294. Solianik R, Sujeta A, Čekanauskaitė A. Effects of 2-day calorie restriction on cardiovascular autonomic response, mood, and cognitive and motor functions in obese young adult women. *Exp Brain Res.* 2018;236(8):2299-308.
4295. Solianik R, Sujeta A, Čekanauskaitė A. Effects of 2-day calorie restriction on cardiovascular autonomic response, mood, and cognitive and motor functions in obese young adult women. *Exp Brain Res.* 2018;236(8):2299-308.

4296. Davis CS, Clarke RE, Coulter SN, et al. Intermittent energy restriction and weight loss: a systematic review. *Eur J Clin Nutr.* 2016;70(3):292-9.
4297. Antoni R, Johnston KL, Collins AL, Robertson MD. Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants. *Br J Nutr.* 2018;119(5):507-16.
4298. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond).* 2011;35(5):714-27.
4299. Davis CS, Clarke RE, Coulter SN, et al. Intermittent energy restriction and weight loss: a systematic review. *Eur J Clin Nutr.* 2016;70(3):292-9.
4300. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond).* 2011;35(5):714-27.
4301. Conley M, Le Fevre L, Haywood C, Proietto J. Is two days of intermittent energy restriction per week a feasible weight loss approach in obese males? A randomised pilot study. *Nutr Diet.* 2018;75(1):65-72.
4302. Sundfør TM, Svendsen M, Tonstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr Metab Cardiovasc Dis.* 2018;28(7):698-706.
4303. Stewart WK, Fleming LW, Robertson PC. Massive obesity treated by intermittent fasting. A metabolic and clinical study. *Am J Med.* 1966;40(6):967-86.
4304. Keogh JB, Pedersen E, Petersen KS, Clifton PM. Effects of intermittent compared to continuous energy restriction on short-term weight loss and long-term weight loss maintenance. *Clin Obes.* 2014;4(3):150-6.
4305. Arguin H, Dionne IJ, Sénéchal M, et al. Short-and long-term effects of continuous versus intermittent restrictive diet approaches on body composition and the metabolic profile in overweight and obese postmenopausal women: a pilot study. *Menopause.* 2012;19(8):870-6.
4306. Arguin H, Dionne IJ, Sénéchal M, et al. Short-and long-term effects of continuous versus intermittent restrictive diet approaches on body composition and the metabolic profile in overweight and obese postmenopausal women: a pilot study. *Menopause.* 2012;19(8):870-6.
4307. Byrne NM, Sainsbury A, King NA, Hills AP, Wood RE. Intermittent energy restriction improves weight loss efficiency in obese men: the MATADOR study. *Int J Obes (Lond).* 2018;42(2):129-38.
4308. Harris L, McGarty A, Hutchison L, Eells L, Hankey C. Short-term intermittent energy restriction interventions for weight management: a systematic review and meta-analysis. *Obes Rev.* 2018;19(1):1-13.
4309. Davis CS, Clarke RE, Coulter SN, et al. Intermittent energy restriction and weight loss: a systematic review. *Eur J Clin Nutr.* 2016;70(3):292-9.
4310. Brandhorst S, Choi IY, Wei M, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. *Cell Metab.* 2015;22(1):86-99.
4311. Wei M, Brandhorst S, Shelehchi M, et al. Fasting-mimicking diet and markers / risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med.* 2017;9(377):8700.
4312. Abbasi J. Can a diet that mimics fasting turn back the clock? *JAMA.* 2017;318(3):227-9.
4313. Wei M, Brandhorst S, Shelehchi M, et al. Fasting-mimicking diet and markers / risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med.* 2017;9(377):8700.
4314. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab.* 2015;22(5):789-98.
4315. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring).* 2018;26(2):254-68.
4316. TestDiet. Published 2013. Available at: <https://docplayer.net/14971978-1942-labdiet-5001-rodent-diet-introduced-first-diet-specifically-for-laboratory-research-animals.html>. Accessed April 17, 2019.
4317. Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab.* 2012;15(6):848-60.
4318. Lai M, Chandrasekera PC, Barnard ND. You are what you eat, or are you? The challenges of translating high-fat-fed rodents to human obesity and diabetes. *Nutr Diabetes.* 2014;4:e135.
4319. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab.* 2015;22(5):789-98.
4320. Rothschild J, Hoddy KK, Jambazian P, Varady KA. Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. *Nutr Rev.* 2014;72(5):308-18.
4321. LeCheminant JD, Christenson E, Bailey BW, Tucker LA. Restricting night-time eating reduces daily energy intake in healthy young men: a short-term cross-over study. *Br J Nutr.* 2013;110(11):2108-13.
4322. Gabel K, Hoddy KK, Haggerty N, et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study. *Nutr Healthy Aging.* 2018;4(4):345-53.
4323. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab.* 2015;22(5):789-98.
4324. Jiang P, Turek FW. Timing of meals: when is as critical as what and how much. *Am J Physiol Endocrinol Metab.* 2017;312(5):E369-80.
4325. Nelson MC, Kocos R, Lytle LA, Perry CL. Understanding the perceived determinants of weight-related behaviors in late adolescence: a qualitative analysis among college youth. *J Nutr Educ Behav.* 2009;41(4):287-92.
4326. Thomson M, Spence JC, Raine K, Laing L. The association of television viewing with snacking behavior and body weight of young adults. *Am J Health Promot.* 2008;22(5):329-35.
4327. LeCheminant JD, Christenson E, Bailey BW, Tucker LA. Restricting night-time eating reduces daily energy intake in healthy young men: a short-term cross-over study. *Br J Nutr.* 2013;110(11):2108-13.
4328. Hirsch EHE, Halberg F, Goetz FC, et al. Body weight change during 1 week on a single daily 2000-calorie meal consumed as breakfast (B) or dinner (D). *Chronobiologia.* 1975;2(Suppl 1):31-2.
4329. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring).* 2013;21(12):2504-12.

4330. Hibi M, Masumoto A, Naito Y, et al. Nighttime snacking reduces whole body fat oxidation and increases LDL cholesterol in healthy young women. *Am J Physiol Regul Integr Comp Physiol*. 2013;304(2):R94-101.
4331. Morris CJ, Garcia JJ, Myers S, Yang JN, Trienekens N, Scheer FA. The human circadian system has a dominating role in causing the morning/evening difference in diet-induced thermogenesis. *Obesity (Silver Spring)*. 2015;23(10):2053-8.
4332. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504-12.
4333. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab*. 2015;22(5):789-98.
4334. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr*. 2007;85(4):981-8.
4335. Moro T, Tinsley G, Bianco A, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J Transl Med*. 2016;14(1):290.
4336. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr*. 2007;85(4):981-8.
4337. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab*. 2018;27(6):1212-21.e3.
4338. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab*. 2015;22(5):789-98.
4339. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab*. 2015;22(5):789-98.
4340. Marinac CR, Sears DD, Natarajan L, Gallo LC, Breen CI, Patterson RE. Frequency and circadian timing of eating may influence biomarkers of inflammation and insulin resistance associated with breast cancer risk. *PLoS ONE*. 2015;10(8):e0136240.
4341. Marinac CR, Natarajan L, Sears DD, et al. Prolonged nightly fasting and breast cancer risk: findings from NHANES (2009-2010). *Cancer Epidemiol Biomarkers Prev*. 2015;24(5):783-9.
4342. Marinac CR, Nelson SH, Breen CI, et al. Prolonged nightly fasting and breast cancer prognosis. *JAMA Oncol*. 2016;2(8):1049-55.
4343. Schloss J, Steel A. Medical synopsis: nightly fasting may assist breast cancer patients and other people with cancer. *Adv Integr Med*. 2016;3(2):66-7.
4344. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645-52.
4345. Kahleova H, Lloren JI, Mashchak A, Hill M, Fraser GE. Meal frequency and timing are associated with changes in body mass index in Adventist Health Study 2. *J Nutr*. 2017;147(9):1722-8.
4346. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am*. 2018;102(1):183-97.
4347. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metab*. 2014;19(2):181-92.
4348. Harris L, Hamilton S, Azevedo LB, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. *JBI Database System Rev Implement Rep*. 2018;16(2):507-47.
4349. Duffey KJ, Popkin BM. Energy density, portion size, and eating occasions: contributions to increased energy intake in the United States, 1977-2006. *PLoS MED*. 2011;8(6):e1001050.
4350. Popkin BM, Duffey KJ. Does hunger and satiety drive eating anymore? Increasing eating occasions and decreasing time between eating occasions in the United States. *Am J Clin Nutr*. 2010;91(5):1342-7.
4351. Mattes R. Energy intake and obesity: ingestive frequency outweighs portion size. *Physiol Behav*. 2014;134:110-8.
4352. McCrory MA, Howarth NC, Roberts SB, Huang TT. Eating frequency and energy regulation in free-living adults consuming self-selected diets. *J Nutr*. 2011;141(1):148-53.
4353. Kulovitz MG, Kravitz LR, Mermier C, et al. Potential role of meal frequency as a strategy for weight loss and health in overweight or obese adults. *Nutrition*. 2014;30(4):386-92.
4354. Palmer M, Capra S, Baines S. To snack or not to snack: what should we advise for weight management? *Nutr Diet*. 2011;68(1):60-4.
4355. Bellisle F. Impact of the daily meal pattern on energy balance. *Food Nutr Res*. 2004;48(3):114-8.
4356. Zhu Y, Hollis JH. Associations between eating frequency and energy intake, energy density, diet quality and body weight status in adults from the USA. *Br J Nutr*. 2016;115(12):2138-44.
4357. Holmbäck I, Ericson U, Gullberg B, Wirfält E. A high eating frequency is associated with an overall healthy lifestyle in middle-aged men and women and reduced likelihood of general and central obesity in men. *Br J Nutr*. 2010;104(7):1065-73.
4358. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. *Br J Nutr*. 1997;77 Suppl 1:S57-70.
4359. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. *Br J Nutr*. 1997;77 Suppl 1:S57-70.
4360. Rothblum ED. Women and weight: fact and fiction. *J Psychol*. 1990;124(1):5-24.
4361. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med*. 1992;327(27):1893-8.
4362. Reynolds J. *A Discourse Upon Prodigious Abstinence: Occasioned by the Twelve Months Fasting of Martha Taylor, the Famed Derbyshire Damosell: Proving That Without Any Miracle, the Texture of Humane Bodies May Be So Altered, That Life May Be Long Continued Without the Supplies of Meat & Drink*. London: RW; 1669.
4363. Heymsfield SB, Darby PC, Muhlheim LS, Gallagher D, Wolper C, Allison DB. The calorie: myth, measurement, and reality. *Am J Clin Nutr*. 1995;62(5 Suppl):1034S-41S.
4364. Breatharian Institute of America.
<https://web.archive.org/web/20151107030359/http://www.breatharian.com/initiationworkshops.html>. Accessed August 29, 2018.
4365. Shay KJ. *Walking through the Wall*. Morrisville, NC: Lulu Press; 2012.

4366. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med*. 1992;327(27):1893-8.
4367. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med*. 1992;327(27):1893-8.
4368. Newburgh LH, Johnston MW. Endogenous obesity—a misconception. *Ann Intern Med*. 1930;3(8):815-25.
4369. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. *Br J Nutr*. 1997;77 Suppl 1:S57-70.
4370. Heitmann BL, Lissner L. Dietary underreporting by obese individuals—is it specific or non-specific? *BMJ*. 1995;311(7011):986-9.
4371. Bellisle F. Impact of the daily meal pattern on energy balance. *Food Nutr Res*. 2004;48(3):114-8.
4372. Murakami K, Livingstone MB. Eating frequency is positively associated with overweight and central obesity in U.S. adults. *J Nutr*. 2015;145(12):2715-24.
4373. McCrory MA, Campbell WW. Effects of eating frequency, snacking, and breakfast skipping on energy regulation: symposium overview. *J Nutr*. 2011;141(1):144-7.
4374. Ohkawara K, Cornier MA, Kohrt WM, Melanson EL. Effects of increased meal frequency on fat oxidation and perceived hunger. *Obesity (Silver Spring)*. 2013;21(2):336-43.
4375. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. *Br J Nutr*. 1997;77 Suppl 1:S57-70.
4376. Ohkawara K, Cornier MA, Kohrt WM, Melanson EL. Effects of increased meal frequency on fat oxidation and perceived hunger. *Obesity (Silver Spring)*. 2013;21(2):336-43.
4377. Kant AK. Evidence for efficacy and effectiveness of changes in eating frequency for body weight management. *Adv Nutr*. 2014;5(6):822-8.
4378. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr*. 2007;85(4):981-8.
4379. Carlson O, Martin B, Stote KS, et al. Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women. *Metab Clin Exp*. 2007;56(12):1729-34.
4380. Mann J. Meal frequency and plasma lipids and lipoproteins. *Br J Nutr*. 1997;77 Suppl 1:S83-90.
4381. Jenkins DJ, Wolever TM, Vuksan V, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med*. 1989;321(14):929-34.
4382. Jenkins DJ, Wolever TM, Vuksan V, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med*. 1989;321(14):929-34.
4383. Mann J. Meal frequency and plasma lipids and lipoproteins. *Br J Nutr*. 1997;77 Suppl 1:S83-90.
4384. Jenkins DJ, Khan A, Jenkins AL, et al. Effect of nibbling versus gorging on cardiovascular risk factors: serum uric acid and blood lipids. *Metab Clin Exp*. 1995;44(4):549-55.
4385. Jenkins DJ, Wolever TM, Vuksan V, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med*. 1989;321(14):929-34.
4386. Goff LM, Cowland DE, Hooper L, Frost GS. Low glycaemic index diets and blood lipids: a systematic review and meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis*. 2013;23(1):1-10.
4387. Mattes RD. Snacking: a cause for concern. *Physiol Behav*. 2018;193(Pt B):279-83.
4388. Koopman KE, Caan MW, Nederveen AJ, et al. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized controlled trial. *Hepatology*. 2014;60(2):545-53.
4389. Hutchison AT, Heilbronn LK. Metabolic impacts of altering meal frequency and timing—does when we eat matter? *Biochimie*. 2016;124:187-97.
4390. Hägele FA, Büsing F, Nas A, et al. High orange juice consumption with or in-between three meals a day differently affects energy balance in healthy subjects. *Nutr Diabetes*. 2018;8(1):19.
4391. Potter M, Vlassopoulos A, Lehmann U. Snacking recommendations worldwide: a scoping review. *Adv Nutr*. 2018;9(2):86-98.
4392. Njike VY, Kavak Y, Treu JA, Doughty K, Katz DL. Snacking, satiety, and weight: a randomized, controlled trial. *Am J Health Promot*. 2017;31(4):296-301.
4393. Wansink B, Painter JE, Lee YK. The office candy dish: proximity's influence on estimated and actual consumption. *Int J Obes (Lond)*. 2006;30(5):871-5. Note: The legitimacy of Brian Wansink's research has been called into serious question. See, for example, <https://www.chronicle.com/article/Spoiled-Science/239529>.
4394. Skorka-Brown J, Andrade J, May J. Playing "Tetris" reduces the strength, frequency and vividness of naturally occurring cravings. *Appetite*. 2014;76:161-5.
4395. Cutting W, Tainter M. Metabolic actions of dinitrophenol. *J Am Med Assoc*. 1933;101(27):193-5.
4396. Clapham JC, Arch JR. Thermogenic and metabolic antiobesity drugs: rationale and opportunities. *Diabetes Obes Metab*. 2007;9(3):259-75.
4397. Seamon MJ, Clauson KA. Yesterday, DSHEA, and tomorrow—a ten year perspective on the Dietary Supplement Health and Education Act of 1994. *J Herb Pharmacother*. 2005;5(3):67-86.
4398. Astrup A, Lundsgaard C, Madsen J, Christensen NJ. Enhanced thermogenic responsiveness during chronic ephedrine treatment in man. *Am J Clin Nutr*. 1985;42(1):83-94.
4399. Shekelle PG, Hardy ML, Morton SC, et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. *JAMA*. 2003;289(12):1537-45.
4400. Woolf AD, Watson WA, Smolinske S, Litovitz T. The severity of toxic reactions to ephedra: comparisons to other botanical products and national trends from 1993-2002. *Clin Toxicol (Phila)*. 2005;43(5):347-55.
4401. Seamon MJ, Clauson KA. Yesterday, DSHEA, and tomorrow—a ten year perspective on the Dietary Supplement Health and Education Act of 1994. *J Herb Pharmacother*. 2005;5(3):67-86.
4402. Seamon MJ, Clauson KA. Yesterday, DSHEA, and tomorrow—a ten year perspective on the Dietary Supplement Health and Education Act of 1994. *J Herb Pharmacother*. 2005;5(3):67-86.
4403. Seamon MJ, Clauson KA. Yesterday, DSHEA, and tomorrow—a ten year perspective on the Dietary Supplement Health and Education Act of 1994. *J Herb Pharmacother*. 2005;5(3):67-86.
4404. Ashar BH, Miller RG, Getz KJ, Pichard CP. A critical evaluation of internet marketing of products that contain ephedra. *Mayo Clin Proc*. 2003;78(8):944-6.

4405. Hilts P. U.S. in criminal inquiry on Metabolife product. *New York Times*. Published August 16, 2002. Available at: <https://www.nytimes.com/2002/08/16/business/us-in-criminal-inquiry-on-metabolife-product.html>. Accessed April 17, 2019.
4406. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Med*. 2016;14(1):191.
4407. Lubetzky R, Mimouni FB, Dollberg S, Reifen R, Ashbel G, Mandel D. Effect of music by Mozart on energy expenditure in growing preterm infants. *Pediatrics*. 2010;125(1):e24-8.
4408. Carlsson E, Helgegren H, Slinde F. Resting energy expenditure is not influenced by classical music. *J Negat Results Biomed*. 2005;4:6.
4409. Keidar HR, Mandel D, Mimouni FB, Lubetzky R. Bach music in preterm infants: no "Mozart effect" on resting energy expenditure. *J Perinatol*. 2014;34(2):153-5.
4410. Snell B, Fullmer S, Eggett DL. Reading and listening to music increase resting energy expenditure during an indirect calorimetry test. *J Acad Nutr Diet*. 2014;114(12):1939-42.
4411. Stork MJ, Kwan MY, Gibala MJ, Martin Gginis KA. Music enhances performance and perceived enjoyment of sprint interval exercise. *Med Sci Sports Exerc*. 2015;47(5):1052-60.
4412. Jarraya M, Chtourou H, Aloui A, et al. The effects of music on high-intensity short-term exercise in well trained athletes. *Asian J Sports Med*. 2012;3(4):233-8.
4413. Manchester RA. Energy expenditure in the performing arts. *Med Probl Perform Art*. 2011;26(4):183-4.
4414. De La Rue SE, Draper SB, Potter CR, Smith MS. Energy expenditure in rock/pop drumming. *Int J Sports Med*. 2013;34(10):868-72.
4415. Romero B, Coburn J, Brown L, Galpin A. Metabolic demands of heavy metal drumming. *IJKSS*. 2016;4(3):32-6.
4416. Vega JL. Edmund Goodwyn and the first description of diving bradycardia. *J Appl Physiol*. 2017;123(2):275-7.
4417. Khurana RK, Watabiki S, Hebel JR, Toro R, Nelson E. Cold face test in the assessment of trigeminal-brainstem-vagal function in humans. *Ann Neurol*. 1980;7(2):144-9.
4418. Smith G, Morgans A, Taylor DM, Cameron P. Use of the human dive reflex for the management of supraventricular tachycardia: a review of the literature. *Emerg Med J*. 2012;29(8):611-6.
4419. Geelen G, Greenleaf JE, Keil LC. Drinking-induced plasma vasopressin and norepinephrine changes in dehydrated humans. *J Clin Endocrinol Metab*. 1996;81(6):2131-5.
4420. Scott EM, Greenwood JP, Gilbey SG, Stoker JB, Mary DA. Water ingestion increases sympathetic vasoconstrictor discharge in normal human subjects. *Clin Sci*. 2001;100(3):335-42.
4421. Scott EM, Greenwood JP, Gilbey SG, Stoker JB, Mary DA. Water ingestion increases sympathetic vasoconstrictor discharge in normal human subjects. *Clin Sci*. 2001;100(3):335-42.
4422. Joannidès R, Moore N, de la Gueronnière V, Thuillez C. Effect of water on arteries. *Lancet*. 1999;354(9177):516.
4423. Lu CC, Li MH, Lin TC, et al. Water ingestion reduces skin blood flow through sympathetic vasoconstriction. *Clin Auton Res*. 2012;22(2):63-9.
4424. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003;108(21):2660-5.
4425. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003;108(21):2660-5.
4426. Ayala ES, Meuret AE, Ritz T. Treatments for blood-injury-injection phobia: a critical review of current evidence. *J Psychiatr Res*. 2009;43(15):1235-42.
4427. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003;108(21):2660-5.
4428. Schroeder C, Bush VE, Norcliffe LJ, et al. Water drinking acutely improves orthostatic tolerance in healthy subjects. *Circulation*. 2002;106(22):2806-11.
4429. Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation*. 2000;101(5):504-9.
4430. Routledge HC, Chowdhary S, Coote JH, Townend JN. Cardiac vagal response to water ingestion in normal human subjects. *Clin Sci*. 2002;103(2):157-62.
4431. Routledge HC, Chowdhary S, Coote JH, Townend JN. Cardiac vagal response to water ingestion in normal human subjects. *Clin Sci*. 2002;103(2):157-62.
4432. Jordan J, Shannon JR, Black BK, et al. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation*. 2000;101(5):504-9.
4433. McKee K, Nelson S, Batra A, Klein JP, Henderson GV. Diving into the ice bucket challenge: intraparenchymal hemorrhage and the mammalian diving reflex. *Neurohospitalist*. 2015;5(3):182-4.
4434. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(1):R40-6.
4435. Boschmann M, Steiniger J, Hille U, et al. Water-induced thermogenesis. *J Clin Endocrinol Metab*. 2003;88(12):6015-9.
4436. Charrière N, Miles-Chan JL, Montani JP, Dulloo AG. Water-induced thermogenesis and fat oxidation: a reassessment. *Nutr Diabetes*. 2015;5:e190.
4437. Boschmann M, Steiniger J, Hille U, et al. Water-induced thermogenesis. *J Clin Endocrinol Metab*. 2003;88(12):6015-9.
4438. Shannon JR, Gottesdiener K, Jordan J, et al. Acute effect of ephedrine on 24-h energy balance. *Clin Sci*. 1999;96(5):483-91.
4439. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(1):R40-6.
4440. Dubnov-Raz G, Constantini NW, Yariv H, Nice S, Shapira N. Influence of water drinking on resting energy expenditure in overweight children. *Int J Obes (Lond)*. 2011;35(10):1295-300.
4441. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, D.C.: National Academies Press; 2006.

4442. Kocetak P, Zak-Gołąb A, Rzemieniuk A, et al. The influence of oral water load on energy expenditure and sympatho-vagal balance in obese and normal weight women. *Arch Med Sci*. 2012;8(6):1003-8.
4443. Brown CM, Dulloo AG, Montani JP. Water-induced thermogenesis reconsidered: the effects of osmolality and water temperature on energy expenditure after drinking. *J Clin Endocrinol Metab*. 2006;91(9):3598-602.
4444. Charrière N, Miles-Chan JL, Montani JP, Dulloo AG. Water-induced thermogenesis and fat oxidation: a reassessment. *Nutr Diabetes*. 2015;5:e190.
4445. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(1):R40-6.
4446. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? *Health Aff (Millwood)*. 2006;25(2):420-8.
4447. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(1):R40-6.
4448. Stookey JD, Constant F, Popkin BM, Gardner CD. Drinking water is associated with weight loss in overweight dieting women independent of diet and activity. *Obesity (Silver Spring)*. 2008;16(11):2481-8.
4449. Vij VA, Joshi AS. Effect of "water induced thermogenesis" on body weight, body mass index and body composition of overweight subjects. *J Clin Diagn Res*. 2013;7(9):1894-6.
4450. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Weight change among people randomized to minimal intervention control groups in weight loss trials. *Obesity (Silver Spring)*. 2016;24(4):772-80.
4451. Dennis EA, Dengo AL, Comber DL, et al. Water consumption increases weight loss during a hypocaloric diet intervention in middle-aged and older adults. *Obesity (Silver Spring)*. 2010;18(2):300-7.
4452. Parretti HM, Aveyard P, Blannin A, et al. Efficacy of water preloading before main meals as a strategy for weight loss in primary care patients with obesity: RCT. *Obesity (Silver Spring)*. 2015;23(9):1785-91.
4453. Jolly K, Lewis A, Beach J, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: Lighten Up randomised controlled trial. *BMJ*. 2011;343:d6500.
4454. Parretti HM, Aveyard P, Blannin A, et al. Efficacy of water preloading before main meals as a strategy for weight loss in primary care patients with obesity: RCT. *Obesity (Silver Spring)*. 2015;23(9):1785-91.
4455. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC / AHA / HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2017;136(5):e60-122.
4456. Lu CC, Li MH, Ho ST, et al. Glucose reduces the effect of water to promote orthostatic tolerance. *Am J Hypertens*. 2008;21(11):1177-82.
4457. Raj SR, Biaggioni I, Black BK, et al. Sodium paradoxically reduces the gastropressor response in patients with orthostatic hypotension. *Hypertension*. 2006;48(2):329-34.
4458. van Orshoven NP, Oey PL, Roelofs JM, Jansen PA, Akkermans LM. Effect of gastric distension on cardiovascular parameters: gastrovascular reflex is attenuated in the elderly. *J Physiol (Lond)*. 2004;555(Pt 2):573-83.
4459. Boschmann M, Steiniger J, Franke G, Birkenfeld AL, Luft FC, Jordan J. Water drinking induces thermogenesis through osmosensitive mechanisms. *J Clin Endocrinol Metab*. 2007;92(8):3334-7.
4460. May M, Jordan J. The osmopressor response to water drinking. *Am J Physiol Regul Integr Comp Physiol*. 2011;300(1):R40-6.
4461. Tank J, Schroeder C, Stoffels M, et al. Pressor effect of water drinking in tetraplegic patients may be a spinal reflex. *Hypertension*. 2003;41(6):1234-9.
4462. May M, Gueler F, Barg-Hock H, et al. Liver afferents contribute to water drinking-induced sympathetic activation in human subjects: a clinical trial. *PLoS ONE*. 2011;6(10):e25898.
4463. Durie B. Senses special: doors of perception. *New Sci*. 2005;2484.
4464. Dubnov-Raz G, Constantini NW, Yariv H, Nice S, Shapira N. Influence of water drinking on resting energy expenditure in overweight children. *Int J Obes (Lond)*. 2011;35(10):1295-300.
4465. Madjd A, Taylor MA, Delavari A, Malekzadeh R, MacDonald IA, Farshchi HR. Beneficial effects of replacing diet beverages with water on type 2 diabetic obese women following a hypo-energetic diet: a randomized, 24-week clinical trial. *Diabetes Obes Metab*. 2017;19(1):125-32.
4466. Madjd A, Taylor MA, Delavari A, Malekzadeh R, MacDonald IA, Farshchi HR. Effects on weight loss in adults of replacing diet beverages with water during a hypoenergetic diet: a randomized, 24-wk clinical trial. *Am J Clin Nutr*. 2015;102(6):1305-12.
4467. Maughan RJ, Watson P, Cordery PA, et al. A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index. *Am J Clin Nutr*. 2016;103(3):717-23.
4468. Wong KV. Temperature of food and drink intake matters. *J Energy Resour Technol*. 2016;138(5):054701.
4469. Bradley TH, Melby CL. Discussion: "Temperature of Food and Drink Intake Matters" (Wong KV, 2016, ASME J. Energy Resour. Technol., 138(5), p. 054701). *J Energy Resour Technol*. 2017;139(1):015501-1-2.
4470. Weiner BC, Weiner AC. The ice diet. *Ann Intern Med*. 2010;153(4):279.
4471. Kocetak P, Zak-Gołąb A, Rzemieniuk A, et al. The influence of oral water load on energy expenditure and sympatho-vagal balance in obese and normal weight women. *Arch Med Sci*. 2012;8(6):1003-8.
4472. Girona N, Grasser EK, Dulloo AG, Montani JP. Cardiovascular and metabolic responses to tap water ingestion in young humans: does the water temperature matter? *Acta Physiol (Oxf)*. 2014;211(2):358-70.
4473. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med*. 2007;120(11 Suppl 1):S1-21.
4474. Boschmann M, Steiniger J, Hille U, et al. Water-induced thermogenesis. *J Clin Endocrinol Metab*. 2003;88(12):6015-9.
4475. Collins S, Bordicchia M. Heart hormones fueling a fire in fat. *Adipocyte*. 2013;2(2):104-8.
4476. Sengenès C, Berlan M, De Glisezinski I, Lafontan M, Galitzky J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *FASEB J*. 2000;14(10):1345-51.

4477. Engeli S, Birkenfeld AL, Badin PM, et al. Natriuretic peptides enhance the oxidative capacity of human skeletal muscle. *J Clin Invest*. 2012;122(12):4675-9.
4478. Birkenfeld AL, Budziarek P, Boschmann M, et al. Atrial natriuretic peptide induces postprandial lipid oxidation in humans. *Diabetes*. 2008;57(12):3199-204.
4479. Engeli S, Birkenfeld AL, Badin PM, et al. Natriuretic peptides enhance the oxidative capacity of human skeletal muscle. *J Clin Invest*. 2012;122(12):4675-9.
4480. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109(5):594-600.
4481. Moro C, Crampes F, Sengenès C, et al. Atrial natriuretic peptide contributes to physiological control of lipid mobilization in humans. *FASEB J*. 2004;18(7):908-10.
4482. Verboven K, Hansen D, Jocken JWE, Blaak EE. Natriuretic peptides in the control of lipid metabolism and insulin sensitivity. *Obes Rev*. 2017;18(11):1243-59.
4483. Thornton SN. Increased hydration can be associated with weight loss. *Front Nutr*. 2016;3:18.
4484. Nishiuchi T, Saito H, Yamasaki Y, Saito S. Radioimmunoassay for atrial natriuretic peptide: method and results in normal subjects and patients with various diseases. *Clin Chim Acta*. 1986;159(1):45-57.
4485. Kimura T, Abe K, Ota K, et al. Effects of acute water load, hypertonic saline infusion, and furosemide administration on atrial natriuretic peptide and vasopressin release in humans. *J Clin Endocrinol Metab*. 1986;62(5):1003-10.
4486. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, D.C.: National Academies Press; 2006.
4487. Moro C, Pillard F, De Glisezinski I, et al. Atrial natriuretic peptide contribution to lipid mobilization and utilization during head-down bed rest in humans. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(2):R612-7.
4488. Lathers CM, Diamandis PH, Riddle JM, et al. Acute and intermediate cardiovascular responses to zero gravity and to fractional gravity levels induced by head-down or head-up tilt. *J Clin Pharmacol*. 1990;30(6):494-523.
4489. van Oosterhout WP, Terwindt GM, Vein AA, Ferrari MD. Space headache on Earth: head-down-tilted bed rest studies simulating outer-space microgravity. *Cephalalgia*. 2015;35(4):335-43.
4490. Liu Q, Zhou R, Chen S, Tan C. Effects of head-down bed rest on the executive functions and emotional response. *PLoS ONE*. 2012;7(12):e52160.
4491. Montmerle S, Spaak J, Linnarsson D. Lung function during and after prolonged head-down bed rest. *J Appl Physiol*. 2002;92(1):75-83.
4492. Liu Q, Zhou R, Chen S, Tan C. Effects of head-down bed rest on the executive functions and emotional response. *PLoS ONE*. 2012;7(12):e52160.
4493. Montmerle S, Spaak J, Linnarsson D. Lung function during and after prolonged head-down bed rest. *J Appl Physiol*. 2002;92(1):75-83.
4494. Kelsen J, Bartels LE, Dige A, et al. 21 days head-down bed rest induces weakening of cell-mediated immunity—some spaceflight findings confirmed in a ground-based analog. *Cytokine*. 2012;59(2):403-9.
4495. Ritz P, Acheson KJ, Gachon P, et al. Energy and substrate metabolism during a 42-day bed-rest in a head-down tilt position in humans. *Eur J Appl Physiol Occup Physiol*. 1998;78(4):308-14.
4496. Johnson PC, Leach CS, Rambaut PC. Estimates of fluid and energy balances of Apollo 17. *Aerosp Med*. 1973;44(11):1227-30.
4497. Krebs JM, Schneider VS, Evans H, et al. Energy absorption, lean body mass, and total body fat changes during 5 weeks of continuous bed rest. *Aviat Space Environ Med*. 1990;61(4):314-8.
4498. Martin JT. The Trendelenburg position: a review of current slants about head down tilt. *AANA J*. 1995;63(1):29-36.
4499. Halm MA. Trendelenburg position: “put to bed” or angled toward use in your unit? *Am J Crit Care*. 2012;21(6):449-52.
4500. Taketani Y, Mayama C, Suzuki N, et al. Transient but significant visual field defects after robot-assisted laparoscopic radical prostatectomy in deep Trendelenburg position. *PLoS ONE*. 2015;10(4):e0123361.
4501. Sanborn GE, Friberg TR, Allen R. Optic nerve dysfunction during gravity inversion. Visual field abnormalities. *Arch Ophthalmol*. 1987;105(6):774-6.
4502. Cramer H, Krucoff C, Dobos G. Adverse events associated with yoga: a systematic review of published case reports and case series. *PLoS ONE*. 2013;8(10):e75515.
4503. Linder BJ, Trick GL, Wolf ML. Altering body position affects intraocular pressure and visual function. *Invest Ophthalmol Vis Sci*. 1988;29(10):1492-7.
4504. Marshall-Goebel K, Mulder E, Bershady E, et al. Intracranial and intraocular pressure during various degrees of head-down tilt. *Aerosp Med Hum Perform*. 2017;88(1):10-6.
4505. Kergoat H, Lovasik JV. Seven-degree head-down tilt reduces choroidal pulsatile ocular blood flow. *Aviat Space Environ Med*. 2005;76(10):930-4.
4506. Linder BJ, Trick GL, Wolf ML. Altering body position affects intraocular pressure and visual function. *Invest Ophthalmol Vis Sci*. 1988;29(10):1492-7.
4507. Marshall-Goebel K, Mulder E, Bershady E, et al. Intracranial and intraocular pressure during various degrees of head-down tilt. *Aerosp Med Hum Perform*. 2017;88(1):10-6.
4508. Marshall-Goebel K, Ambarki K, Eklund A, et al. Effects of short-term exposure to head-down tilt on cerebral hemodynamics: a prospective evaluation of a spaceflight analog using phase-contrast MRI. *J Appl Physiol*. 2016;120(12):1466-73.
4509. Federenko YF, Charapakhin KP, Yaroshenko YN, Denogratov SK. Bone density benefits with periodic fluid redistribution during diminished muscular activity in humans. *Indian J Physiol Pharmacol*. 2015;59(1):100-8.
4510. Kakuris KK, Yaroshenko YN, Charapakhin KP, Neofitov NH. Chronic head-down-tilt sleeping as physiological regulator of bone remodelling during diminished muscular activity in humans. *Clin Physiol Funct Imaging*. 2017;37(4):428-36.
4511. Kakuris KK, Yaroshenko YN, Charapakhin KP, Neofitov NH. Chronic head-down-tilt sleeping as physiological regulator of bone remodelling during diminished muscular activity in humans. *Clin Physiol Funct Imaging*. 2017;37(4):428-36.
4512. Kirsch KA, Baartz FJ, Gunga HC, Röcker L. Fluid shifts into and out of superficial tissues under microgravity and terrestrial conditions. *Clin Invest*. 1993;71(9):687-9.

4513. Butler GC, Xing HC, Northey DR, Hughson RL. Reduced orthostatic tolerance following 4 h head-down tilt. *Eur J Appl Physiol Occup Physiol*. 1991;62(1):26-30.
4514. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. *Cleve Clin J Med*. 2010;77(5):298-306.
4515. Mailliet A, Pavy-Le Traon A, Allevard AM, et al. Hormone changes induced by 37.5-h head-down tilt (-6 degrees) in humans. *Eur J Appl Physiol Occup Physiol*. 1994;68(6):497-503.
4516. Davy BM, Dennis EA, Dengo AL, Wilson KL, Davy KP. Water consumption reduces energy intake at a breakfast meal in obese older adults. *J Am Diet Assoc*. 2008;108(7):1236-9.
4517. Van Walleghen EL, Orr JS, Gentile CL, Davy BM. Pre-meal water consumption reduces meal energy intake in older but not younger subjects. *Obesity (Silver Spring)*. 2007;15(1):93-9.
4518. Clarkston WK, Pantano MM, Morley JE, Horowitz M, Littlefield JM, Burton FR. Evidence for the anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs. young adults. *Am J Physiol*. 1997;272(1 Pt 2):R243-8.
4519. Vist GE, Maughan RJ. Gastric emptying of ingested solutions in man: effect of beverage glucose concentration. *Med Sci Sports Exerc*. 1994;26(10):1269-73.
4520. Corney RA, Sunderland C, James LJ. Immediate pre-meal water ingestion decreases voluntary food intake in lean young males. *Eur J Nutr*. 2016;55(2):815-9.
4521. Dennis EA, Dengo AL, Comber DL, et al. Water consumption increases weight loss during a hypocaloric diet intervention in middle-aged and older adults. *Obesity (Silver Spring)*. 2010;18(2):300-7.
4522. Dennis EA, Dengo AL, Comber DL, et al. Water consumption increases weight loss during a hypocaloric diet intervention in middle-aged and older adults. *Obesity (Silver Spring)*. 2010;18(2):300-7.
4523. Wakisaka S, Nagai H, Mura E, Matsumoto T, Moritani T, Nagai N. The effects of carbonated water upon gastric and cardiac activities and fullness in healthy young women. *J Nutr Sci Vitaminol*. 2012;58(5):333-8.
4524. Moorhead SA, Livingstone MB, Dunne A, Welch RW. The level of carbonation of a sugar-sweetened beverage preload affects satiety and short-term energy and food intakes. *Br J Nutr*. 2008;99(6):1362-9.
4525. Cuomo R, Savarese MF, Sarnelli G, et al. The role of a pre-load beverage on gastric volume and food intake: comparison between non-caloric carbonated and non-carbonated beverage. *Nutr J*. 2011;10:114.
4526. Suzuki M, Mura E, Taniguchi A, Moritani T, Nagai N. Oral carbonation attenuates feeling of hunger and gastric myoelectrical activity in young women. *J Nutr Sci Vitaminol*. 2017;63(3):186-92.
4527. Takagi A, Taniguchi A, Komai N, et al. Evaluation of postprandial core or peripheral temperatures after oral stimulation with carbonated water using a modified sham-feeding test. *Nihon Eiyo Shokuryo Gakkai Shi*. 2014;67(1):19-25.
4528. Chapelot D, Payen F. Comparison of the effects of a liquid yogurt and chocolate bars on satiety: a multidimensional approach. *Br J Nutr*. 2010;103(5):760-7.
4529. Harper A, James A, Flint A, Astrup A. Increased satiety after intake of a chocolate milk drink compared with a carbonated beverage, but no difference in subsequent ad libitum lunch intake. *Br J Nutr*. 2007;97(3):579-83.
4530. Orvani S, Haghighatdoost F, Surkan PJ, Azadbakht L. Dairy products, satiety and food intake: a meta-analysis of clinical trials. *Clin Nutr*. 2017;36(2):389-98.
4531. Westerterp-Plantenga MS, Verwegen CR. The appetizing effect of an apéritif in overweight and normal-weight humans. *Am J Clin Nutr*. 1999;69(2):205-12.
4532. Caton SJ, Ball M, Ahern A, Hetherington MM. Dose-dependent effects of alcohol on appetite and food intake. *Physiol Behav*. 2004;81(1):51-8.
4533. Christiansen P, Rose A, Randall-Smith L, Hardman CA. Alcohol's acute effect on food intake is mediated by inhibitory control impairments. *Health Psychol*. 2016;35(5):518-22.
4534. Poppitt SD, Eckhardt JW, McGonagle J, Murgatroyd PR, Prentice AM. Short-term effects of alcohol consumption on appetite and energy intake. *Physiol Behav*. 1996;60(4):1063-70.
4535. Williamson DA, Geiselman PJ, Lovejoy J, et al. Effects of consuming mycoprotein, tofu or chicken upon subsequent eating behaviour, hunger and safety. *Appetite*. 2006;46(1):41-8.
4536. Jane M, McKay J, Pal S. Effects of daily consumption of psyllium, oat bran and polyGlycopleX on obesity-related disease risk factors: a critical review. *Nutrition*. 2018;57:84-91.
4537. Thompson SV, Hannon BA, An R, Holscher HD. Effects of isolated soluble fiber supplementation on body weight, glycemia, and insulinemia in adults with overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2017;106(6):1514-28.
4538. Hylander B, Rössner S. Effects of dietary fiber intake before meals on weight loss and hunger in a weight-reducing club. *Acta Med Scand*. 1983;213(3):217-20.
4539. Georg Jensen M, Kristensen M, Astrup A. Can alginate-based preloads increase weight loss beyond calorie restriction? A pilot study in obese individuals. *Appetite*. 2011;57(3):601-4.
4540. Lambert JE, Parnell JA, Tunnicliffe JM, Han J, Sturzenegger T, Reimer RA. Consuming yellow pea fiber reduces voluntary energy intake and body fat in overweight/obese adults in a 12-week randomized controlled trial. *Clin Nutr*. 2017;36(1):126-33.
4541. Au-Yeung F, Jovanovski E, Jenkins AL, Zurbau A, Ho HVT, Vuksan V. The effects of gelled konjac glucomannan fibre on appetite and energy intake in healthy individuals: a randomised cross-over trial. *Br J Nutr*. 2018;119(1):109-16.
4542. Jackman C, Waddell R, Fisher L, et al. Konjac flour noodles associated with gastric outlet obstruction. *Emerg Med Australas*. 2018;30(2):283-4.
4543. Seidel JS, Gausche-Hill M. Lychee-flavored gel candies: a potentially lethal snack for infants and children. *Arch Pediatr Adolesc Med*. 2002;156(11):1120-2.
4544. Walker MJ, Colwell P, Craston D, Axford IP, Crane J. Analytical strategy for the evaluation of a specific food choking risk, a case study on jelly mini-cups. *Food Anal Methods*. 2011;5(1):54-61.
4545. Lyon MR, Reichert RG. The effect of a novel viscous polysaccharide along with lifestyle changes on short-term weight loss and associated risk factors in overweight and obese adults: an observational retrospective clinical program analysis. *Altern Med Rev*. 2010;15(1):68-75.
4546. Onakpoya IJ, Heneghan CJ. Effect of the novel functional fibre, polyglycoplex (PGX), on body weight and metabolic parameters: a systematic review of randomized clinical trials. *Clin Nutr*. 2015;34(6):1109-14.

4547. Pal S, Ho S, Gahler RJ, Wood S. Effect on body weight and composition in overweight/obese Australian adults over 12 months consumption of two different types of fibre supplementation in a randomized trial. *Nutr Metab (Lond)*. 2016;13:82.
4548. Pal S, Khossousi A, Binns C, Dhaliwal S, Ellis V. The effect of a fibre supplement compared to a healthy diet on body composition, lipids, glucose, insulin and other metabolic syndrome risk factors in overweight and obese individuals. *Br J Nutr*. 2011;105(1):90-100.
4549. Cicero A, Derosa G, Bove M, Imola F, Borghi C, Gaddi A. Psyllium improves dyslipidaemia, hyperglycaemia and hypertension, while guar gum reduces body weight more rapidly in patients affected by metabolic syndrome following an AHA Step 2 diet. *Med J Nutrition Metab*. 2009;3(1):47-54.
4550. McRorie JW. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 2: what to look for and how to recommend an effective fiber therapy. *Nutr Today*. 2015;50(2):90-7.
4551. Dubnov-Raz G, Constantini NW, Yariv H, Nice S, Shapira N. Influence of water drinking on resting energy expenditure in overweight children. *Int J Obes (Lond)*. 2011;35(10):1295-300.
4552. Clegg M, Cooper C. Exploring the myth: does eating celery result in a negative energy balance? *Proc Nutr Soc*. 2012;71(OCE3):E217.
4553. Rolls BJ, Roe LS, Meengs JS. Salad and satiety: energy density and portion size of a first-course salad affect energy intake at lunch. *J Am Diet Assoc*. 2004;104(10):1570-6.
4554. Rolls BJ, Roe LS, Meengs JS. Salad and satiety: energy density and portion size of a first-course salad affect energy intake at lunch. *J Am Diet Assoc*. 2004;104(10):1570-6.
4555. Buckland NJ, Finlayson G, Hetherington MM. Slimming starters. Intake of a diet-congruent food reduces meal intake in active dieters. *Appetite*. 2013;71:430-7.
4556. Rolls BJ, Roe LS. Effect of the volume of liquid food infused intragastrically on satiety in women. *Physiol Behav*. 2002;76(4-5):623-31.
4557. Rolls BJ, Castellanos VH, Halford JC, et al. Volume of food consumed affects satiety in men. *Am J Clin Nutr*. 1998;67(6):1170-7.
4558. Azadbakht L, Haghghatdoost F, Karimi G, Esmailzadeh A. Effect of consuming salad and yogurt as preload on body weight management and cardiovascular risk factors: a randomized clinical trial. *Int J Food Sci Nutr*. 2013;64(4):392-9.
4559. Gutzwiller JP, Drewe J, Ketterer S, Hildebrand P, Krautheim A, Beglinger C. Interaction between CCK and a preload on reduction of food intake is mediated by CCK-A receptors in humans. *Am J Physiol Regul Integr Comp Physiol*. 2000;279(1):R189-95.
4560. Roe LS, Meengs JS, Rolls BJ. Salad and satiety. The effect of timing of salad consumption on meal energy intake. *Appetite*. 2012;58(1):242-8.
4561. Boffa MJ, Gilmour E, Ead RD. Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol*. 1996;135(2):334.
4562. Birmingham D. Phototoxic bullae among celery harvesters. *Arch Dermatol*. 1961;83(1):73-87.
4563. Seligman PJ, Mathias CG, O'Malley MA, et al. Phytophotodermatitis from celery among grocery store workers. *Arch Dermatol*. 1987;123(11):1478-82.
4564. Dobson J, Ondhia C, Skellett AM, Coelho R. Image gallery: phototoxic rash from celery diet. *Br J Dermatol*. 2016;175(5):e133.
4565. Ljunggren B. Severe phototoxic burn following celery ingestion. *Arch Dermatol*. 1990;126(10):1334-6.
4566. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-22.
4567. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-22.
4568. Lubransky A, Monro J, Mishra S, Yu H, Haszard JJ, Venn BJ. Postprandial glycaemic, hormonal and satiety responses to rice and kiwifruit preloads in Chinese adults: a randomised controlled crossover trial. *Nutrients*. 2018;10(8):1110.
4569. Rolls BJ, Fedoroff IC, Guthrie JF, Laster LJ. Foods with different satiating effects in humans. *Appetite*. 1990;15(2):115-26.
4570. Rogers PJ, Shahrokni R. A comparison of the satiety effects of a fruit smoothie, its fresh fruit equivalent and other drinks. *Nutrients*. 2018;10(4):431.
4571. de Oliveira MC, Sichieri R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite*. 2008;51(2):291-5.
4572. Silver HJ, Dietrich MS, Niswender KD. Effects of grapefruit, grapefruit juice and water preloads on energy balance, weight loss, body composition, and cardiometabolic risk in free-living obese adults. *Nutr Metab (Lond)*. 2011;8(1):8.
4573. Cunningham E, Marcason W. Is it possible to burn calories by eating grapefruit or vinegar? *J Am Diet Assoc*. 2001;101(10):1198.
4574. Silver HJ, Dietrich MS, Niswender KD. Effects of grapefruit, grapefruit juice and water preloads on energy balance, weight loss, body composition, and cardiometabolic risk in free-living obese adults. *Nutr Metab (Lond)*. 2011;8(1):8.
4575. Bertrais S, Galan P, Renault N, Zarebska M, Preziosi P, Hercberg S. Consumption of soup and nutritional intake in French adults: consequences for nutritional status. *J Hum Nutr Diet*. 2001;14(2):121-8.
4576. Kuroda M, Ohta M, Okufuji T, et al. Frequency of soup intake is inversely associated with body mass index, waist circumference, and waist-to-hip ratio, but not with other metabolic risk factors in Japanese men. *J Am Diet Assoc*. 2011;111(1):137-42.
4577. Zhu Y, Hollis JH. Soup consumption is associated with a lower dietary energy density and a better diet quality in US adults. *Br J Nutr*. 2014;111(8):1474-80.
4578. Zhu Y, Hollis JH. Soup consumption is associated with a reduced risk of overweight and obesity but not metabolic syndrome in US adults: NHANES 2003-2006. *PLoS ONE*. 2013;8(9):e75630.
4579. Zhu Y, Hollis JH. Soup consumption is associated with a lower dietary energy density and a better diet quality in US adults. *Br J Nutr*. 2014;111(8):1474-80.
4580. Rolls BJ, Roe LS, Beach AM, Kris-Etherton PM. Provision of foods differing in energy density affects long-term weight loss. *Obes Res*. 2005;13(6):1052-60.

4581. Spiegel TA, Kaplan JM, Alavi A, Kim PS, Tse KK. Effects of soup preloads on gastric emptying and fullness ratings following an egg sandwich meal. *Physiol Behav.* 1994;56(3):571-5.
4582. Flood JE, Rolls BJ. Soup preloads in a variety of forms reduce meal energy intake. *Appetite.* 2007;49(3):626-34.
4583. Himaya A, Louis-Sylvestre J. The effect of soup on satiation. *Appetite.* 1998;30(2):199-210.
4584. Spill MK, Birch LL, Roe LS, Rolls BJ. Serving large portions of vegetable soup at the start of a meal affected children's energy and vegetable intake. *Appetite.* 2011;57(1):213-9.
4585. Rolls BJ, Bell EA, Thorwart ML. Water incorporated into a food but not served with a food decreases energy intake in lean women. *Am J Clin Nutr.* 1999;70(4):448-55.
4586. Rolls BJ, Fedoroff IC, Guthrie JF, Laster LJ. Foods with different satiating effects in humans. *Appetite.* 1990;15(2):115-26.
4587. Clegg ME, Ranawana V, Shafat A, Henry CJ. Soups increase satiety through delayed gastric emptying yet increased glycaemic response. *Eur J Clin Nutr.* 2013;67(1):8-11.
4588. Lucassen EA, Rother KI, Cizza G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. *Ann NY Acad Sci.* 2012;1264:110-34.
4589. Sleeplessness. *BMJ.* 1894;2(1761):719.
4590. Matricciani L, Olds T, Petkov J. In search of lost sleep: secular trends in the sleep time of school-aged children and adolescents. *Sleep Med Rev.* 2012;16(3):203-11.
4591. Youngstedt SD, Goff EE, Reynolds AM, et al. Has adult sleep duration declined over the last 50+ years? *Sleep Med Rev.* 2016;28:69-85.
4592. Youngstedt SD, Goff EE, Reynolds AM, et al. Has adult sleep duration declined over the last 50+ years? *Sleep Med Rev.* 2016;28:69-85.
4593. Marshall NS, Lallukka T. Sleep pirates—are we really living through a sleep deprivation epidemic and what's stealing our sleep? *Eur J Public Health.* 2018;28(3):394-5.
4594. Marshall NS. The sleep loss epidemic: hunting ninjas in the dark. *J Sleep Res.* 2015;24(1):1-2.
4595. Ogilvie RP, Patel SR. The epidemiology of sleep and obesity. *Sleep Health.* 2017;3(5):383-8.
4596. Everson CA, Bergmann BM, Rechtschaffen A. Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep.* 1989;12(1):13-21.
4597. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;342(6156):373-7.
4598. Absinta M, Ha SK, Nair G, et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *Elife.* 2017;6:e29738.
4599. Wu L, Sun D, Tan Y. A systematic review and dose-response meta-analysis of sleep duration and the occurrence of cognitive disorders. *Sleep Breath.* 2018;22(3):805-14.
4600. Shokri-Kojori E, Wang G, Wiers C, et al. β -Amyloid accumulation in the human brain after one night of sleep deprivation. *PNAS.* 2018;115(17):4483-8.
4601. Wu L, Sun D, Tan Y. A systematic review and dose-response meta-analysis of sleep duration and the occurrence of cognitive disorders. *Sleep Breath.* 2018;22(3):805-14.
4602. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. *Sleep Med Rev.* 2016;30:11-24.
4603. Yin J, Jin X, Shan Z, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Am Heart Assoc.* 2017;6(9):e005947.
4604. Yetish G, Kaplan H, Gurven M, et al. Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol.* 2015;25(21):2862-8.
4605. García-Perdomo HA, Zapata-Copete J, Rojas-Cerón CA. Sleep duration and risk of all-cause mortality: a systematic review and meta-analysis. *Epidemiol Psychiatr Sci.* 2018;Jul 30:1-11.
4606. Knutson KL, Turek FW. The U-shaped association between sleep and health: the 2 peaks do not mean the same thing. *Sleep.* 2006;29(7):878-9.
4607. Li L, Zhang S, Huang Y, Chen K. Sleep duration and obesity in children: a systematic review and meta-analysis of prospective cohort studies. *J Paediatr Child Health.* 2017;53(4):378-85.
4608. Wu Y, Zhai L, Zhang D. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med.* 2014;15(12):1456-62.
4609. Ogilvie RP, Patel SR. The epidemiology of sleep and obesity. *Sleep Health.* 2017;3(5):383-8.
4610. Kim AM, Keenan BT, Jackson N, et al. Tongue fat and its relationship to obstructive sleep apnea. *Sleep.* 2014;37(10):1639-48.
4611. Ng WL, Stevenson CE, Wong E, et al. Does intentional weight loss improve daytime sleepiness? A systematic review and meta-analysis. *Obes Rev.* 2017;18(4):460-75.
4612. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity (Silver Spring).* 2008;16(3):643-53.
4613. Knutson KL. Does inadequate sleep play a role in vulnerability to obesity? *Am J Hum Biol.* 2012;24(3):361-71.
4614. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. *Obesity (Silver Spring).* 2008;16(3):643-53.
4615. Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J Sleep Res.* 2008;17(3):331-4.
4616. Hogenkamp PS, Nilsson E, Nilsson VC, et al. Acute sleep deprivation increases portion size and affects food choice in young men. *Psychoneuroendocrinology.* 2013;38(9):1668-74.
4617. Calvin AD, Carter RE, Adachi T, et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest.* 2013;144(1):79-86.
4618. McNeil J, St-Onge MP. Increased energy intake following sleep restriction in men and women: a one-size-fits-all conclusion? *Obesity (Silver Spring).* 2017;25(6):989-92.
4619. St-Onge MP, Grandner MA, Brown D, et al. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. *Circulation.* 2016;134(18):e367-86.

4620. Heath G, Roach GD, Dorrian J, Ferguson SA, Darwent D, Sargent C. The effect of sleep restriction on snacking behaviour during a week of simulated shiftwork. *Accid Anal Prev.* 2012;45 Suppl:62-7.
4621. Lv W, Finlayson G, Dando R. Sleep, food cravings and taste. *Appetite.* 2018;125:210-6.
4622. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. *Nat Commun.* 2013;4:2259.
4623. St-Onge MP. Sleep-obesity relation: underlying mechanisms and consequences for treatment. *Obes Rev.* 2017;18 Suppl 1:34-9.
4624. Hanlon EC, Tasali E, Leproult R, et al. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. *Sleep.* 2016;39(3):653-64.
4625. St-Onge MP, Grandner MA, Brown D, et al. Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. *Circulation.* 2016;134(18):e367-86.
4626. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metab Clin Exp.* 2018;84:56-66.
4627. St-Onge MP. Sleep-obesity relation: underlying mechanisms and consequences for treatment. *Obes Rev.* 2017;18 Suppl 1:34-9.
4628. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metab Clin Exp.* 2018;84:56-66.
4629. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. *Ann Intern Med.* 2010;153(7):435-41.
4630. Cedernaes J, Schönke M, Westholm JO, et al. Acute sleep loss results in tissue-specific alterations in genome-wide DNA methylation state and metabolic fuel utilization in humans. *Sci Adv.* 2018;4(8):eaar8590.
4631. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. *Ann Intern Med.* 2010;153(7):435-41.
4632. Wang X, Sparks JR, Bowyer KP, Youngstedt SD. Influence of sleep restriction on weight loss outcomes associated with caloric restriction. *Sleep.* 2018;41(5):1-11.
4633. Hart CN, Carskadon MA, Considine RV, et al. Changes in children's sleep duration on food intake, weight, and leptin. *Pediatrics.* 2013;132(6):e1473-80.
4634. Chaput JP, Després JP, Bouchard C, Tremblay A. Longer sleep duration associates with lower adiposity gain in adult short sleepers. *Int J Obes (Lond).* 2012;36(5):752-6.
4635. Chaput JP, Tremblay A. Sleeping habits predict the magnitude of fat loss in adults exposed to moderate caloric restriction. *Obes Facts.* 2012;5(4):561-6.
4636. Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. *Appetite.* 2014;80:220-4.
4637. Al Khatib HK, Hall WL, Creedon A, et al. Sleep extension is a feasible lifestyle intervention in free-living adults who are habitually short sleepers: a potential strategy for decreasing intake of free sugars? A randomized controlled pilot study. *Am J Clin Nutr.* 2018;107(1):43-53.
4638. Logue EE, Bourguet CC, Palmieri PA, et al. The better weight-better sleep study: a pilot intervention in primary care. *Am J Health Behav.* 2012;36(3):319-34.
4639. Haines J, McDonald J, O'Brien A, et al. Healthy Habits, Happy Homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. *JAMA Pediatr.* 2013;167(11):1072-9.
4640. Anderson SE, Whitaker RC. Household routines and obesity in US preschool-aged children. *Pediatrics.* 2010;125(3):420-8.
4641. Haines J, McDonald J, O'Brien A, et al. Healthy Habits, Happy Homes: randomized trial to improve household routines for obesity prevention among preschool-aged children. *JAMA Pediatr.* 2013;167(11):1072-9.
4642. Capers PL, Fobian AD, Kaiser KA, Borah R, Allison DB. A systematic review and meta-analysis of randomized controlled trials of the impact of sleep duration on adiposity and components of energy balance. *Obes Rev.* 2015;16(9):771-82.
4643. Puhan MA, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendli O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. *BMJ.* 2006;332(7536):266-70.
4644. Patel SR. Reduced sleep as an obesity risk factor. *Obes Rev.* 2009;10 Suppl 2:61-8.
4645. Nielsen LS, Danielsen KV, Sørensen TI. Short sleep duration as a possible cause of obesity: critical analysis of the epidemiological evidence. *Obes Rev.* 2011;12(2):78-92.
4646. Marshall NS, Glozier N, Grunstein RR. Is sleep duration related to obesity? A critical review of the epidemiological evidence. *Sleep Med Rev.* 2008;12(4):289-98.
4647. Bioulac S, Franchi JM, Arnaud M, et al. Risk of motor vehicle accidents related to sleepiness at the wheel: a systematic review and meta-analysis. *Sleep.* 2017;40(10):1-31.
4648. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep.* 2003;26(2):117-26.
4649. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open.* 2012;2(1):1-10.
4650. Baber R. Climacteric commentaries. Better sleep but higher mortality risk. *Climacteric.* 2012;15(4):401.
4651. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open.* 2012;2(1):1-10.
4652. Rabin RC. New worries about sleeping pills. *New York Times: Well.* Published March 12, 2012. Available at: <https://well.blogs.nytimes.com/2012/03/12/new-worries-about-sleeping-pills>. Accessed April 17, 2019.
4653. Kripke DF. Mortality risk of hypnotics: strengths and limits of evidence. *Drug Saf.* 2016;39(2):93-107.
4654. Bianchi MT, Thomas RJ, Ellenbogen JM. Hypnotics and mortality risk. *J Clin Sleep Med.* 2012;8(4):351-2.
4655. Kripke DF, Langer RD, Kline LE. Do no harm: not even to some degree. *J Clin Sleep Med.* 2012;8(4):353-4.
4656. Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract.* 2012;13:40.

4657. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125-33.
4658. Bjorvatn B, Fiske E, Pallesen S. A self-help book is better than sleep hygiene advice for insomnia: a randomized controlled comparative study. *Scand J Psychol.* 2011;52(6):580-5.
4659. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23-36.
4660. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23-36.
4661. Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. *Sleep.* 1997;20(3):203-14.
4662. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23-36.
4663. Landolt HP, Werth E, Borbély AA, Dijk DJ. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res.* 1995;675(1-2):67-74.
4664. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23-36.
4665. Landolt HP, Roth C, Dijk DJ, Borbély AA. Late-afternoon ethanol intake affects nocturnal sleep and the sleep EEG in middle-aged men. *J Clin Psychopharmacol.* 1996;16(6):428-36.
4666. Jaehne A, Loessel B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev.* 2009;13(5):363-77.
4667. Hayley AC, Downey LA. Quitters never sleep: the effect of nicotine withdrawal upon sleep. *Curr Drug Abuse Rev.* 2015;8(2):73-4.
4668. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: a review of empirical evidence. *Sleep Med Rev.* 2015;22:23-36.
4669. Xie H, Kang J, Mills GH. Clinical review: the impact of noise on patients' sleep and the effectiveness of noise reduction strategies in intensive care units. *Crit Care.* 2009;13(2):208.
4670. Golem DL, Martin-Biggers JT, Koenings MM, Davis KF, Byrd-Bredbenner C. An integrative review of sleep for nutrition professionals. *Adv Nutr.* 2014;5(6):742-59.
4671. Black DS, O'Reilly GA, Olmstead R, Breen EC, Irwin MR. Mindfulness meditation and improvement in sleep quality and daytime impairment among older adults with sleep disturbances: a randomized clinical trial. *JAMA Intern Med.* 2015;175(4):494-501.
4672. Feng F, Zhang Y, Hou J, et al. Can music improve sleep quality in adults with primary insomnia? A systematic review and network meta-analysis. *Int J Nurs Stud.* 2018;77:189-96.
4673. Brown RF, Thorsteinsson EB, Smithson M, Birmingham CL, Aljarallah H, Nolan C. Can body temperature dysregulation explain the co-occurrence between overweight/obesity, sleep impairment, late-night eating, and a sedentary lifestyle? *Eat Weight Disord.* 2017;22(4):599-608.
4674. Brown RF, Thorsteinsson EB, Smithson M, Birmingham CL, Aljarallah H, Nolan C. Can body temperature dysregulation explain the co-occurrence between overweight/obesity, sleep impairment, late-night eating, and a sedentary lifestyle? *Eat Weight Disord.* 2017;22(4):599-608.
4675. Sung EJ, Tochiwara Y. Effects of bathing and hot footbath on sleep in winter. *J Physiol Anthropol Appl Human Sci.* 2000;19(1):21-7.
4676. St-Onge MP, Roberts A, Shechter A, Choudhury AR. Fiber and saturated fat are associated with sleep arousals and slow wave sleep. *J Clin Sleep Med.* 2016;12(1):19-24.
4677. Grandner MA, Kripke DF, Naidoo N, Langer RD. Relationships among dietary nutrients and subjective sleep, objective sleep, and napping in women. *Sleep Med.* 2010;11(2):180-4.
4678. McClernon FJ, Yancy WS, Eberstein JA, Atkins RC, Westman EC. The effects of a low-carbohydrate ketogenic diet and a low-fat diet on mood, hunger, and other self-reported symptoms. *Obesity (Silver Spring).* 2007;15(1):182-7.
4679. Majid MS, Ahmad HS, Bizhan H, Hosein HZM, Mohammad A. The effect of vitamin D supplement on the score and quality of sleep in 20-50 year-old people with sleep disorders compared with control group. *Nutr Neurosci.* 2018;21(7):511-9.
4680. Tomiyama AJ. Stress and obesity. *Annu Rev Psychol.* 2019;70:703-18.
4681. Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an "epidemic" of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. *Depress Anxiety.* 2014;31(6):506-16.
4682. Wardle J, Chida Y, Gibson EL, Whitaker KL, Steptoe A. Stress and adiposity: a meta-analysis of longitudinal studies. *Obesity (Silver Spring).* 2011;19(4):771-8.
4683. Scherrer JF, Salas J, Lustman PJ, et al. The role of obesity in the association between posttraumatic stress disorder and incident diabetes. *JAMA Psychiatry.* 2018;75(11):1189-98.
4684. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. *Sports Med.* 2014;44(1):81-121.
4685. Kiecolt-Glaser JK, Habash DL, Fagundes CP, et al. Daily stressors, past depression, and metabolic responses to high-fat meals: a novel path to obesity. *Biol Psychiatry.* 2015;77(7):653-60.
4686. Adam TC, Epel ES. Stress, eating and the reward system. *Physiol Behav.* 2007;91(4):449-58.
4687. Tomiyama A. Stress and obesity. *Annu Rev Psychol.* 2019;70:703-18.
4688. Tryon MS, DeCant R, Laugero KD. Having your cake and eating it too: a habit of comfort food may link chronic social stress exposure and acute stress-induced cortisol hyporesponsiveness. *Physiol Behav.* 2013;114-5:32-7.
4689. Zellner DA, Loaiza S, Gonzalez Z, et al. Food selection changes under stress. *Physiol Behav.* 2006;87(4):789-93.
4690. Al'Absi M, Nakajima M, Hooker S, Wittmers L, Cragin T. Exposure to acute stress is associated with attenuated sweet taste. *Psychophysiology.* 2012;49(1):96-103.
4691. Aguiar-Bloemer AC, Diez-Garcia RW. Influence of emotions evoked by life events on food choice. *Eat Weight Disord.* 2018;23(1):45-53.

4692. Tenk J, Mátrai P, Hegyi P, et al. Perceived stress correlates with visceral obesity and lipid parameters of the metabolic syndrome: a systematic review and meta-analysis. *Psychoneuroendocrinology*. 2018;95:63-73.
4693. van der Valk ES, Savas M, van Rossum EFC. Stress and obesity: are there more susceptible individuals? *Curr Obes Rep*. 2018;7(2):193-203.
4694. Tomiyama A. Stress and obesity. *Annu Rev Psychol*. 2019;70:703-18.
4695. van der Valk ES, Savas M, van Rossum EFC. Stress and obesity: are there more susceptible individuals? *Curr Obes Rep*. 2018;7(2):193-203.
4696. George SA, Khan S, Briggs H, Abelson JL. CRH-stimulated cortisol release and food intake in healthy, non-obese adults. *Psychoneuroendocrinology*. 2010;35(4):607-12.
4697. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep*. 1985;69(7-8):751-4.
4698. Berthon BS, MacDonald-Wicks LK, Wood LG. A systematic review of the effect of oral glucocorticoids on energy intake, appetite, and body weight in humans. *Nutr Res*. 2014;34(3):179-90.
4699. Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E. Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol*. 1996;271(2 Pt 1):E317-25.
4700. Tryon MS, DeCant R, Laugero KD. Having your cake and eating it too: a habit of comfort food may link chronic social stress exposure and acute stress-induced cortisol hyporesponsiveness. *Physiol Behav*. 2013;114-5:32-7.
4701. Rebuffé-Scrive M, Lundholm K, Björntorp P. Glucocorticoid hormone binding to human adipose tissue. *Eur J Clin Invest*. 1985;15(5):267-71.
4702. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev*. 2001;2(2):73-86.
4703. Tomiyama A. Stress and obesity. *Annu Rev Psychol*. 2019;70:703-18.
4704. Drapeau V, Therrien F, Richard D, Tremblay A. Is visceral obesity a physiological adaptation to stress? *Panminerva Med*. 2003;45(3):189-95.
4705. Wester VL, Staufienbiel SM, Veldhorst MA, et al. Long-term cortisol levels measured in scalp hair of obese patients. *Obesity (Silver Spring)*. 2014;22(9):1956-8.
4706. van Rossum EF. Obesity and cortisol: new perspectives on an old theme. *Obesity (Silver Spring)*. 2017;25(3):500-1.
4707. Stalder T, Steudte-Schmiedgen S, Alexander N, et al. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. *Psychoneuroendocrinology*. 2017;77:261-74.
4708. Noppe G, van den Akker EL, de Rijke YB, Koper JW, Jaddoe VW, van Rossum EF. Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution. *Int J Obes (Lond)*. 2016;40(10):1503-9.
4709. Bergendahl M, Vance ML, Iranmanesh A, Thorner MO, Veldhuis JD. Fasting as a metabolic stress paradigm selectively amplifies cortisol secretory burst mass and delays the time of maximal nyctohemeral cortisol concentrations in healthy men. *J Clin Endocrinol Metab*. 1996;81(2):692-9.
4710. Nakamura Y, Walker BR, Ikuta T. Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. *Stress*. 2016;19(2):151-7.
4711. Tomiyama AJ. Weight stigma is stressful. A review of evidence for the Cyclic Obesity / Weight-Based Stigma model. *Appetite*. 2014;82:8-15.
4712. Jackson SE, Kirschbaum C, Steptoe A. Perceived weight discrimination and chronic biochemical stress: a population-based study using cortisol in scalp hair. *Obesity (Silver Spring)*. 2016;24(12):2515-21.
4713. Jackson SE, Steptoe A. Obesity, perceived weight discrimination, and hair cortisol: a population-based study. *Psychoneuroendocrinology*. 2018;98:67-73.
4714. Jackson SE, Kirschbaum C, Steptoe A. Perceived weight discrimination and chronic biochemical stress: a population-based study using cortisol in scalp hair. *Obesity (Silver Spring)*. 2016;24(12):2515-21.
4715. Himmelstein MS, Incollingo Belsky AC, Tomiyama AJ. The weight of stigma: cortisol reactivity to manipulated weight stigma. *Obesity (Silver Spring)*. 2015;23(2):368-74.
4716. Schvey NA, Puhl RM, Brownell KD. The stress of stigma: exploring the effect of weight stigma on cortisol reactivity. *Psychosom Med*. 2014;76(2):156-62.
4717. Schvey NA, Puhl RM, Brownell KD. The impact of weight stigma on caloric consumption. *Obesity (Silver Spring)*. 2011;19(10):1957-62.
4718. Salvy SJ, Bowker JC, Nitecki LA, Kluczynski MA, Germeroth LJ, Roemmich JN. Impact of simulated ostracism on overweight and normal-weight youths' motivation to eat and food intake. *Appetite*. 2011;56(1):39-45.
4719. Incollingo Rodriguez AC, Heldreth CM, Tomiyama AJ. Putting on weight stigma: a randomized study of the effects of wearing a fat suit on eating, well-being, and cortisol. *Obesity (Silver Spring)*. 2016;24(9):1892-8.
4720. Meadows A, Daniëlsdóttir S, Calogero R, O'Reilly C. Why fat suits do not advance the scientific study of weight stigma. *Obesity (Silver Spring)*. 2017;25(2):275.
4721. Leow S, Jackson B, Alderson JA, Guelfi KJ, Dimmock JA. A role for exercise in attenuating unhealthy food consumption in response to stress. *Nutrients*. 2018;10(2):176.
4722. Dedovic K, Renwick R, Mahani NK, Engert V, Lupien SJ, Pruessner JC. The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci*. 2005;30(5):319-25.
4723. Zschucke E, Renneberg B, Dimeo F, Wüstenberg T, Ströhle A. The stress-buffering effect of acute exercise: evidence for HPA axis negative feedback. *Psychoneuroendocrinology*. 2015;51:414-25.
4724. Neumeier WH, Goodner E, Biasini F, et al. Exercise following mental work prevented overeating. *Med Sci Sports Exerc*. 2016;48(9):1803-9.
4725. Buchowski MS, Majchrzak KM, Blomquist K, Chen KY, Byrne DW, Bachorowski JA. Energy expenditure of genuine laughter. *Int J Obes (Lond)*. 2007;31(1):131-7.
4726. Gervais M, Wilson DS. The evolution and functions of laughter and humor: a synthetic approach. *Q Rev Biol*. 2005;80(4):395-430.
4727. Berk LS, Tan SA, Fry WF, et al. Neuroendocrine and stress hormone changes during mirthful laughter. *Am J Med Sci*. 1989;298(6):390-6.

4728. Bennett MP, Lengacher C. Humor and laughter may influence health IV. Humor and immune function. *Evid Based Complement Alternat Med*. 2009;6(2):159-64.
4729. Bennett MP, Zeller JM, Rosenberg L, McCann J. The effect of mirthful laughter on stress and natural killer cell activity. *Altern Ther Health Med*. 2003;9(2):38-45.
4730. Fujisawa A, Ota A, Matsunaga M, et al. Effect of laughter yoga on salivary cortisol and dehydroepiandrosterone among healthy university students: a randomized controlled trial. *Complement Ther Clin Pract*. 2018;32:6-11.
4731. Tanaka A, Tokuda N, Ichihara K. Psychological and physiological effects of laughter yoga sessions in Japan: a pilot study. *Nurs Health Sci*. 2018;20(3):304-12.
4732. Fujisawa A, Ota A, Matsunaga M, et al. Effect of laughter yoga on salivary cortisol and dehydroepiandrosterone among healthy university students: a randomized controlled trial. *Complement Ther Clin Pract*. 2018;32:6-11.
4733. Tanaka A, Tokuda N, Ichihara K. Psychological and physiological effects of laughter yoga sessions in Japan: a pilot study. *Nurs Health Sci*. 2018;20(3):304-12.
4734. Cramer H, Ward L, Steel A, Lauche R, Dobos G, Zhang Y. Prevalence, patterns, and predictors of yoga use: results of a U.S. nationally representative survey. *Am J Prev Med*. 2016;50(2):230-5.
4735. Cramer H, Thoms MS, Anheyer D, Lauche R, Dobos G. Yoga in women with abdominal obesity: a randomized controlled trial. *Dtsch Arztebl Int*. 2016;113(39):645-52.
4736. Pascoe MC, Thompson DR, Ski CF. Yoga, mindfulness-based stress reduction and stress-related physiological measures: a meta-analysis. *Psychoneuroendocrinology*. 2017;86:152-68.
4737. Kristal AR, Littman AJ, Benitez D, White E. Yoga practice is associated with attenuated weight gain in healthy, middle-aged men and women. *Altern Ther Health Med*. 2005;11(4):28-33.
4738. Kristal AR, Littman AJ, Benitez D, White E. Yoga practice is associated with attenuated weight gain in healthy, middle-aged men and women. *Altern Ther Health Med*. 2005;11(4):28-33.
4739. Yadav R, Yadav RK, Khadgawat R, Pandey RM. Comparative efficacy of a 12 week yoga-based lifestyle intervention and dietary intervention on adipokines, inflammation, and oxidative stress in adults with metabolic syndrome: a randomized controlled trial. *Transl Behav Med*. 2018;Jul 17.
4740. Cramer H, Thoms MS, Anheyer D, Lauche R, Dobos G. Yoga in women with abdominal obesity: a randomized controlled trial. *Dtsch Arztebl Int*. 2016;113(39):645-52.
4741. Hagins M, Moore W, Rundle A. Does practicing hatha yoga satisfy recommendations for intensity of physical activity which improves and maintains health and cardiovascular fitness? *BMC Complement Altern Med*. 2007;7:40.
4742. Ruby M, Repka CP, Arciero PJ. Comparison of protein-pacing alone or with yoga/stretching and resistance training on glycemia, total and regional body composition, and aerobic fitness in overweight women. *J Phys Act Health*. 2016;13(7):754-64.
4743. Telles S, Sharma SK, Yadav A, Singh N, Balkrishna A. A comparative controlled trial comparing the effects of yoga and walking for overweight and obese adults. *Med Sci Monit*. 2014;20:894-904.
4744. Larson-Meyer DE. A systematic review of the energy cost and metabolic intensity of yoga. *Med Sci Sports Exerc*. 2016;48(8):1558-69.
4745. Larson-Meyer DE. A systematic review of the energy cost and metabolic intensity of yoga. *Med Sci Sports Exerc*. 2016;48(8):1558-69.
4746. Rshikesan PB, Subramanya P, Nidhi R. Yoga practice for reducing the male obesity and weight related psychological difficulties—a randomized controlled trial. *J Clin Diagn Res*. 2016;10(11):OC22-8.
4747. Juneau AL, Aita M, Héon M. Review and critical analysis of massage studies for term and preterm infants. *Neonatal Netw*. 2015;34(3):165-77.
4748. Holst S, Lund I, Petersson M, Uvnäs-Moberg K. Massage-like stroking influences plasma levels of gastrointestinal hormones, including insulin, and increases weight gain in male rats. *Auton Neurosci*. 2005;120(1-2):73-9.
4749. He J, Zhang X, Qu Y, et al. Effect of combined manual acupuncture and massage on body weight and body mass index reduction in obese and overweight women: a randomized, short-term clinical trial. *J Acupunct Meridian Stud*. 2015;8(2):61-5.
4750. Donoyama N, Suoh S, Ohkoshi N. Adiponectin increase in mildly obese women after massage treatment. *J Altern Complement Med*. 2018;24(7):741-2.
4751. Adler DS. Archaeology: the earliest musical tradition. *Nature*. 2009;460(7256):695-6.
4752. Kane E. Phonograph in operating-room. *J Am Med Assoc*. 1914;LXII(23):1829.
4753. Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. *Eur J Anaesthesiol*. 2001;18(12):789-97.
4754. Bringman H, Giesecke K, Thörne A, Bringman S. Relaxing music as pre-medication before surgery: a randomised controlled trial. *Acta Anaesthesiol Scand*. 2009;53(6):759-64.
4755. Mamalaki E, Zachari K, Karfopoulou E, Zervas E, Yannakoulia M. Presence of music while eating: effects on energy intake, eating rate and appetite sensations. *Physiol Behav*. 2017;168:31-3.
4756. Fancourt D, Ockelford A, Belai A. The psychoneuroimmunological effects of music: a systematic review and a new model. *Brain Behav Immun*. 2014;36:15-26.
4757. McCraty R, Barrios-Choplin B, Atkinson M, Tomasino D. The effects of different types of music on mood, tension, and mental clarity. *Altern Ther Health Med*. 1998;4(1):75-84.
4758. Gerra G, Zaimovic A, Franchini D, et al. Neuroendocrine responses of healthy volunteers to “techno-music”: relationships with personality traits and emotional state. *Int J Psychophysiol*. 1998;28(1):99-111.
4759. Bernardi L, Porta C, Sleight P. Cardiovascular, cerebrovascular, and respiratory changes induced by different types of music in musicians and non-musicians: the importance of silence. *Heart*. 2006;92(4):445-52.
4760. Bowman A, Dowell FJ, Evans NP. The effect of different genres of music on the stress levels of kennelled dogs. *Physiol Behav*. 2017;171:207-15.
4761. Kogan L, Schoenfeld-Tacher R, Simon A. Behavioral effects of auditory stimulation on kennelled dogs. *Journal of Veterinary Behavior*. 2012;7(5):268-75.
4762. Labbé E, Schmidt N, Babin J, Pharr M. Coping with stress: the effectiveness of different types of music. *Appl Psychophysiol Biofeedback*. 2007;32(3-4):163-8.

4763. Nater UM, Abbruzzese E, Krebs M, Ehlert U. Sex differences in emotional and psychophysiological responses to musical stimuli. *Int J Psychophysiol.* 2006;62(2):300-8.
4764. Chatterton RT, Vogelsoong KM, Lu YC, Hudgens GA. Hormonal responses to psychological stress in men preparing for skydiving. *J Clin Endocrinol Metab.* 1997;82(8):2503-9.
4765. Speirs RL, Herring J, Cooper WD, Hardy CC, Hind CR. The influence of sympathetic activity and isoprenaline on the secretion of amylase from the human parotid gland. *Arch Oral Biol.* 1974;19(9):747-52.
4766. Nater UM, Abbruzzese E, Krebs M, Ehlert U. Sex differences in emotional and psychophysiological responses to musical stimuli. *Int J Psychophysiol.* 2006;62(2):300-8.
4767. Schell LK, Monsef I, Wöckel A, Skoetz N. Mindfulness-based stress reduction for women diagnosed with breast cancer. *Cochrane Database Syst Rev.* 2019;3:CD011518.
4768. Mathieu J. What should you know about mindful and intuitive eating? *J Am Diet Assoc.* 2009;109(12):1982-7.
4769. Blass EM, Anderson DR, Kirkorian HL, Pempek TA, Price I, Koleini MF. On the road to obesity: television viewing increases intake of high-density foods. *Physiol Behav.* 2006;88(4-5):597-604.
4770. Gore SA, Foster JA, Dilillo VG, Kirk K, Smith West D. Television viewing and snacking. *Eat Behav.* 2003;4(4):399-405.
4771. Matheson DM, Killen JD, Wang Y, Varady A, Robinson TN. Children's food consumption during television viewing. *Am J Clin Nutr.* 2004;79(6):1088-94.
4772. Boon B, Stroebe W, Schut H, Ijntema R. Ironic processes in the eating behaviour of restrained eaters. *Br J Health Psychol.* 2002;7(Pt 1):1-10.
4773. Bellisle F, Dalix AM. Cognitive restraint can be offset by distraction, leading to increased meal intake in women. *Am J Clin Nutr.* 2001;74(2):197-200.
4774. Hetherington MM, Anderson AS, Norton GN, Newson L. Situational effects on meal intake: a comparison of eating alone and eating with others. *Physiol Behav.* 2006;88(4-5):498-505.
4775. Oldham-Cooper RE, Hardman CA, Nicoll CE, Rogers PJ, Brunstrom JM. Playing a computer game during lunch affects fullness, memory for lunch, and later snack intake. *Am J Clin Nutr.* 2011;93(2):308-13.
4776. Seguias L, Tapper K. The effect of mindful eating on subsequent intake of a high calorie snack. *Appetite.* 2018;121:93-100.
4777. Robinson E, Kersbergen I, Higgs S. Eating "attentively" reduces later energy consumption in overweight and obese females. *Br J Nutr.* 2014;112(4):657-61.
4778. Yeomans MR. Adverse effects of consuming high fat-sugar diets on cognition: implications for understanding obesity. *Proc Nutr Soc.* 2017;76(4):455-65.
4779. Whitelock V, Higgs S, Brunstrom JM, Halford JCG, Robinson E. No effect of focused attention whilst eating on later snack food intake: two laboratory experiments. *Appetite.* 2018;128:188-96.
4780. Van Dam NT, van Vugt MK, Vago DR, et al. Mind the hype: a critical evaluation and prescriptive agenda for research on mindfulness and meditation. *Perspect Psychol Sci.* 2018;13(1):36-61.
4781. Jenkins KT, Tapper K. Resisting chocolate temptation using a brief mindfulness strategy. *Br J Health Psychol.* 2014;19(3):509-22.
4782. Moffitt R, Brinkworth G, Noakes M, Mohr P. A comparison of cognitive restructuring and cognitive defusion as strategies for resisting a craved food. *Psychol Health.* 2012;27 Suppl 2:74-90.
4783. Jenkins KT, Tapper K. Resisting chocolate temptation using a brief mindfulness strategy. *Br J Health Psychol.* 2014;19(3):509-22.
4784. Moffitt R, Brinkworth G, Noakes M, Mohr P. A comparison of cognitive restructuring and cognitive defusion as strategies for resisting a craved food. *Psychol Health.* 2012;27 Suppl 2:74-90.
4785. Jenkins KT, Tapper K. Resisting chocolate temptation using a brief mindfulness strategy. *Br J Health Psychol.* 2014;19(3):509-22.
4786. Lindahl JR, Fisher NE, Cooper DJ, Rosen RK, Britton WB. The varieties of contemplative experience: a mixed-methods study of meditation-related challenges in Western Buddhists. *PLoS ONE.* 2017;12(5):e0176239.
4787. Wolever RQ, Schwartz ER, Schoenberg PLA. Mindfulness in corporate America: is the Trojan Horse ethical? *J Altern Complement Med.* 2018;24(5):403-6.
4788. Mantzios M, Wilson JC. Mindfulness, eating behaviours, and obesity: a review and reflection on current findings. *Curr Obes Rep.* 2015;4(1):141-6.
4789. Hyland T. McDonaldizing spirituality. *J Transform Educ.* 2017;15(4):334-56.
4790. Van Dam NT, van Vugt MK, Vago DR, et al. Mind the hype: a critical evaluation and prescriptive agenda for research on mindfulness and meditation. *Perspect Psychol Sci.* 2018;13(1):36-61.
4791. Van Dam NT, van Vugt MK, Vago DR, et al. Mind the hype: a critical evaluation and prescriptive agenda for research on mindfulness and meditation. *Perspect Psychol Sci.* 2018;13(1):36-61.
4792. Shapiro DH. Adverse effects of meditation: a preliminary investigation of long-term meditators. *Int J Psychosom.* 1992;39(1-4):62-7.
4793. Lindahl JR, Fisher NE, Cooper DJ, Rosen RK, Britton WB. The varieties of contemplative experience: a mixed-methods study of meditation-related challenges in Western Buddhists. *PLoS ONE.* 2017;12(5):e0176239.
4794. Van Dam NT, van Vugt MK, Vago DR, et al. Reiterated concerns and further challenges for mindfulness and meditation research: a reply to Davidson and Dahl. *Perspect Psychol Sci.* 2018;13(1):66-9.
4795. Crawford MJ, Thanu L, Farquharson L, et al. Patient experience of negative effects of psychological treatment: results of a national survey. *Br J Psychiatry.* 2016;208(3):260-5.
4796. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. *Natl Health Stat Report.* 2015;(79):1-16.
4797. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report.* 2008;(12):1-23.
4798. Farias M, Wikholm C. Has the science of mindfulness lost its mind? *BJPsych Bull.* 2016;40(6):329-32.
4799. Farias M, Wikholm C. Has the science of mindfulness lost its mind? *BJPsych Bull.* 2016;40(6):329-32.
4800. Farias M, Wikholm C. Has the science of mindfulness lost its mind? *BJPsych Bull.* 2016;40(6):329-32.
4801. Lilienfeld SO. Psychology's replication crisis and the grant culture: righting the ship. *Perspect Psychol Sci.* 2017;12(4):660-4.

4802. Camerer C, Dreber A, Holzmeister F, et al. Evaluating the replicability of social science experiments in *Nature and Science* between 2010 and 2015. *Nat Hum Behav*. 2018;2(9):637-44.
4803. Coronado-Montoya S, Levis AW, Kwakkenbos L, Steele RJ, Turner EH, Thombs BD. Reporting of positive results in randomized controlled trials of mindfulness-based mental health interventions. *PLoS ONE*. 2016;11(4):e0153220.
4804. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med*. 2014;174(3):357-68.
4805. Sharma M, Rush SE. Mindfulness-based stress reduction as a stress management intervention for healthy individuals: a systematic review. *J Evid Based Complementary Altern Med*. 2014;19(4):271-86.
4806. Jenkins KT, Tapper K. Resisting chocolate temptation using a brief mindfulness strategy. *Br J Health Psychol*. 2014;19(3):509-22.
4807. Ruffault A, Czernichow S, Hagger MS, et al. The effects of mindfulness training on weight-loss and health-related behaviours in adults with overweight and obesity: a systematic review and meta-analysis. *Obes Res Clin Pract*. 2017;11(5 Suppl 1):90-111.
4808. Katterman SN, Kleinman BM, Hood MM, Nackers LM, Corsica JA. Mindfulness meditation as an intervention for binge eating, emotional eating, and weight loss: a systematic review. *Eat Behav*. 2014;15(2):197-204.
4809. Katterman SN, Kleinman BM, Hood MM, Nackers LM, Corsica JA. Mindfulness meditation as an intervention for binge eating, emotional eating, and weight loss: a systematic review. *Eat Behav*. 2014;15(2):197-204.
4810. Tapper K, Shaw C, Ilsley J, Hill AJ, Bond FW, Moore L. Exploratory randomised controlled trial of a mindfulness-based weight loss intervention for women. *Appetite*. 2009;52(2):396-404.
4811. Daubenmier J, Kristeller J, Hecht FM, et al. Mindfulness intervention for stress eating to reduce cortisol and abdominal fat among overweight and obese women: an exploratory randomized controlled study. *J Obes*. 2011;2011:651936.
4812. Carrière K, Khoury B, Günak MM, Knäuper B. Mindfulness-based interventions for weight loss: a systematic review and meta-analysis. *Obes Rev*. 2018;19(2):164-77.
4813. Jakulj F, Zernicke K, Bacon SL, et al. A high-fat meal increases cardiovascular reactivity to psychological stress in healthy young adults. *J Nutr*. 2007;137(4):935-9.
4814. Agricultural Research Service, United States Department of Agriculture. Basic report: 01123, egg, whole, raw, fresh. National Nutrient Database for Standard Reference 1. Published April 2018. Available at: <https://ndb.nal.usda.gov/ndb/foods/show/01123>. Accessed April 17, 2019.
4815. Kalmijn S, van Boxtel MP, Ocké M, Verschuren WM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology*. 2004;62(2):275-80.
4816. The Epidemiology and Genomics Research Program. Top food sources of saturated fat among U.S. population, 2005-2006 NHANES. National Cancer Institute's Division of Cancer Control and Population Sciences, National Institutes of Health. Updated April 20, 2018. Available at: https://epi.grants.cancer.gov/diet/foodsources/sat_fat/sf.html. Accessed April 17, 2019.
4817. Beezhold B, Radnitz C, Rinne A, Dimatteo J. Vegans report less stress and anxiety than omnivores. *Nutr Neurosci*. 2015;18(7):289-96.
4818. Beezhold BL, Johnston CS, Daigle DR. Vegetarian diets are associated with healthy mood states: a cross-sectional study in Seventh Day Adventist adults. *Nutr J*. 2010;9:26.
4819. Food sources of arachidonic acid (PFA 20:4), listed in descending order by percentages of their contribution to intake, based on data from the National Health and Nutrition Examination Survey 2005-2006. National Institutes of Health. Updated April 20, 2018. Available at: https://epi.grants.cancer.gov/diet/foodsources/fatty_acids/table4.html. Accessed April 17, 2019.
4820. The Epidemiology and Genomics Research Program. Top food sources of saturated fat among U.S. population, 2005-2006 NHANES. National Cancer Institute's Division of Cancer Control and Population Sciences, National Institutes of Health. Updated April 20, 2018. Available at: https://epi.grants.cancer.gov/diet/foodsources/sat_fat/sf.html. Accessed April 17, 2019.
4821. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotrophic factor and behavior in mice. *Gastroenterology*. 2011;141(2):599-609.609.e1-3.
4822. Null G, Pennesi L. Diet and lifestyle intervention on chronic moderate to severe depression and anxiety and other chronic conditions. *Complement Ther Clin Pract*. 2017;29:189-93.
4823. Agarwal U, Mishra S, Xu J, Levin S, Gonzales J, Barnard ND. A multicenter randomized controlled trial of a nutrition intervention program in a multiethnic adult population in the corporate setting reduces depression and anxiety and improves quality of life: the GEICO study. *Am J Health Promot*. 2015;29(4):245-54.
4824. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with type 2 diabetes. *Diabet Med*. 2011;28(5):549-59.
4825. Kahleova H, Hrachovinova T, Hill M, Pelikanova T. Vegetarian diet in type 2 diabetes—improvement in quality of life, mood and eating behaviour. *Diabet Med*. 2013;30(1):127-9.
4826. Beezhold BL, Johnston CS. Restriction of meat, fish, and poultry in omnivores improves mood: a pilot randomized controlled trial. *Nutr J*. 2012;11:9.
4827. Slag MF, Ahmad M, Gannon MC, Nuttall FQ. Meal stimulation of cortisol secretion: a protein induced effect. *Metabolism*. 1981;30(11):1104-8.
4828. Gibson EL, Checkley S, Papadopoulos A, Poon L, Daley S, Wardle J. Increased salivary cortisol reliably induced by a protein-rich midday meal. *Psychosom Med*. 1999;61(2):214-24.
4829. Gibson EL, Checkley S, Papadopoulos A, Poon L, Daley S, Wardle J. Increased salivary cortisol reliably induced by a protein-rich midday meal. *Psychosom Med*. 1999;61(2):214-24.
4830. Vogelzangs N, Beekman AT, Milaneschi Y, Bandinelli S, Ferrucci L, Penninx BW. Urinary cortisol and six-year risk of all-cause and cardiovascular mortality. *J Clin Endocrinol Metab*. 2010;95(11):4959-64.
4831. Buckley T, McKinley S, Tofler G, Bartrop R. Cardiovascular risk in early bereavement: a literature review and proposed mechanisms. *Int J Nurs Stud*. 2010;47(2):229-38.
4832. T Buckley, D Sunari, A Marshall, R Bartrop, S McKinley, G Tofler. Physiological correlates of bereavement and the impact of bereavement interventions. *Dialogues Clin Neurosci*. 2012;14(2):129-39.

4833. Anderson KE, Rosner W, Khan MS, et al. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. *Life Sci.* 1987;40(18):1761-8.
4834. Anderson KE, Rosner W, Khan MS, et al. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. *Life Sci.* 1987;40(18):1761-8.
4835. Cook TM, Russell JM, Barker ME. Dietary advice for muscularity, leanness and weight control in *Men's Health* magazine: a content analysis. *BMC Public Health.* 2014;14:1062.
4836. Anderson KE, Rosner W, Khan MS, et al. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. *Life Sci.* 1987;40(18):1761-8.
4837. Hill P, Wynder EL, Garbaczewski L, Walker AR. Effect of diet on plasma and urinary hormones in South African black men with prostatic cancer. *Cancer Res.* 1982;42(9):3864-9.
4838. Khaw KT, Barrett-Connor E. Lower endogenous androgens predict central adiposity in men. *Ann Epidemiol.* 1992;2(5):675-82.
4839. Slag MF, Ahmad M, Gannon MC, Nuttall FQ. Meal stimulation of cortisol secretion: a protein induced effect. *Metabolism.* 1981;30(11):1104-8.
4840. Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. *J Clin Endocrinol Metab.* 2003;88(8):3554-60.
4841. Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York City. *Pediatrics.* 1980;65(4):683-97.
4842. Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. *J Clin Endocrinol Metab.* 2003;88(8):3554-60.
4843. Carter JP, Furman T, Hutcheson HR. Preeclampsia and reproductive performance in a community of vegans. *South Med J.* 1987;80(6):692-7.
4844. Duhig KE, Shennan AH. Recent advances in the diagnosis and management of pre-eclampsia. *F1000Prime Rep.* 2015;7:24.
4845. Carter JP, Furman T, Hutcheson HR. Preeclampsia and reproductive performance in a community of vegans. *South Med J.* 1987;80(6):692-7.
4846. Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. *J Clin Endocrinol Metab.* 2003;88(8):3554-60.
4847. Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. *J Clin Endocrinol Metab.* 2003;88(8):3554-60.
4848. Maslova E, Rytter D, Bech BH, et al. Maternal protein intake during pregnancy and offspring overweight 20 y later. *Am J Clin Nutr.* 2014;100(4):1139-48.
4849. Swartz J, Stenius F, Alm J, Theorell T, Lindblad F. Lifestyle and salivary cortisol at the age of 12 and 24 months. *Acta Paediatr.* 2012;101(9):979-84.
4850. Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. Maternal consumption of a high-meat, low-carbohydrate diet in late pregnancy: relation to adult cortisol concentrations in the offspring. *J Clin Endocrinol Metab.* 2003;88(8):3554-60.
4851. Yin J, Quinn S, Dwyer T, Ponsonby AL, Jones G. Maternal diet, breastfeeding and adolescent body composition: a 16-year prospective study. *Eur J Clin Nutr.* 2012;66(12):1329-34.
4852. Reynolds RM, Godfrey KM, Barker M, Osmond C, Phillips DI. Stress responsiveness in adult life: influence of mother's diet in late pregnancy. *J Clin Endocrinol Metab.* 2007;92(6):2208-10.
4853. Maslova E, Rytter D, Bech BH, et al. Maternal protein intake during pregnancy and offspring overweight 20 y later. *Am J Clin Nutr.* 2014;100(4):1139-48.
4854. Roseboom TJ, Watson ED. The next generation of disease risk: are the effects of prenatal nutrition transmitted across generations? Evidence from animal and human studies. *Placenta.* 2012;33 Suppl 2:e40-4.
4855. Mattes RD. Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav.* 1996;59(1):179-87.
4856. Brownell KD, Frieden TR. Ounces of prevention—the public policy case for taxes on sugared beverages. *N Engl J Med.* 2009;360(18):1805-8.
4857. Woodward-Lopez G, Kao J, Ritchie L. To what extent have sweetened beverages contributed to the obesity epidemic? *Public Health Nutr.* 2011;14(3):499-509.
4858. Brownell KD, Frieden TR. Ounces of prevention—the public policy case for taxes on sugared beverages. *N Engl J Med.* 2009;360(18):1805-8.
4859. Basu S, Seligman HK, Gardner C, Bhattacharya J. Ending SNAP subsidies for sugar-sweetened beverages could reduce obesity and type 2 diabetes. *Health Aff (Millwood).* 2014;33(6):1032-9.
4860. Brownell KD, Ludwig DS. The Supplemental Nutrition Assistance Program, soda, and USDA policy: who benefits? *JAMA.* 2011;306(12):1370-1.
4861. Food and Nutrition Service. Implications of restricting the use of food stamp benefits—summary. United States Department of Agriculture. Published March 1, 2007. Available at: <https://fns-prod.azureedge.net/sites/default/files/FSPFoodRestrictions.pdf>. Accessed April 17, 2019.
4862. Laraia BA. Carrots, sticks, or carrot sticks?: using federal food policy to engineer dietary change. *Am J Prev Med.* 2012;43(4):456-7.
4863. Long MW, Leung CW, Cheung LW, Blumenthal SJ, Willett WC. Public support for policies to improve the nutritional impact of the Supplemental Nutrition Assistance Program (SNAP). *Public Health Nutr.* 2014;17(1):219-24.

4864. Hillier-Brown FC, Bambra CL, Cairns JM, Kasim A, Moore HJ, Summerbell CD. A systematic review of the effectiveness of individual, community and societal-level interventions at reducing socio-economic inequalities in obesity among adults. *Int J Obes (Lond)*. 2014;38(12):1483-90.
4865. Ohri-Vachaspati P, Isgor Z, Rimkus L, Powell LM, Barker DC, Chaloupka FJ. Child-directed marketing inside and on the exterior of fast food restaurants. *Am J Prev Med*. 2015;48(1):22-30.
4866. Gentry E, Poirier K, Wilkinson T, Nhean S, Nyborn J, Siegel M. Alcohol advertising at Boston subway stations: an assessment of exposure by race and socioeconomic status. *Am J Public Health*. 2011;101(10):1936-41.
4867. Hackbarth DP, Silvestri B, Cosper W. Tobacco and alcohol billboards in 50 Chicago neighborhoods: market segmentation to sell dangerous products to the poor. *J Public Health Policy*. 1995;16(2):213-30.
4868. Moran AJ, Musicus A, Gorski Findling MT, et al. Increases in sugary drink marketing during Supplemental Nutrition Assistance Program benefit issuance in New York. *Am J Prev Med*. 2018;55(1):55-62.
4869. Bates C, Rowell A. Tobacco explained. Action on Smoking and Health. Available at: <http://www.who.int/tobacco/media/en/TobaccoExplained.pdf>. Accessed July 27, 2018.
4870. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. *Liver Int*. 2017;37 Suppl 1:81-4.
4871. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA*. 2015;313(22):2263-73.
4872. Lockman KA. Editorial: alcohol and obesity—the double peril. *Aliment Pharmacol Ther*. 2015;41(7):694.
4873. Mahli A, Hellerbrand C. Alcohol and obesity: a dangerous association for fatty liver disease. *Dig Dis*. 2016;34 Suppl 1:32-9.
4874. Bendsen NT, Christensen R, Bartels EM, et al. Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. *Nutr Rev*. 2013;71(2):67-87.
4875. Sonko BJ, Prentice AM, Murgatroyd PR, Goldberg GR, van de Ven ML, Coward WA. Effect of alcohol on postmeal fat storage. *Am J Clin Nutr*. 1994;59(3):619-25.
4876. Flechtner-Mors M, Biesalski HK, Jenkinson CP, Adler G, Ditschuneit HH. Effects of moderate consumption of white wine on weight loss in overweight and obese subjects. *Int J Obes Relat Metab Disord*. 2004;28(11):1420-6.
4877. Jatoi A, Qin R, Satele D, et al. "Enjoy glass of wine before eating": a randomized trial to test the orexigenic effects of this advice in advanced cancer patients. *Support Care Cancer*. 2016;24(9):3739-46.
4878. Bueemann B, Toubro S, Astrup A. The effect of wine or beer versus a carbonated soft drink, served at a meal, on ad libitum energy intake. *Int J Obes Relat Metab Disord*. 2002;26(10):1367-72.
4879. Golan R, Shelef I, Shemesh E, et al. Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. *Public Health Nutr*. 2017;20(3):549-55.
4880. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018;5(12):987-1012.
4881. Haber GB, Heaton KW, Murphy D, Burroughs LF. Depletion and disruption of dietary fibre. Effects on satiety, plasma-glucose, and serum-insulin. *Lancet*. 1977;2(8040):679-82.
4882. Martens MJ, Lemmens SG, Born JM, Westerterp-Plantenga MS. A solid high-protein meal evokes stronger hunger suppression than a liquefied high-protein meal. *Obesity (Silver Spring)*. 2011;19(3):522-7.
4883. Anne Moorhead S, Welch RW, Barbara M, et al. The effects of the fibre content and physical structure of carrots on satiety and subsequent intakes when eaten as part of a mixed meal. *Br J Nutr*. 2006;96(3):587-95.
4884. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-22.
4885. Cassady BA, Considine RV, Mattes RD. Beverage consumption, appetite, and energy intake: what did you expect? *Am J Clin Nutr*. 2012;95(3):587-93.
4886. Levine AS, Silvis SE. Absorption of whole peanuts, peanut oil, and peanut butter. *N Engl J Med*. 1980;303(16):917-8.
4887. Grundy MM, Grassby T, Mandalari G, et al. Effect of mastication on lipid bioaccessibility of almonds in a randomized human study and its implications for digestion kinetics, metabolizable energy, and postprandial lipemia. *Am J Clin Nutr*. 2015;101(1):25-33.
4888. Gebauer SK, Novotny JA, Bornhorst GM, Baer DJ. Food processing and structure impact the metabolizable energy of almonds. *Food Funct*. 2016;7(10):4231-8.
4889. Gebauer SK, Novotny JA, Bornhorst GM, Baer DJ. Food processing and structure impact the metabolizable energy of almonds. *Food Funct*. 2016;7(10):4231-8.
4890. Cassady BA, Hollis JH, Fulford AD, Considine RV, Mattes RD. Mastication of almonds: effects of lipid bioaccessibility, appetite, and hormone response. *Am J Clin Nutr*. 2009;89(3):794-800.
4891. Brand JC, Nicholson PL, Thorburn AW, Truswell AS. Food processing and the glycemic index. *Am J Clin Nutr*. 1985;42(6):1192-6.
4892. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281-3.
4893. Mackie AR, Bajka BH, Rigby NM, et al. Oatmeal particle size alters glycemic index but not as a function of gastric emptying rate. *Am J Physiol Gastrointest Liver Physiol*. 2017;313(3):G239-46.
4894. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics*. 1999;103(3):E26.
4895. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281-3.
4896. Brand JC, Nicholson PL, Thorburn AW, Truswell AS. Food processing and the glycemic index. *Am J Clin Nutr*. 1985;42(6):1192-6.
4897. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281-3.
4898. Granfeldt Y, Björck I, Hagander B. On the importance of processing conditions, product thickness and egg addition for the glycaemic and hormonal responses to pasta: a comparison with bread made from "pasta ingredients." *Eur J Clin Nutr*. 1991;45(10):489-99.
4899. Campfield LA, Smith FJ, Rosenbaum M, Hirsch J. Human eating: evidence for a physiological basis using a modified paradigm. *Neurosci Biobehav Rev*. 1996;20(1):133-7.

4900. Page KA, Seo D, Belfort-Deaguiar R, et al. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. *J Clin Invest*. 2011;121(10):4161-9.
4901. Bornet FR, Jardy-Gennetier AE, Jacquet N, Stowell J. Glycaemic response to foods: impact on satiety and long-term weight regulation. *Appetite*. 2007;49(3):535-53.
4902. Geliebter A, Grillot CL, Aviram-Friedman R, Haq S, Yahav E, Hashim SA. Effects of oatmeal and corn flakes cereal breakfasts on satiety, gastric emptying, glucose, and appetite-related hormones. *Ann Nutr Metab*. 2015;66(2-3):93-103.
4903. Crapo PA, Henry RR. Postprandial metabolic responses to the influence of food form. *Am J Clin Nutr*. 1988;48(3):560-4.
4904. Anguah KO, Wonnell BS, Campbell WW, McCabe GP, McCrory MA. A blended-rather than whole-lentil meal with or without α -galactosidase mildly increases healthy adults' appetite but not their glycemic response. *J Nutr*. 2014;144(12):1963-9.
4905. Jenkins DJ, Thorne MJ, Camelon K, et al. Effect of processing on digestibility and the blood glucose response: a study of lentils. *Am J Clin Nutr*. 1982;36(6):1093-101.
4906. Anderson GH, Liu Y, Smith CE, et al. The acute effect of commercially available pulse powders on postprandial glycaemic response in healthy young men. *Br J Nutr*. 2014;112(12):1966-73.
4907. Würsch P, Del Vedovo S, Koellreutter B. Cell structure and starch nature as key determinants of the digestion rate of starch in legume. *Am J Clin Nutr*. 1986;43(1):25-9.
4908. Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr*. 2003;12(4):477-82.
4909. Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr*. 2003;12(4):477-82.
4910. Hellström PM, Grybäck P, Jacobsson H. The physiology of gastric emptying. *Best Pract Res Clin Anaesthesiol*. 2006;20(3):397-407.
4911. Grundy MM, Edwards CH, Mackie AR, Gidley MJ, Butterworth PJ, Ellis PR. Re-evaluation of the mechanisms of dietary fibre and implications for macronutrient bioaccessibility, digestion and postprandial metabolism. *Br J Nutr*. 2016;116(5):816-33.
4912. Edwards CH, Grundy MM, Grassby T, et al. Manipulation of starch bioaccessibility in wheat endosperm to regulate starch digestion, postprandial glycemia, insulinemia, and gut hormone responses: a randomized controlled trial in healthy ileostomy participants. *Am J Clin Nutr*. 2015;102(4):791-800.
4913. Hareland G. Evaluation of flour particle size distribution by laser diffraction, sieve analysis and near-infrared reflectance spectroscopy. *J Cereal Sci*. 1994;20(2):183-90.
4914. Grassby T, Picout DR, Mandalari G, et al. Modelling of nutrient bioaccessibility in almond seeds based on the fracture properties of their cell walls. *Food Funct*. 2014;5(12):3096-106.
4915. Ellis PR, Kendall CW, Ren Y, et al. Role of cell walls in the bioaccessibility of lipids in almond seeds. *Am J Clin Nutr*. 2004;80(3):604-13.
4916. Gebauer SK, Novotny JA, Bornhorst GM, Baer DJ. Food processing and structure impact the metabolizable energy of almonds. *Food Funct*. 2016;7(10):4231-8.
4917. Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. *Nutrients*. 2018;10(2):126.
4918. Nilsson A, Johansson E, Ekström L, Björck I. Effects of a brown beans evening meal on metabolic risk markers and appetite regulating hormones at a subsequent standardized breakfast: a randomized cross-over study. *PLoS ONE*. 2013;8(4):e59985.
4919. McArthur BM, Mattes RD, Considine RV. Mastication of nuts under realistic eating conditions: implications for energy balance. *Nutrients*. 2018;10(6):710.
4920. Mori AM, Considine RV, Mattes RD. Acute and second-meal effects of almond form in impaired glucose tolerant adults: a randomized crossover trial. *Nutr Metab (Lond)*. 2011;8(1):6.
4921. Ibrügger S, Vignæs LK, Blennow A, et al. Second meal effect on appetite and fermentation of wholegrain rye foods. *Appetite*. 2014;80:248-56.
4922. Isaksson H, Rakha A, Andersson R, Fredriksson H, Olsson J, Aman P. Rye kernel breakfast increases satiety in the afternoon—an effect of food structure. *Nutr J*. 2011;10:31.
4923. Seal CJ, Nugent AP, Tee ES, Thielecke F. Whole-grain dietary recommendations: the need for a unified global approach. *Br J Nutr*. 2016;115(11):2031-8.
4924. Seal CJ, Nugent AP, Tee ES, Thielecke F. Whole-grain dietary recommendations: the need for a unified global approach. *Br J Nutr*. 2016;115(11):2031-8.
4925. Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet*. 1972;2(7792):1408-12.
4926. Dietary fiber market to reach \$3.25 billion by 2017. *Neutraceuticals World*. Published October 29, 2012. Available at: https://neutraceuticalsworld.com/contents/view_breaking-news/2012-10-29/dietary-fiber-market-to-reach-325-billion-by-2017. Accessed April 17, 2019.
4927. Eastwood M, Kritchevsky D. Dietary fiber: how did we get where we are? *Annu Rev Nutr*. 2005;25:1-8.
4928. Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2013;347:f6879.
4929. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-22.
4930. Fardet A. A shift toward a new holistic paradigm will help to preserve and better process grain products' food structure for improving their health effects. *Food Funct*. 2015;6(2):363-82.
4931. Wahlqvist ML. Food structure is critical for optimal health. *Food Funct*. 2016;7(3):1245-50.
4932. Hlebowicz J, Lindstedt S, Björgell O, Höglund P, Almér LO, Darwiche G. The botanical integrity of wheat products influences the gastric distention and satiety in healthy subjects. *Nutr J*. 2008;7:12.

4933. Luo K, Wang X, Zhang G. The anti-obesity effect of starch in a whole grain-like structural form. *Food Funct.* 2018;9(7):3755-63.
4934. Zinöcker MK, Lindseth IA. The Western diet-microbiome-host interaction and its role in metabolic disease. *Nutrients.* 2018;10(3):365.
4935. Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. *Diabetes Metab Syndr Obes.* 2012;5:175-89.
4936. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care.* 2008;31(12):2281-3.
4937. Grundy MM, Carrière F, Mackie AR, Gray DA, Butterworth PJ, Ellis PR. The role of plant cell wall encapsulation and porosity in regulating lipolysis during the digestion of almond seeds. *Food Funct.* 2016;7(1):69-78.
4938. Loria Kohen V, Gómez Candela C, Fernández Fernández C, Pérez Torres A, Villarino Sanz M, Bermejo LM. Impact of two low-calorie meals with and without bread on the sensation of hunger, satiety and amount of food consumed. *Nutr Hosp.* 2011;26(5):1155-60.
4939. Holt SH, Miller JC, Petocz P, Farmakalidis E. A satiety index of common foods. *Eur J Clin Nutr.* 1995;49(9):675-90.
4940. Grimes DS, Gordon C. Satiety value of wholemeal and white bread. *Lancet.* 1978;2(8080):106.
4941. Gonzalez-Anton C, Artacho R, Ruiz-Lopez MD, Gil A, Mesa MD. Modification of appetite by bread consumption: a systematic review of randomized controlled trials. *Crit Rev Food Sci Nutr.* 2017;57(14):3035-50.
4942. Bautista-Castaño I, Sánchez-Villegas A, Estruch R, et al. Changes in bread consumption and 4-year changes in adiposity in Spanish subjects at high cardiovascular risk. *Br J Nutr.* 2013;110(2):337-46.
4943. Mann KD, Pearce MS, McKeivith B, Thielecke F, Seal CJ. Whole grain intake and its association with intakes of other foods, nutrients and markers of health in the National Diet and Nutrition Survey rolling programme 2008-11. *Br J Nutr.* 2015;113(10):1595-602.
4944. Bautista-Castaño I, Sánchez-Villegas A, Estruch R, et al. Changes in bread consumption and 4-year changes in adiposity in Spanish subjects at high cardiovascular risk. *Br J Nutr.* 2013;110(2):337-46.
4945. De La Fuente-Arrillaga C, Martínez-González MA, Zazpe I, Vázquez-Ruiz Z, Benito-Corchon S, Bes-Rastrollo M. Glycemic load, glycemic index, bread and incidence of overweight/obesity in a Mediterranean cohort: the SUN project. *BMC Public Health.* 2014;14:1091.
4946. Romaguera D, Ångquist L, Du H, et al. Food composition of the diet in relation to changes in waist circumference adjusted for body mass index. *PLoS ONE.* 2011;6(8):e23384.
4947. Mofidi A, Ferraro ZM, Stewart KA, et al. The acute impact of ingestion of sourdough and whole-grain breads on blood glucose, insulin, and incretins in overweight and obese men. *J Nutr Metab.* 2012;2012:184710.
4948. Scazzina F, Siebenhandl-Ehn S, Pellegrini N. The effect of dietary fibre on reducing the glycaemic index of bread. *Br J Nutr.* 2013;109(7):1163-74.
4949. Burton P, Lightowler HJ. The impact of freezing and toasting on the glycaemic response of white bread. *Eur J Clin Nutr.* 2008;62(5):594-9.
4950. Scazzina F, Siebenhandl-Ehn S, Pellegrini N. The effect of dietary fibre on reducing the glycaemic index of bread. *Br J Nutr.* 2013;109(7):1163-74.
4951. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care.* 2008;31(12):2281-3.
4952. The University of Sydney. GI foods: search results. Updated May 2, 2017. Available at: <http://www.glycemicindex.com/foodSearch.php?num=643&ak=detail>. Accessed April 17, 2019.
4953. Jenkins DJ, Wesson V, Wolever TM, et al. Wholemeal versus wholegrain breads: proportion of whole or cracked grain and the glycaemic response. *BMJ.* 1988;297(6654):958-60.
4954. Hlebowicz J, Lindstedt S, Björgell O, Höglund P, Almér LO, Darwiche G. The botanical integrity of wheat products influences the gastric distention and satiety in healthy subjects. *Nutr J.* 2008;7:12.
4955. Breen C, Ryan M, Gibney MJ, Corrigan M, O'Shea D. Glycemic, insulinemic, and appetite responses of patients with type 2 diabetes to commonly consumed breads. *Diabetes Educ.* 2013;39(3):376-86.
4956. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care.* 2008;31(12):2281-3.
4957. Suhr J, Vuholm S, Iversen KN, Landberg R, Kristensen M. Wholegrain rye, but not wholegrain wheat, lowers body weight and fat mass compared with refined wheat: a 6-week randomized study. *Eur J Clin Nutr.* 2017;71(8):959-67.
4958. Suhr J, Vuholm S, Iversen KN, Landberg R, Kristensen M. Wholegrain rye, but not wholegrain wheat, lowers body weight and fat mass compared with refined wheat: a 6-week randomized study. *Eur J Clin Nutr.* 2017;71(8):959-67.
4959. Mishra S, Monro J. Wholeness and primary and secondary food structure effects on in vitro digestion patterns determine nutritionally distinct carbohydrate fractions in cereal foods. *Food Chem.* 2012;135(3):1968-74.
4960. Simonato B, Curioni A, Pasini G. Digestibility of pasta made with three wheat types: a preliminary study. *Food Chem.* 2015;174:219-25.
4961. Jenkins DJ, Wolever TM, Jenkins AL, Lee R, Wong GS, Josse R. Glycemic response to wheat products: reduced response to pasta but no effect of fiber. *Diabetes Care.* 1983;6(2):155-9.
4962. Sicignano A, Di Monaco R, Masi P, Cavella S. From raw material to dish: pasta quality step by step. *J Sci Food Agric.* 2015;95(13):2579-87.
4963. Granfeldt Y, Björck I, Hagander B. On the importance of processing conditions, product thickness and egg addition for the glycaemic and hormonal responses to pasta: a comparison with bread made from "pasta ingredients." *Eur J Clin Nutr.* 1991;45(10):489-99.
4964. Hoebler C, Devaux MF, Karinthi A, Belleville C, Barry JL. Particle size of solid food after human mastication and in vitro simulation of oral breakdown. *Int J Food Sci Nutr.* 2000;51(5):353-66.
4965. Granfeldt Y, Björck I, Hagander B. On the importance of processing conditions, product thickness and egg addition for the glycaemic and hormonal responses to pasta: a comparison with bread made from "pasta ingredients." *Eur J Clin Nutr.* 1991;45(10):489-99.
4966. Wolever TM, Jenkins DJ, Kalmusky J, et al. Glycemic response to pasta: effect of surface area, degree of cooking, and protein enrichment. *Diabetes Care.* 1986;9(4):401-4.

4967. Akilen R, Deljoomanesh N, Hunschede S, et al. The effects of potatoes and other carbohydrate side dishes consumed with meat on food intake, glycemia and satiety response in children. *Nutr Diabetes*. 2016;6:e195.
4968. Costabile G, Griffo E, Cipriano P, et al. Subjective satiety and plasma PYY concentration after wholemeal pasta. *Appetite*. 2018;125:172-81.
4969. Kristensen M, Jensen MG, Riboldi G, et al. Wholegrain vs. refined wheat bread and pasta. Effect on postprandial glycemia, appetite, and subsequent ad libitum energy intake in young healthy adults. *Appetite*. 2010;54(1):163-9.
4970. Sieri S, Krogh V. Dietary glycemic index, glycemic load and cancer: an overview of the literature. *Nutr Metab Cardiovasc Dis*. 2017;27(1):18-31.
4971. Runchey SS, Pollak MN, Valsta LM, et al. Glycemic load effect on fasting and post-prandial serum glucose, insulin, IGF-1 and IGFBP-3 in a randomized, controlled feeding study. *Eur J Clin Nutr*. 2012;66(10):1146-52.
4972. Augustin LS, Malerba S, Lugo A, et al. Associations of bread and pasta with the risk of cancer of the breast and colorectum. *Ann Oncol*. 2013;24(12):3094-9.
4973. Pounis G, Castelnuovo AD, Costanzo S, et al. Association of pasta consumption with body mass index and waist-to-hip ratio: results from Moli-sani and INHES studies. *Nutr Diabetes*. 2016;6(7):e218.
4974. Chiavaroli L, Kendall CWC, Braunstein CR, et al. Effect of pasta in the context of low-glycaemic index dietary patterns on body weight and markers of adiposity: a systematic review and meta-analysis of randomised controlled trials in adults. *BMJ Open*. 2018;8(3):e019438.
4975. Huang M, Li J, Ha MA, Riccardi G, Liu S. A systematic review on the relations between pasta consumption and cardio-metabolic risk factors. *Nutr Metab Cardiovasc Dis*. 2017;27(11):939-48.
4976. Drewnowski A, Rehm CD. Sodium intakes of US children and adults from foods and beverages by location of origin and by specific food source. *Nutrients*. 2013;5(6):1840-55.
4977. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362(7):590-9.
4978. Willett WC. The dietary pyramid: does the foundation need repair? *Am J Clin Nutr*. 1998;68(2):218-9.
4979. Rebello CJ, O'Neil CE, Greenway FL. Dietary fiber and satiety: the effects of oats on satiety. *Nutr Rev*. 2016;74(2):131-47.
4980. Decker EA, Rose DJ, Stewart D. Processing of oats and the impact of processing operations on nutrition and health benefits. *Br J Nutr*. 2014;112 Suppl 2:S58-64.
4981. Decker EA, Rose DJ, Stewart D. Processing of oats and the impact of processing operations on nutrition and health benefits. *Br J Nutr*. 2014;112 Suppl 2:S58-64.
4982. Alshikh N, de Camargo A, Shahidi F. Phenolics of selected lentil cultivars: antioxidant activities and inhibition of low-density lipoprotein and DNA damage. *J Funct Foods*. 2015;18:1022-38.

Chapter 5

- 4983. Ramage S, Farmer A, Eccles KA, McCargar L. Healthy strategies for successful weight loss and weight maintenance: a systematic review. *Appl Physiol Nutr Metab*. 2014;39(1):1-20.
- 4984. Guth E. JAMA patient page. Healthy weight loss. *JAMA*. 2014;312(9):974.
- 4985. Greger M. Dr. Greger in the kitchen: my new favorite beverage. NutritionFacts.org. Published November 13, 2017. Available at: <https://nutritionfacts.org/video/dr-greger-in-the-kitchen-my-new-favorite-beverage>. Accessed April 17, 2019.

Conclusion

4986. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
4987. U.S. News Best Diets: how we rated 41 eating plans. *U.S. News & World Report*. Published January 2, 2019. Available at: <https://health.usnews.com/wellness/food/articles/how-us-news-ranks-best-diets>. Accessed April 17, 2019.
4988. Brasher P. Diet advice alarms meat, egg groups. *Des Moines Register*. Published July 8, 2010.
4989. Ungar N, Sieverding M, Stadnitski T. Increasing fruit and vegetable intake. “Five a day” versus “just one more.” *Appetite*. 2013;65:200–4.
4990. Nestle M. *Unsavory Truth*. New York: Basic Books; 2018:116.

Acknowledgments

To all the amazing NutritionFacts.org research volunteers who made this book possible: Adriana, Alexandra, Aliena, Allen, Allie, Amy, Andrew, Ann Marie, Annette, Anthony, Becky, Ben, Brenna, Brian, Cara, Carina, Carly, Carmen, Carolina, Chavy, Chetan, Chris, Christine, Clarissa, Cody, Courtney, Cristina, Damon, Darlene, Deanna, Deborah, Devra, Dorothy, Elijah, Eliot, Ellen, Emelyn, Emma, Erin, Frank, Giang, Greg, Hala, Hannah, Isabel, Ivy, Jack, Jakub, James, Jane, Janelle, Jared, Jason, Jeff, Jenna, Jennifer, Jeremy, Jerold, Jo, Julie, Kacie, Karen, Katie, Katy, Kevin, Kimberley, Krissy, Laura, Lisa, Lora, Lori, Lucie, Luis, Luke, Lynda, Margaret, Maria, Maricela, Mary, Matthew, Michele, Michelle, Mike, Natalie, Nick, Nika, Olga, Patricia, Patrick, Peter, Preethi, Renatta, Rob, Robert, Roberto, Sabrina, Sashwat, Shannon, Sharon, Shevonn, Shireen, Shirley, Silvia, Suzie, Tammy, Theo, Thuy, Todd, Toni, Tracy, Travis, Valeria, Veronica, Yashaar, and Yhonatan.

Index

The index that appeared in the print version of this title does not match the pages in your e-book. Please use the search function on your e-reading device to search for terms of interest. For your reference, the terms that appear in the print index are listed below.

- abdominal exercises
- abdominal fat
- Academy of Nutrition and Dietetics
- acarbose
- accountability
 - self-weighing
 - Trevoze Behavior Modification Program
- ACE inhibitors
- acetaldehyde
- acetic acid
 - see also* vinegar
- acetol
- acetone
- acid reflux
- acne
- Acomplia
- adenosine monophosphate (AMP)
 - see also* AMPK
- adenosine triphosphate (ATP)
- addictive drugs
- addictive foods
 - and changing your tastes
 - fat and sugar in
 - processing and
- additives
- adrenal glands
- adrenaline
- advanced glycation end products (AGEs)

advertising, see marketing
Africans and African Americans
agriculture
 animal
air content of foods
Air Force, U.S.
alcohol
Alli (orlistat)
allulose
almonds
Alzheimer's disease
Ambien
American Academy of Family Physicians
American Academy of Pediatrics
American Cancer Society
American College of Cardiology
American College of Obstetricians and Gynecologists
American Diabetes Association
American Dietetic Association
American Heart Association
American Institute for Cancer Research
American Journal of Clinical Nutrition
American Medical Association
American Psychological Association
American Society of Clinical Oncology
amino acids
 branched-chain (BCAAs)
Amish
amnesia
AMP (adenosine monophosphate)
amphetamines
AMPK (AMP-activated protein kinase)
 barberries and
 nicotine and
 vinegar and
ancestral history, see evolution and ancestral diet
ANF (atrial natriuretic factor)
angiotensin
animal products
 agricultural practices and
 dairy
 pollutants in
 see also meat; protein, animal
Annals of Internal Medicine
antibiotics
antioxidants
anxiety disorders
apes

apnea
appetite, hunger, and satiety
 brain and
 circadian rhythms and
 cortisol and
 dieting and
 drinks and
 eating rate and, see eating rate
 exercise and
 fat calories and carb calories in
 fiber and
 food-dispensing device experiment and
 food variety and
 glycemic load and
 greens and
 gum chewing and
 hard foods and
 hedonic system and
 homeostatic system and
 hunger hormones and
 hyperpalatable foods and
 ketogenic diet and
 legumes and
 mono diets and
 oral stimulation and
 overeating and
 potatoes and
 Prader-Willi syndrome and
 protein and
 second-meal effect and
 sensory-specific satiety
 soup and
 sugar and
 vinegar and
 and water content of foods
appetite suppression
 black cumin for
 chia for
 cumin for
 flaxseed for
 saffron for
apple juice
apples
apricot kernels
arachidonic acid
Army Rangers, U.S.
arsenic
arthritis

artificial sweeteners
artery function
aspartame
asthma
astronauts
Atkins diet
ATP (adenosine triphosphate)
atrazine
atrial natriuretic factor (ANF)
autoimmune conditions
autonomic failure
Avandia

back pain
bacteria, gut, *see* gut bacteria
Bacteroides
balloon, intragastric
banana bags
bananas
barberries
bariatric surgery
 alcohol problems and
 for children and teens
 consequences of
 diabetes and
 gastric bypass
 intestinal bypass
 intragastric balloon
 jejunoileal bypass
 pollutants and
 self-harm and attempted suicide following
 stomach stapling
 weight maintenance following
barley, rye, oats, and lentils (BROL) bowl
BAT (brown adipose tissue)
 cannabis and
 chili peppers and
 cinnamon and
 coffee and
 foods that turn on
 ginger and
 peppermint and
 tea and
 temperature and
Bath Breakfast Project
BCAAs (branched-chain amino acids)
beans and other legumes

- blood sugar and
- BPA and
- canned
- cooking of
- flatulence and
- gut bacteria and
- Hispanic paradox and
- inflammation and
- kidney beans
- lectins and
- lentils, *see* lentils
- longevity and
- satiety and
- second-meal effect and
- starch in
- weight and
- beer
- beet greens
- Belviq
- Bengay
- berberine
- beriberi
- Bernays, Edward
- berries
 - barberries
 - blueberries
 - cranberries
 - goji berries
- beta amyloid
- beta-blockers
- beta-glucans
- beta receptors
- beverages
 - alcoholic
 - caffeinated
 - carbonated
 - coffee, *see* coffee
 - diet
 - energy drinks
 - fruit juice
 - hibiscus tea
 - orangeade experiment
 - polyphenols in
 - as preloads
 - salt and
 - satiety and
 - smoothies
 - soda and other sugary drinks

sports drinks
sugary, water as replacement for
tea, see tea, black or green; teas, herbal
vegetable juice
water, see water

Bifidobacteria

Big Fat Surprise, The (Teicholz)

Biggest Loser, The

Bilophila wadsworthia

birth:

vaginal flora and
weight at

black cumin (black seed)

bladder cancer

bliss point

blood donation, fainting and

blood pressure

autonomic failure and
calcium and
high (hypertension)

high, medications for
intermittent fasting and

blood sugar (glucose)

artificial sweeteners and
beans and

brain and

bread and

circadian rhythm of

exercise and

food combining and

glucose tolerance

grains and

ketogenic diet and

and order of eating foods

time of day and

vinegar and

blood type diet

Bloomberg, Michael

blueberries

BMI, see body mass index

body fat, see fat, body

body image issues:

self-weighing and

stigma attached to being overweight

body mass index (BMI)

body fat percentage vs.

longevity and

plant-based diet and

in super obesity
body temperature
bok choy
bones
 alternative-day fasting and
 ketogenic diet and
 mild Trendelenburg and
BPA (bisphenol A)
brain:
 addictive substances and
 AMPK in
 appetite and
 artificial sweeteners and
 blood sugar and
 caloric density and
 disease and damage to
 dopamine and
 fat and
 glycemic load and
 hippocampus in
 inflammation and
 internal clock and
 memory and
 salt and
 sugar and
 tumors in
bread
 pasta vs.
 salt in
 vinegar and
breakfast
 calories in
 diabetes and
 importance of
 skipping
 vinegar in
breakfast cereals
 oats
 rye porridge
 sugary
breast cancer
breastfeeding
breast implants
breast milk
Breatharian Institute
Brewer's yeast
BROAD study
BROL bowl

brown adipose tissue, *see* BAT
Buettner, Dan
Burger King

cadmium

caffeine

in energy drinks

sleep and

calcium

supplements

caloric restriction

CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy) trial

intermittent fasting compared with

longevity and

potential pitfalls of

see also fasting

calorie density

air content and

evolution and

fruit and

obesity epidemic and

portion sizes and

stomach size and

in three pounds of food

water content and

weight and

calories

absorption of

balance of

in breakfast

in celery

in coffee

CRAP (calorie-rich and processed foods)

eating frequency and

energy-balance equation and

exercise and

fat vs. carbohydrate

fecal losses of

fiber and

gut flora and

increased consumption of

intracellular and extracellular

from liquids

in low-fat diets

meat consumption and

metabolizable energy and

- negative calorie preloading
 - in nuts
 - in plant-based diet
 - in refined grains
 - resting metabolic rate and
 - self-deception about consumption of
 - sexual activity and
 - sleep and
 - in soda-vs.-jelly beans study
 - stomach size and
 - from sugar
 - ten-calorie rule
 - thermogenesis and, see thermogenesis
 - 3,500-calorie rule
 - Time-Calorie Displacement Program and
 - timing of consuming
 - walling off
 - water and
 - weight gain and
 - weight loss and
- camphor
- cancer
 - alcohol and
 - bladder
 - brain tumors
 - breast
 - colorectal
 - ketogenic diet and
 - prostate
 - sugar and
 - weight loss and
- cancer patients
 - chemotherapy timing for
 - fresh produce and
- candy
- cannabis
- canned foods
- capsaicin
- captopril
- carbohydrates
 - carbohydrate-insulin model of obesity
 - fat calories vs. calories from
 - as fuel
 - glycemic load and
 - grains, see grains
 - insulin and
 - low-carb diets, see low-carb diets
 - refined, combining with protein

carboxymethylcellulose
cardiovascular disease, see heart disease
carnitine
carrots
casein
cashews
catechins
cayenne peppers
cells and cell walls
cats and dogs
celery
 sun rash and
Centers for Disease Control and Prevention (CDC)
cereals, see breakfast cereals
chaga mushroom powder
chairs
Cheerios
cheese
Cheetos
chemical pollutants
 hormone-disrupting
 in meat
microplastics in seafood
 organic foods and
 organotins
 plastics
cherries
chewing
 gum
chia seeds
chicken
 insulin and
 salt in
chickpeas
children
 bariatric surgery for
 diabetes in
 fast food and
 food preferences of
 fruit for
 fruit juice for
 grain consumption and
 hidden vegetables and
 ketogenic diet and
 marketing to
 obesity in
 and order of eating foods
 plant-based diet and

salt intake of
sleep in
sugar and
vegetarian
weight stigma and
chili peppers
China
CHIP (Coronary Health Improvement Project)
chlorophyll
cholesterol
 breakfast and
 HDL
 intermittent fasting and
 LDL
choline
chronobiology
 blood sugar and
 breakfast and
 chronodisruption
 circadian rhythms
 exercise and
 jet lag and social jet lag
 light and
 melatonin and
 night-shift workers and
 nighttime food consumption
 timing of calorie intake
cigarettes
 anti-smoking campaigns
 anti-tobacco industry strategies
 light
 menthol
 smoking cessation aids
 taxes on
cinnamon
circadian rhythms
Citizens United
cliffing
Clostridium difficile
Coca-Cola
cocaine
Cochrane Collaboration
coconut oil
coffee
 calories in
 green coffee extract
 see *also* caffeine
cognitive behavioral therapy

cognitive defusion
cognitive restructuring
cold face test
collard greens
colon
colorectal cancer
Columbia University
commodities
constipation
Contrace
cookies
corn
cortisol
 animal protein and
 exercise and
 laughter and
 music and
 pregnancy and
costs, medical
cranberries
CRAP (calorie-rich and processed foods)
craveability
cravings, dealing with
C-reactive protein
crocin
Crohn's disease
Cronise, Ray
CrossFit
CR Society International
C-section
cumin
cumin, black (*Nigella sativa*)
curcumin
Current Drug Abuse Reviews
Cushing's syndrome
cyanide
cycling

Daily Dozen
dairy products
D.A.R.E. (Drug Abuse Resistance Education)
Darwin, Charles
DDT
dementia and Alzheimer's disease
depression
dessert effect
dexfenfluramine

- diabetes
 - bariatric surgery and
 - breakfast and
 - in children
 - drugs for
 - exercise and
 - eye disease and
 - glucose tolerance test and
 - intermittent fasting and
 - ketogenic diet and
 - reversal of
 - sleep and
 - vinegar and
- didgeridoo
- Diehl, Hans
 - Dietary Goals for the United States*
 - Dietary Guidelines Advisory Committee, U.S.
 - Dietary Guidelines for Americans*
 - Dietary Inflammatory Index
- diet beverages
- diet books
- diet drugs
 - amphetamines
 - DNP
 - ephedra
 - in supplements
- diets, dieting
 - adherence to
 - Atkins
 - fad and trending
 - failure of
 - ketogenic, *see* ketogenic diets
 - low-calorie; *see also* caloric restriction
 - low-carb, *see* low-carb diets
 - low-fat, *see* low-fat diets
 - mono
 - portion-controlled
 - sustainability of
 - yo-yo
- Dilantin
- dinitrophenol (DNP)
- DIOGENES trial
- dioxin
- dishwashing detergent
- disidentification (cognitive defusion)
- diuretic drugs
- diuretic effect (water loss)
- diving reflex

dizziness when standing up
DMAA
DNA
DNP (dinitrophenol)
Dodd, Thomas
dogs and cats
dopamine
drugs, addictive
 campaigns against
drugs, diet, see diet drugs
drugs, prescription, see medications
dyslipidemia

eating habits, see habits
eating rate
 chewing and
chopsticks and
 distraction and
 of hard vs. soft foods
 meal duration
 oral stimulation and
 of soup
 Time-Calorie Displacement Program and
EatRight program
E. coli
EGCG
eggplant
eggs
ego depletion
electrolytes
emulsifiers
encephalopathy
endorphins
energy-balance equation
energy drinks
Environmental Protection Agency
ephedra
EPIC study
epigenetics
epilepsy
EPOC (excess post-exercise oxygen consumption)
ER
erythritol
estrogen
estrogenic chemicals
evolution and ancestral diet
 appetite and

energy conservation and
scarcity and
exercise and physical activity
abdominal exercises
AMPK and
appetite and
baseline metabolic rate and
benefits of
blood sugar and
calories and
compliance to regimen of
cortisol and
cycling
energy-balance equation and
enjoyability of
EPOC (excess post-exercise oxygen consumption) and
fidgeting
heart disease and
high-intensity interval training (HIIT)
increase in, and decrease in nonexercised activity
ketogenic diet and
lack of
laziness and
longevity and
meals and
muscle mass and
music and
“myth” of
NEAT (nonexercise activity thermogenesis) and
non-exercise activities
obesity and
overeating and
recommended amounts of
resistance training
running
small moments of movement
stepping devices
stress and
swimming
and temperature of environment
timing of
visceral fat and
walking
water intake and
weight loss and

Exercise and Sports Science Reviews

- fainting
- Fairness Doctrine
- false hope syndrome
- fast food
- fasting
 - AMPK and
 - BPA and
 - breaking the fast
 - cortisol and
 - death during
 - effectiveness of
 - heart and
 - intermittent, *see* intermittent fasting
 - loss of lean tissue during
 - medically supervised
 - mood enhancement during
 - nutrients and
 - and realignment of perceptions and motivations
 - safety of
 - water-only
- fasting-induced adipose factor (FIAF)
- fasting-mimicking diet (FMD)
- fat, body
 - abdominal
 - beige (brite)
 - body mass index vs.
 - brown, *see* BAT
 - energy-balance equation and
 - fat stored as
 - leptin and
 - low-fat diet and
 - overfat
 - pollutants in
 - salt and
 - 3,500-calorie rule and
 - visceral
 - waist circumference and
 - waist-to-height ratio and
 - weight loss and
 - see also* weight; weight gain; weight loss
- fat activists
- fat blockers
 - calcium
 - hibiscus tea
 - thylakoids
- fat-blocking drugs
 - orlistat (Alli)
- fat burners

- drugs, see diet drugs
- see also BAT
- “fat gene” (FTO)
- fats and oils
 - in addictive foods
 - avoiding high-fat foods, vs. eating more fruits and vegetables
 - brain and
 - carbohydrate calories vs. calories from
 - coconut oil
 - differences in types of
 - as fattening
 - government calls to reduce intake of
 - high-fat diets
 - insulin sensitivity and
 - low-fat diet, see low-fat diets
 - “normal” intake of
 - oil-free cooking and baking
 - olive oil
 - saturated
 - stored as body fat
 - sugar combined with
 - trans fat
- FDA, see Food and Drug Administration
- fecal bulk
- fecal loss of calories
- fecal transplants
- Federal Trade Commission (FTC), U.S.
- fenfluramine, fen-phen
- fertility
- fetal nutrition
- FIAF (fasting-induced adipose factor)
- fiber
 - AMPK and
 - beta-glucan
 - calories and
 - deficiencies of
 - and eating the way nature intended
 - in fruit and fruit juices
 - gelling
 - gut bacteria and
 - gut barrier and
 - hunger hormones and
 - hunger suppression and
 - inflammation and
 - intestines and
 - ketogenic diet and
 - as matrix
 - prebiotics, see prebiotics

- sources of
- studies on
- sugars and
- supplements
- fidgiting
- Firmicutes*
- fish and seafood:
 - antibiotics in
- cortisol and
- farming of
- insulin and
- mercury in
- microplastics in
- omega-3 fatty acids in
- organotins in
- TMAO and

5:2 diet

flame-retardant chemicals

flavones

flaxseeds

- cyanide concerns and

Fletcher, Horace

flossing

flour

FODMAPs (fermentable oligo-, di-, and monosaccharides and polyols)

food(s):

- air content of
- addictive, see addictive foods
- additives in
- chewing of
- combining of
- context of eating
- cravings for
- decisions about
- different forms of
- eating rate and, see eating rate
- four categories of
- hyperpalatable
- nighttime consumption of
- order of eating
- organic, see organic foods
- physical form of
- processed, see processed foods
- timing of meals
- variety of
- water content of, see water content of foods

Food and Drug Administration (FDA)

food industry

- marketing by
 - salt and
 - sugar industry
 - and water content of foods
 - see *also* agribulture; processed foods
- Framingham Heart Study
- Frito-Lay
- Froot Loops
- frosting
- fructans
- fructose
- fruit juice
- fruits
 - buying
 - for children
 - cost of
 - dried
 - eating more, vs. avoiding high-fat foods
 - fiber in
 - insulin spikes and
 - organic
 - probiotics from
 - promotion of
 - recommended daily servings of
 - sugar in
 - timing of eating
 - washing
 - water content of
 - weight loss and
- FTO (“fat gene”)
- fungicides

- gallbladder removal
- gallstones
- garlic
- gastric bypass surgery
- gastrovascular reflex
- Gatorade
- General Electric
- General Mills
- genetics
 - epigenetics
 - “fat gene” (FTO)
 - vegetables and
- GERD (gastroesophageal reflux disease)
- ghrelin
- ginger

Ginsburg, Ruth Bader
ginseng
Global BMI Mortality Collaboration
Global Energy Balance Network
GLP-1
Glucophage
glucose, *see* blood sugar
gluten-free foods
glycemic index, glycemic load
 food combining and
 per serving, chart of
 and timing of eating
 vinegar and
glycogen
goals
 acquisitional vs. inhibitional
 what-the-hell effect and
goji berries
gout
G proteins
grains:
 BROL bowl
 flour
 intact (groats)
 oats
 pasta
 refined
 rice
 rye
 whole
 see also bread
grapefruit
grape juice
grapes
green coffee extract
Green Light foods
greens
 calcium in
 cooking
 kale
 oxalates in
 satiety and
 spinach
 thylakoids in
green tea extract
growth hormone IGF-1
guarana
Guinness Book of World Records

gum chewing
gut bacteria (microbiome)
 acetic acid and
 antibiotics and
 artificial sweeteners and
 Bacteroides
 beans and
 Bifidobacteria
 calories and
 changing with diet
 circadian rhythms and
 diversity of
 enterotypes and
 family home and
 fecal transplants and
 fiber and
 ketogenic diet and
 Lactobacillus
 nuts and
 obesity and
 polyphenols and
 prebiotics and, see prebiotics
 Prevotella
 probiotics and, see probiotics
 saturated fat and
 TMAO and
 twin studies and

habits
 bad, breaking
 changing the action
 changing the cue for
 decision-making in
 defined
 flossing
 formation of
 formation of, length of time needed for
 formation of, missing a day in
 implementation intentions and
 self-licensing and
 situational triggers and
 teenagers and
 what-the-hell effect and
Hall, Kevin
halo effect
Harlem Trial
Harvard Children's Hospital

Harvard Health Letter
Harvard Health Policy Review
Harvard Nurses' Health Study
Hawaii
HDTBR (head-down-tilt bed rest)
heart
 death from a broken heart
 diving reflex and
 rhythms
 transplants of
 water and
heartburn
heart disease
 breakfast and
 calcium supplements and
 CHIP program and
 cortisol and
 exercise and
 intermittent fasting and
 ketogenic diet and
 plant-based diet and
 tea and
 TMAO and
heavy metals
 see also lead
Helicobacter pylori
herbs
 cannabis
 ginger
 peppermint
 weight-loss supplements
hibernation
hibernoma
hibiscus tea
hidradenitis suppurativa
high-fructose corn syrup
high-intensity interval training (HIIT)
hippocampus
Hispanic paradox
honey
hormesis
hormones
 chemical disruptors of
 hunger
 stress; *see also* cortisol
hunger, *see* appetite, hunger, and satiety
hydration
 urine color and

see also water
hyperpalatability
hypertension (high blood pressure)
medications for
hypothalamus

IBS (irritable bowel syndrome)
ice, eating
IGF-1
ileal brake
immune function
implementation intentions
inactivity
inflammation
 arthritis
 back pain
 beans and
 brain and
 chronic (metabolic)
 C-reactive protein and
 Dietary Inflammatory Index
 fiber and
 goji berries and
 gout
 nutritional yeast and
 obesity and
 omega-3 fats and
 plant-based diet and
 tomatoes and
 turmeric and
inflammatory bowel disease
ingredients for the ideal weight-loss diet
 anti-inflammatory
 clean
 fiber-rich
 low-glycemic-load
 low in added fat
 low in added sugar
 low in addictive foods
 low in calorie density
 low in meat
 low in refined grains
 low in salt
 low insulin index
 microbiome-friendly
 recipe for success
 rich in fruits and vegetables

rich in legumes
water-rich
insomnia
 see also sleep
Institute of Medicine
insulin
 branched-chain amino acids (BCAAs) and
 carbohydrate-insulin model of obesity
 chewing and
 fruit and
 insulin resistance
 ketogenic diet and
 lowering spikes of
 meal frequency and
 obesity and
 and order of eating foods
 sensitivity to
 and timing of caloric intake
 vinegar and
intermittent fasting
 alternate-day, disease states and
 alternate-day, efficacy of
 alternate-day, longevity and
 alternate-day, safety of
 alternate-week
 bones and
 caloric restriction compared with
 fasting-mimicking diet
 5:2 diet
 lean body mass and
 time-restricted feeding
International Journal of Exercise Science
interoception
intestines
 bean starch and
 fiber and
 ileum in
 intestinal bypass surgery
 lining of
intra-gastric balloon
inulin
iron
irritable bowel syndrome (IBS)

jaundice
Jefferson, Thomas
jejunioileal bypass

Jenny Craig

jet lag and social jet lag

Jillette, Penn

Journal of Clinical Endocrinology & Metabolism

Journal of the American College of Cardiology

Journal of the American College of Nutrition

Journal of the American Dietetic Association

Journal of the American Medical Association

Journal of the Society of Chemical Industry

juice:

drinking between meals

fruit

vegetable

junk food, see processed foods

Kahn, Richard

kale

oxalates in

Katz, David L.

Kempner, Walter

Kentucky Fried Chicken

ketogenic diets

appetite and

bone loss and

cancer and

constipation and

diabetes and

as epilepsy treatment

exercise and

gut and

heart and

insomnia and

nutrients and

trials of

ketones

acetone

cancer and

ketosis

Keys, Ancel

kidney beans

kidneys

fasting and

kidney stones

water intake and

King, Martin Luther, Jr.

knee surgery

konjac gel cups

Lactobacillus
laughter
lead
 in tea
leaky gut
leanwashing
lectins
legumes, see beans and other legumes
lentils
 BROL bowl
 cooking of
leptin
life expectancy, see longevity
Lifestyle Heart Trial
light exposure
lipase
liposuction
lipotoxicity
liver
 green tea extract supplements and
longevity
 alternate-day fasting and
 beans and
 BMI and
 body weight and mortality
 caloric restriction and
 chili peppers and
 exercise and
 plant-based diet and
 Seventh-day Adventists and
 sleep and
Longo, Valter
Lopressor
Louisiana State University (LSU) Weight Loss Predictor
low-carb diets
 low-fat diets vs.
low-fat diets
 low-carb diets vs.
lycopene

MAC (microbiota-accessible carbohydrates), see prebiotics
macrophages
macronutrients
manganese
marijuana
marketing
 to children

- of fruits and vegetables
- massage
- Mayer, Jean
- Mayo Clinic
- McDonald's
- McDougall, John
- MCTs (medium-chain triglycerides)
- meals
 - breakfast, *see* breakfast
 - duration of
 - exercise and
 - number and frequency of
 - planning of
 - size of
 - time-restricted feeding and
 - timing of
 - two a day
 - water before
 - water with
- meat
 - calories and
 - cooked, cured, and smoked
 - cortisol and
 - dioxin levels in
 - insulin and
 - mushrooms as replacement for
 - organic
 - pregnancy and
 - reducing intake of
 - stress and
 - switching from red to white
 - weight gain and
- medications, 109@IXS:
 - blood pressure
 - deaths from
 - diabetes
 - diet, *see* diet drugs
 - G proteins and
 - timing of
- Mediterranean diet
- Medrol
- melatonin
 - dietary
- memory
- men:
 - body fat and
 - penis of
 - protein and

Men's Health

menthol

mercury

Meridia

metabolic imprinting

metabolic ward

Metabolife

metabolism

- boosting

- music and

- and order of eating foods

- plant-based diet and

- resting metabolic rate

- slowing of

- water and

metabolomics

Metamucil

methionine

methylglyoxal

methylprednisolone

methyl salicylate

metoprolol

microbiome:

- family home and

- vaginal flora

- see also* gut bacteria

microbiota-accessible carbohydrates (MAC), *see* prebiotics

micronutrients

midazolam

mild Trendelenburg

milk

- in tea

milk, breast

milkshake study

mindfulness

- cognitive defusion

- cravings and

- stress and

Minnesota Starvation Experiment

mint

MIT

mitochondria

monk fruit

mono diets

Montreal Imaging Stress Task protocol

moral licensing

mouthwash

muscle mass

mushroom powder, chaga

mushrooms

music:

exercise and

metabolism and

stress and

mustard greens

naltrexone

Narcan

National Academy of Medicine

National Institute on Aging

National Institutes of Health (NIH)

Body Weight Planner

National Weight Control Registry

Nature

NEAT (nonexercise activity thermogenesis)

Nestlé

Nestle, Marion

New England Journal of Medicine

New York Times Magazine

nicotine

Nigella sativa (black cumin)

nightshade family

night-shift workers

nighttime eating

1970s

noradrenaline

water and

Novick, Jeff

nutrients:

in breakfast cereals

deficiencies in

ketogenic diet and

requirements for

Nutrisystem

nutrition

nutritional yeast

Nutritional Neuroscience

NutritionFacts.org

Nutrition Science Initiative

nutri-washing

nuts and nut butters

pistachios

oats

BROL bowl

Obama, Michelle
obesity
 ancestral diet and
benign
 carbohydrate-insulin model of
 in children and teens
 as contagious
 costs of
 defining
 disabilities compared to
 as disease
 epidemic of
 exercise and
 FTO (“fat gene”) and
 gut microbes and
 healthy
 hypothalamus and
 inflammation and
 insulin and
 leptin and
 overeating and
 oxidative stress and
 paradox of
 physical inactivity and
 poverty and
 salt intake and
 skeptics and
 sleep and
 stigma attached to
 super
 and temperature of environment
 TMAO and
 in vegans
 water intake and
obesity causes
 brain damage
 chemical pollutants, see chemical pollutants
 CRAP (calorie-rich and processed foods)
 evolution
 fetal overnutrition
 food industry
 food marketing
 food ubiquity
 genetics
 inactivity
 in 1970s
 passive overconsumption
 portion sizes

- processed foods
- toxic food environment
- obesity consequences
 - and appetite-regulating brain circuits
 - arthritis
 - back pain
 - blood pressure increase
 - cancer
 - diabetes
 - encephalopathy
 - fertility problems
 - gallstones
 - GERD
 - heart disease
 - immune function
 - jaundice
 - kidney disease
- obesity solutions
 - bariatric surgery, *see* bariatric surgery
 - diet drugs
 - fasting, *see* fasting
 - policy approaches, *see* policy approaches
 - small-changes approach
 - supplements, *see* weight-loss supplements
 - Trevoe Behavior Modification Program
- oils, *see* fats and oils
- olive oil
- omega-3 fatty acids
- omega-6 fatty acids
- opiate-blocking drugs
- opioids
- optimal weight-loss diet
- orangeade experiment
- orange juice
- organic foods:
 - chemical pollutants and
 - meat
 - produce
- organotins
- orlistat (Alli)
- Ornish, Dean
- orthostatic intolerance
- osmolarity
- osteoarthritis
- osteoporosis
- overeating
 - exercise and
 - what-the-hell effect and

overweight
antibiotics and
stigma attached to
see *also* obesity
oxalates
oxidative stress

PAHs (polycyclic aromatic hydrocarbons)
paleo diets
pancreatitis
paper, thermal
Parkinson's disease
passive overconsumption
pasta
pawpaws
PBDE flame-retardant chemicals
PCBs
peanuts
pears
pectin
penis
peppermint
peppers:
bell
chili
PepsiCo
pesticides
pets
PGX (PolyGlycopleX)
phenytoin
phosphorus
photosynthesis
phthalates
phytonutrients
Pima Indians
pistachios
plant-based diet
BMI and
calories in
children and
CHIP program and
ease and sustainability of
Green Light foods in
heart disease and
inflammation and
insulin and
longevity and

metabolism and
microbiome and
nutrients in
portions and
preeclampsia and
residential programs for
stress and
weight and
weight loss and
Plant Paradox, The (Gundry)
plant protein vs. animal protein
plastics
 microplastics in seafood
policy approaches
 advertising and
 anti-tobacco example
 leveling the playing field
 taxes
 trans fat example
 unintended consequences of
pollutants, see chemical pollutants
polyphenols
polysorbate 80
pomegranate seeds
popcorn
portion sizes
 control of
 control of, vs. adding beans to diet
 in plant-based diet
post-traumatic stress disorder (PTSD)
potassium
potatoes
 satiety and
poultry
 dioxin levels in
 insulin and
 see *also* chicken
POUNDS Lost Trial
poverty
PPAR- γ
Prader-Willi syndrome
prebiotics (microbiota-accessible carbohydrates; MAC)
 BROL bowl
prednisolone
prednisone
preeclampsia
pregnancy
 cortisol and

fetal nutrition in
meat consumed in
microbiome an
preeclampsia in
tea and
prescription drugs, see medications
Prevotella
Pringles
prison studies
Pritikin, Nathan
Pritikin Center
probiotics
 from fruits and vegetables
 from supplements
Proceedings of the National Academy of Sciences
processed foods
 as addictive
 BPA in
 CRAP (calorie-rich and processed foods)
 eliminating
 reduced-fat
 ultraprocessed
Propaganda (Bernays)
prostate cancer
protein
 amino acids as building blocks of
 satiety and
protein, animal:
 combining carbohydrates with
 dairy
 plant protein vs.
 in pregnancy
 stress and
 weight gain and
Prozac
psoralens
psyllium
PTSD (post-traumatic stress disorder)
Public Health Nutrition
public policies, see policy approaches
PYY

Qsymia
Quorn

raisins
Ramadan

raw food diet
Red Bull
remedy messaging
resistance training
resistant starch
restaurants
 fast food
resting metabolic rate
Rezulin
rhubarb
riboflavin
rice
ricin
rimonabant
Roberts, John
running
rye
 BROL bowl

saffron
Sagan, Carl
salads, “negative calorie”
salt
sauerkraut
Saxenda
scarcity
SCFAs (short-chain fatty acids)
Science
scientific literature
Scripps Clinic Sleep Center
scurvy
seafood, see fish and seafood
seasonal affective disorder
sedentary lifestyle
seeds
selenium
self-licensing effect
semolina
Seventh-day Adventists
sexual activity
shareholders
shirataki noodles
short-chain fatty acids (SCFAs)
sibutramine
sitting
 dynamic
sleep

apnea in
caffeine and
calories and
catch-up
in children and adolescents
conditioning
dementia and
deprivation of
deprivation of, and motor vehicle accidents
diabetes and
enhancing
food and
hygiene
insomnia
longevity and
in mild Trendelenburg position
napping
noise and
obesity and
relaxation techniques and
weight loss and
sleeping pills
SlimFast
Smith, Adam
Smith v. Linn
smoking, see cigarettes
smoothies
snacks
 best and worst
 sleep and
SnackWell's
SNAP program
soda and other sugary drinks
 diet
sodium (salt)
sorbitol
sorghum
SOS (Swedish Obese Subjects) trial
soup
soy
soy milk
SPAM
spices
 black cumin
 cinnamon
 cumin
 ginger
 saffron

- turmeric
- spinach
 - cooking
 - oxalates in
- Splenda (sucralose)
- Spock, Benjamin
- sports drinks
- squash
- Standard American Diet
- standing
- starch:
 - bean
 - resistant
- starch blocker supplements
- star fruit
- stepping devices
- steroids
- stevia
- stomach size
 - water and
- stomach stapling
- stress
 - animal protein and
 - eating and
 - exercise and
 - laughter and
 - massage and
 - managing
 - mindfulness and
 - music and
 - plant-based diet and
 - yoga and
- stress hormones
 - see also* cortisol
- stroke
 - calcium supplements and
 - TMAO and
- sucralose (Splenda)
- sugar
 - in addictive foods
 - brain and
 - calories from
 - cancer and
 - fat combined with
 - fiber and
 - in fruit
 - limiting
 - studies on

- sugar industry and
- sweet tooth and
- sugary breakfast cereals
- suicide
- sun rash
- Sunshine Act
- Supreme Court
- supplements:
 - calcium
 - fiber
 - green coffee extract
 - green tea extract
 - herbal
 - lack of regulation of
 - prebiotic
 - probiotic
 - starch blocker
 - weight-loss, see weight-loss supplements
- Supreme Court
- surgery:
 - bariatric, see bariatric surgery
 - gallbladder
 - knee
 - liposuction
 - sham-surgery trials
- sweeteners, artificial
- sweet potatoes
- swimming
- swiss chard
- syncope (fainting)

- Take Off Pounds Sensibly (TOPS)
- tastes, changing
- Taubes, Gary
- taurine
- taxes
- tea, black or green
 - green tea extract
 - kidney damage and
 - lead in
 - milk in
- teas, herbal
 - hibiscus
- Teicholz, Nina
- temperature, environmental
 - brown fat and
 - exercise and

obesity and
ten-calorie rule
testosterone
THC
thermogenesis
 diet-induced
 NEAT (nonexercise activity thermogenesis)
thiamine
3,500-calorie rule
“thrifty gene” hypothesis
thylakoids
Tiger Balm
Time
time-restricted feeding
TMAO (trimethylamine oxide)
tobacco, see cigarettes
tomatoes and tomato products
 BPA and
 inflammation and
 tomato salad
toothpaste
topiramate
tortoises
toxic food environment
toxins, see chemical pollutants
treadmill desks
Trendelenburg, Friedrich
Trendelenburg position
 mild
 steep
Trevoze Behavior Modification Program
tributyltin
triglycerides
 MCTs (medium-chain triglycerides)
TrueNorth Health Center
Tufts University
turmeric
Twain, Mark
twenty-one tweaks
Twinkies
twins
 microbiomes and
Tyson, Neil deGrasse

USDA (U.S. Department of Agriculture)
U.S. News & World Report

vaginal flora
Valium
vegan diet
 obesity and
vegetable juice
vegetables
 buying
 calorie density of
 cost of
 eating more, vs. avoiding high-fat foods
 fiber in
 genes and
 green leafy, see greens
 hidden
 nightshade
 organic
 preloading with
 promotion of
 recommended daily servings of
 timing of eating
 washing
 water content of
 weight loss and
vegetarian diet
 pollutants in
 vegan, see vegan diet
 weight and
Vermont prison studies
Versed
vicarious goal fulfillment
vinegar
 optimal dosing of
 varieties of
visceral fat
vitamins:
 B1
 B2
 B12
 C
 D

waist circumference
waist-to-height ratio
walking
Walmart
water
 calories and

carbonated
chlorination of
drinking with a meal
excess intake of
exercise and
fainting and
filtered
healthy foods and
heart rate and
hydration
kidneys and
metabolism and
noradrenaline and
obesity and
optimum dose, type, and temperature of
preloading with
recommended daily amount of
sources of
stomach expansion and
weight loss and
water content of foods
sieving and
soup
and trapped vs. free water
water content of common foods, chart of
water loss
water-only fasting
Wealth of Nations, The (Smith)
weight:
beans and
birth
body's regulation of
cycling of
ideal
mortality and
plant-based diet and
vegetarians and
weighing yourself
weight gain
animal protein and
calories and
cortisol and
fruit juice and
meat consumption and
prison studies on
weight loss
beans and
on *The Biggest Loser*

- body fat and
- body's survival mechanisms against
- boosters for; *see also specific boosters*
- calories and
- cancer and
- exercise and
- financial incentives for
- fruit and
- health benefits from
- lifestyle change and
- low-carb diets for, *see low-carb diets*
- low-fat diets for, *see low-fat diets*
- maintaining
- mental performance and
- mortality and
- muscle mass and
- mushrooms and
- optimal diet for
- past and future performance in
- plant-based diet and
- plateaus in
- polyphenols and
- portion control and
- probiotics and
- resting metabolic rate and
- sleep and
- sustained
- ten-calorie rule and
- 3,500-calorie rule and
- thylakoids and
- vegetables and
- from water
- water intake and
- see also* ingredients for the ideal weight-loss diet
- weight-loss drugs, *see diet drugs*
- weight-loss industry:
 - anecdotes used as evidence in
 - controlled trials of commercial weight-loss programs
- diet books
 - see also* diets, dieting
- weight-loss supplements
 - drugs in
 - herbal
 - self-licensing and
- Weight Watchers
- Westman, Eric
- what-the-hell effect
- whey

White House Conference on Food, Nutrition, and Health

WHOLEheart study

Wilde, Oscar

Willett, Walter

wine

Winfrey, Oprah

wintergreen

wolfberries (goji berries)

women

- BMI and waist circumference in

- estrogen levels in

- pregnancy and, see pregnancy

Women's Health Initiative

World Health Organization (WHO)

World War I

World War II

yacon syrup

Yanomami tribe

yeast:

- Brewer's

- nutritional

Yoder, Seth

yoga

- laughter

yogurt

- chia in

Yom Kippur

yo-yo dieting

Zyprexa

Also by [Michael Greger, M.D., FACLM](#)

How Not to Die
The How Not to Die Cookbook

About the Author



© Dustin Kirkpatrick

A founding member and fellow of the American College of Lifestyle Medicine, **Dr. Michael Greger** is a physician, *New York Times* bestselling author, and internationally recognized speaker on nutrition, food safety, and public health issues. He runs the popular website [NutritionFacts.org](https://www.nutritionfacts.org), a nonprofit science-based public service site providing free daily updates on the latest in nutrition research. All the proceeds he receives from his books and speaking are donated to charity.

Visit him online at [NutritionFacts.org](https://www.nutritionfacts.org), or sign up for email updates [here](#).



**Thank you for buying this
Flatiron Books ebook.**

To receive special offers, bonus content,
and info on new releases and other great reads,
sign up for our newsletters.

[Sign Up](#)

Or visit us online at
us.macmillan.com/newslettersignup

For email updates on the author, click [here](#).

This book contains the opinions and ideas of its author. It is intended to provide helpful general information on the subjects that it addresses. It is not in any way a substitute for the advice of the reader's own physician(s) or other medical professionals based on the reader's own individual conditions, symptoms, or concerns. If the reader needs personal medical, health, dietary, exercise, or other assistance or advice, the reader should consult a competent physician and/or other qualified health care professionals. The author and publisher specifically disclaim all responsibility for injury, damage, or loss that the reader may incur as a direct or indirect consequence of following any directions or suggestions given in the book or participating in any programs described in the book.

HOW NOT TO DIET. Copyright © 2019 by NutritionFacts.org Inc. All rights reserved. For information, address Flatiron Books, 120 Broadway, New York, NY 10271.

www.flatironbooks.com

Graphs and charts by Dustin Kirkpatrick

Cover design by Jason Gabbert

The Library of Congress Cataloging-in-Publication Data is available upon request.

ISBN 978-1-250-19922-5 (hardcover)

ISBN 978-1-250-19924-9 (ebook)

eISBN 9781250199249

Our books may be purchased in bulk for promotional, educational, or business use. Please contact your local bookseller or the Macmillan Corporate and Premium Sales Department at 1-800-221-7945, extension 5442, or by email at MacmillanSpecialMarkets@macmillan.com.

First Edition: December 2019

Contents

TITLE PAGE
COPYRIGHT NOTICE
DEDICATION
PREFACE
INTRODUCTION

I. THE PROBLEM

THE CAUSES
THE CONSEQUENCES
THE SOLUTIONS
Bariatric Surgery
Diet Drugs
Weight-Loss Supplements
Policy Approaches

II. INGREDIENTS FOR THE IDEAL WEIGHT-LOSS DIET

INTRODUCTION
ANTI-INFLAMMATORY
CLEAN
HIGH IN FIBER-RICH FOODS
HIGH IN WATER-RICH FOODS
LOW GLYCEMIC LOAD
LOW IN ADDED FAT
LOW IN ADDED SUGAR
LOW IN ADDICTIVE FOODS
LOW IN CALORIE DENSITY
LOW IN MEAT
LOW IN REFINED GRAINS
LOW IN SALT
LOW INSULIN INDEX
MICROBIOME-FRIENDLY
RICH IN FRUITS AND VEGETABLES
RICH IN LEGUMES
SATIATING
RECIPE FOR SUCCESS

III. THE OPTIMAL WEIGHT-LOSS DIET

INTRODUCTION
PLANT YOURSELF

IV. WEIGHT-LOSS BOOSTERS

INTRODUCTION
ACCOUNTABILITY
AMPING AMPK
APPETITE SUPPRESSION
CHRONOBIOLOGY
EATING RATE
EXERCISE TWEAKS
FAT BLOCKERS
FAT BURNERS
HABIT FORMATION
HYDRATION
INFLAMMATION QUENCHERS
INTERMITTENT FASTING
Caloric Restriction
Fasting
Ketogenic Diets
Intermittent Fasting

MEAL FREQUENCY
METABOLIC BOOSTERS
MILD TRENDELENBURG
NEGATIVE CALORIE PRELOADING
SLEEP ENHANCEMENT
STRESS HORMONE RELIEF
WALL OFF YOUR CALORIES

V. DR. GREGER'S TWENTY-ONE TWEAKS

VI. CONCLUSION

REFERENCES

NOTES

ACKNOWLEDGMENTS

INDEX

ALSO BY MICHAEL GREGER, M.D., FACLM

ABOUT THE AUTHOR

COPYRIGHT