Current Nutrition Reports
https://doi.org/10.1007/s13668-018-0238-x

GASTROENTEROLOGY, CRITICAL CARE, AND LIFESTYLE MEDICINE (SA MCCLAVE, SECTION EDITOR)

Saturated Fat: Part of a Healthy Diet

Victoria M. Gershuni [1,2]

Abstract

Purpose of Review Despite the American public following recommendations to decrease absolute dietary fat intake and specifically decrease saturated fat intake, we have seen a dramatic rise over the past 40 years in the rates of non-communicable diseases associated with obesity and overweight, namely cardiovascular disease. The development of the diet-heart hypothesis in the mid twentieth century led to faulty but long-held beliefs that dietary intake of saturated fat led to heart disease. Saturated fat can lead to increased LDL cholesterol levels, and elevated plasma cholesterol levels have been shown to be a risk factor for cardiovascular disease; however, the correlative nature of their association does not assign causation.

Recent Findings Advances in understanding the role of various lipoprotein particles and their atherogenic risk have been helpful for understanding how different dietary components may impact CVD risk. Numerous meta-analyses and systematic reviews of both the historical and current literature reveals that the diet-heart hypothesis was not, and still is not, supported by the evidence. There appears to be no consistent benefit to all-cause or CVD mortality from the reduction of dietary saturated fat. Further, saturated fat has been shown in some cases to have an inverse relationship with obesity-related type 2 diabetes.

Summary Rather than focus on a single nutrient, the overall diet quality and elimination of processed foods, including simple carbohydrates, would likely do more to improve CVD and overall health. It is in the best interest of the American public to clarify dietary guidelines to recognize that dietary saturated fat is not the villain we once thought it was.

Keywords Saturated fat · SFA · Fatty acids · Dietary fat · Triglycerides · PUFA · LDL cholesterol · Diet · Cardiovascular disease · CVD · Atherosclerosis · Diet-heart hypothesis · Dietary guidelines

Introduction

With the rise of obesity, overweight, and chronic disease in Western countries, there has been a flurry of interest in understanding both why we get fat and how we can deal with it. Over the last half century, there have been various dietary strategies promoted to combat obesity and its associated diseases. By the 1980s, the diet-heart hypothesis aka "lipid hypothesis"—the assumption of a causal relationship between dietary fat consumption and coronary heart disease (CHD)—was widely accepted by the nutritional and medical community as dogma [1]. However, this hypothesis has not been proven to be correct despite its widespread acceptance.

The low-fat fad with recommendations to limit saturated fat to minimal levels has been the result of multiple influences. These include the relationship between the U.S. government and dietary guidelines, ecological and epidemiological studies investigating the relationship between diet and chronic disease, and most importantly, a misunderstanding of the biochemistry of different types of fat and their ultimate impact on human physiology.

Dietary fat is an essential nutrient that is a component of every cell in the human body; the human brain is made up of approximately 60% fat. Fatty acids are essential to all body tissues as components of phospholipid bilayers that make up

This article is part of the Topical Collection on *Gastroenterology, Critical Care, and Lifestyle Medicine*

✉ Victoria M. Gershuni
Victoria.Gershuni@uphs.upenn.edu

[1] Department of Surgery, Hospital of the University of Pennsylvania, 3400 Spruce Street, 4 Maloney, Philadelphia, PA 19104, USA

[2] Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Published online: 07 August 2018

info@ernaehrungsmediziner.de

Von:	Nicolai Worm <Nicolai.Worm@t-online.de>
Gesendet:	Mittwoch, 15. August 2018 16:04
An:	kmichels@hsph.harvard.edu
Cc:	tumorepidemiologie@uniklinik-freiburg.de
Betreff:	Superfood, Vitamin D und Kokosöl

https://www.youtube.com/watch?v=Mnc_aoN7IMM

Sehr geehrte Frau Prof. Michels,

Ihren Aussagen zu Superfood und Vitamin D kann ich gut beistimmen. Hingegen haben mich Ihre Aussagen zu gesättigten Fettsäuren, Schweineschmalz und Kokosöl regelrecht erschreckt.

Zum Beispiel besteht ja Schweineschmalz überwiegend aus ungesättigten Fettsäuren, wie man jeder Nahrungsmitteltabelle
entnehmen kann. Deswegen ist es bei Raumtemperatur auch nicht fest, wie von ihnen postuliert, sondern pastös.

Oder: Gesättigte Fettsäuren sind in Dutzenden Kohortenstudien ohne Risiko für kardiovaskuläre Erkrankungen ausgewiesen worden. Meta-Analysen dieser Studien haben das bestätigt. Anbei die neueste Übersichtsarbeit zum Thema,
die auch die Meta-Analysen auflistet.

Würden Sie mir deshalb bitte Belege für Ihre Aussagen schicken, dass Kokosöl bzw. gesättigte Fette „die Koronargefäße
verstopfen“ und Atherosklerose fördern würden.

Vielen Dank und Grüße,
Nicolai Worm

Dr. Nicolai Worm
Geibelstrasse 9
D-81679 München
Fon: +49-89-41929387
Fax: +49-89-41929432
Website Facebook Twitter

cell membranes. They are used as a source of fuel, especially within the myocardium. Rather than avoiding dietary fat, we need to understand the role of each type and how it can be a part of a healthy diet. Not all fat is created equal, and the chemical structure of the fat molecule will dictate how it is processed by the human body.

The big question this review seeks to answer is whether saturated fat can be a part of a healthy diet. The short answer to this question is yes. The long answer is that it is complicated. This review will attempt to clarify the history and background of our current dietary guidelines and describe the up-to-date scientific literature that exists on the relationship between dietary saturated fat (SFA) and human health.

Understanding Dietary Fat: What Is Saturated Fat?

Fatty Acids and Triglycerides

The majority of dietary fat is composed of triglycerides (aka triacylglycerides), the storage form of fatty acids that make up 95% of dietary fat. Triglycerides are composed of three different fatty acids attached to a glycerol backbone and contain the primary source of energy and calories derived from dietary fat. Fatty acids are the simplest class of lipid and structurally are composed of a hydrocarbon chain that terminates in a carboxylic acid group. This allows them to have different polarity on either end and affects their ability to mix with water (solubility). Different properties are also conferred to fatty acids dependent on carbon chain length (4–24 carbons) and degree of saturation (location and number of double bonds). These structural differences contribute to variable absorption, transport, and destination [2, 3].

Short chain fatty acids (SCFA, two to six carbons)—which are derived from fiber and non-digestible polysaccharides—are not only used as fuel sources for the cells of the colon but also function as signaling molecules that can impact gene expression [4–9]. The majority of dietary fat is in the form of either medium chain fatty acids (MCFA), which are composed of eight to 12 carbons, or long chain fatty acids (LCFA) that have 14 to 20+ carbons. The length of the carbon chain dictates whether the fat will be absorbed directly into the bloodstream via the portal circulation (i.e., SCFA and MCFA) or if it will be packaged by bile acids into micelles in the gut lumen and delivered via the lymphatics in the form of chylomicrons (LCFA).

The degree of saturation determines whether a fat is solid or liquid at room temperature. A greater number of double bonds in the carbon chain confer more flexibility and thus fluidity to the fatty acid, which can impact physiology as fatty acids form cell membrane lipid bilayers. In saturated fats, there are no double bonds, so the fatty acids are straight, compact, and rigid molecules that are able to pack tightly next to each other to form a solid. Unsaturated fats, however, are liquid at room temp due to double bonds that interfere with the stacking of the lipid molecules. Monounsaturated fatty acids (MUFA) have a single double bond, which produces a kink in the chain. This bend then produces a dietary fat that is liquid at room temperature but solid when chilled (i.e., olive oil, avocado oil). Multiple double bonds are found in polyunsaturated fatty acids (PUFA, i.e., soybean, corn, fish, flaxseed, and most "vegetable" oils). These are liquid at room temperature as well as when chilled due to the multiple kinks along the length of the chain that interfere with the molecules packing tightly. Further classification of PUFA is dependent on the location of the double bond that impacts oxidation and metabolism of the fatty acid. The bonds are identified by their distance from the end of the chain and can be referred to as omega-3, omega-6, omega-7, or omega-9 fatty acids. These variations of PUFAs have distinct metabolites that have reciprocal impacts on inflammation and metabolism (i.e., omega-3 fatty acids found in fish oil are considered anti-inflammatory, whereas omega-6 fatty acids like those in soybean oil are considered pro-inflammatory).

It is important to note that the industrialization of vegetable oils also brought with it the creation of trans-fatty acids. This process of hydrogenation takes an unsaturated fat and forcibly introduces hydrogen atoms into the double bond to remove the kink present in the carbon chain. By rearranging the orientation around the double bond (change from cis to trans position), trans fats are solid at room temperature and have a long shelf life, which ultimately led to their use in the processed food industry. Industrially produced trans fats have been shown to be unequivocally detrimental to human health and are not recommended for consumption [10••]. This topic is beyond the scope of this review.

Biological Consequences of Dietary Fats

Dietary fat is a fundamental component of a healthy diet and provides energy, a source of essential fatty acids (linoleic and alpha-linolenic fatty acids), and is necessary for the absorption of fat-soluble vitamins (A, D, E, K). Dietary fats are important for gastric emptying, digestion, and satiety. They are also principal components of hormones, including steroid and sex hormones. Their metabolic and overall health effect may not be adequately predicted by the general classification of saturated versus unsaturated fatty acids. There is evidence to suggest that chain length of individual fatty acids, processing methods, dietary source, and the dietary pattern associated with consuming fat may be more helpful in predicting a physiologic effect [11–14].

The triglycerides found in food can be composed of multiple types of fatty acids. Dietary saturated fat is often found in animal products—milk (varies by species), cheese, butter,

eggs, meat, and fish—and in plant foods as well, like coconut, cacao, cashews, palm, and palm kernel. Despite food items containing varying combinations and different proportions, nutrition labels are unable to discriminate between particular fatty acids. The saturated fat found in meat, eggs, cacao, and nuts is primarily composed of triglycerides containing palmitic and stearic acids. Over 90% of fatty acids found in the standard American diet are either palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), or linoleic acid (18:2). Linoleic acid is the predominant fatty acid found in omega 6 PUFA, representing the shift toward increased consumption of vegetable oils in the American diet in order to decrease intake of SFA.

Even within similar fat sources, i.e., conventional grain-fed beef vs. pastured grass-fed beef [15], there can be substantial variation in the fatty acid content. The type of fatty acid found in meat from animals is dependent on what the animal ate, so a grass-fed cow will have significantly greater omega-3 PUFA content than conventionally raised, grain-fed cows that have higher amounts of omega-6 PUFA. The quality and fatty acid makeup of the dietary fat we choose to consume has far-reaching implications. Research over the past three decades has revealed that grain-fed cattle have fattier meat, fewer micronutrients and minerals (i.e., beta-carotene, conjugated linoleic acid), a different fatty acid profile (less omega 3, more omega 6), and less antioxidant potential than grass-fed cows [15]. Similarly, the dairy produced by cattle has a different fatty acid profile. For example, butter contains large amounts of the SCFA butyrate (C4:0), in addition to 3, 11, and 29% of lauric, myristic, and palmitic acids, respectively.

Thus, when incorporating these foods into our diets, we must also remember that the source of our SFA matters.

In grass-fed beef, there are greater amounts of cholesterol neutral stearic acid (C18:0) and decreased levels of myristic acid (C14:0) and palmitic acid (C16:0), which have been shown to raise LDL-C [15]. The saturated fatty acids lauric acid (C12:0) and myristic acid (C14:0) have a greater cholesterol raising effect than palmitic acid (C16:0). A caveat to lauric acid's cholesterol raising effects is that it is predominantly a rise in HDL-C cholesterol, which has been shown to be more protective against CVD. Stearic acid (C18:0), on the other hand, has a neutral effect on total serum cholesterol and does not impact LDL-C or HDL-C. This may be due to conversion of stearic acid to oleate, which is similar to the monounsaturated oleic acid.

Within plant-sourced saturated fat, there is also considerable variability in the fatty acid composition. Despite being from the same plant, coconut oil is composed of primarily MCFA (47% lauric acid) with a smaller proportion from LCFA (18% myristic acid and only 9% palmitic acid), whereas palm kernel oil contains similar MCFA (48%) but only negligible myristic acid (1%) and dramatically more palmitic acid (48%). Evidence suggests that palmitic acid (PA) may have a differential effect on the development of obesity. In a study looking at the development of diet-induced obesity (DIO) in mice fed high-fat diets that compared cholesterol-rich lard versus cholesterol-free palm oil, researchers found that germ-free mice were resistant to DIO when fed a lard-based high-fat diet. However, germ-free mice fed an isocaloric palm-oil-based diet developed obesity [16]. The mechanisms behind these differences point to the ability for different fatty acids to significantly impact gut microbial species and bile acid metabolism in a way that affects crosstalk between the gut microbiota and host metabolism. It is imperative that we understand that the diet we eat impacts both the human and the microbes that live within us [9].

Importantly, the human body is capable of endogenous synthesis of fatty acids, specifically PA. Despite the villainization of dietary saturated fat, it is necessary to recognize that PA has crucial physiologic activities and, if not provided by the diet, it will be synthesized by the body via de novo lipogenesis (DNL) [17]. More important than the absolute intake of PA is the balance of a certain ratio with unsaturated fatty acids, specifically omega 6 and omega 3 PUFAs. Factors such as positive energy balance, sedentary lifestyle, and excessive intake of carbohydrates (in particular mono and disaccharides), and a sedentary lifestyle contribute to dysregulation of the mechanisms that maintain a steady state of PA concentration. This homeostatic disruption can lead to over accumulation of tissue PA that results in altered lipid profiles, elevated blood sugar, body fat accumulation, and increased inflammatory signaling via toll-like receptor 4 [17]. Rather than focus on eliminating this single nutrient—PA found in SFA—we need to focus on the totality of our diet, including the content of other macronutrients and the quality of the food we consume.

As mentioned earlier, SCFA and MCFA are absorbed directly into the bloodstream and go to the liver via the portal vein for direct utilization by the hepatocytes. LCFA, on the other hand, are solubilized by bile acids in the intestine before they are packaged into micelles and absorbed by the cells lining the intestine. Once there, they are repackaged into chylomicrons and sent through the lymphatic system before reaching the blood stream and eventually making their way to the liver. They then need to be unpackaged to be metabolized by the liver. If there is a surplus, they are stored—in the liver, adipose, and muscle. The breakdown of these LCFA occurs via beta-oxidation, which is dependent on lipoprotein lipase (LPL), an insulin-sensitive hormone. When insulin levels are high, LPL is inhibited and effectively turned off, so LCFA are not able to be broken down and instead get stored. After eating a sugar heavy meal (i.e., anything with processed food), we get an insulin spike that inhibits our ability to break down fat for fuel. Further, any excess carbohydrate is converted to fat that is also stored. This relationship underscores the importance of context when talking about dietary macronutrients.

Understanding Disease Risk: What Is Atherogenic Dyslipidemia?

Cardiovascular disease risk is traditionally assessed with a fasting lipoprotein profile that measures total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL-C), and triglycerides (TG). Cholesterol is carried throughout the body in multiple lipoprotein particles that vary by size and amount of cholesterol they carry; these particle characteristics impact the way they are absorbed and utilized by cells.

LDL-C is composed of a heterogeneous group of particles that are characterized based on size (larger is better than smaller) and the density of cholesterol within the particle (particles with less cholesterol are more buoyant, which is good). At least four different categories of LDL-C exist that are subdivided further into eight sub-fractions [18]. One of the simpler classifications of LDL-C is into large, buoyant type A particles and small, dense type B particles. The interaction between diet and lipoprotein particle size and density is a complex topic that continues to evolve.

Multiple studies suggest that the small, dense LDL-C particles possess greater atherogenic risk and are more likely to promote development of CVD [19–23]. This may be due to higher potential for oxidation of these small LDL-C particles that ultimately promotes inflammation and atherosclerosis. Dietary studies have demonstrated that saturated fat intake impacts large, buoyant type A particles, whereas small, dense type B particles are impacted by carbohydrate intake [18]. Without categorizing by particle size, LDL-C is a suboptimal biomarker for understanding potential CVD risk in a population or for evaluating and targeting dietary interventions.

Based on epidemiological associations with cardiovascular disease, higher levels of HDL-C are considered to have a protective effect against cardiovascular disease and act by carrying cholesterol from peripheral tissues back to the liver for metabolism. There are two to three different sub-fractions of HDL-C that confer different behaviors. Evidence shows that the HDL-C to TG ratio is far more predictive of CVD events than LDL-C.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial, a randomized, double-blind clinical trial attempting to alter lipid profiles with extended release niacin and statins in patients with established cardiovascular disease, found that fasting lipoprotein profiles at baseline were not predictive of clinical CVD events in either group [24]. Despite increasing levels of HDL-C in the intervention arm, they did not see a respective decrease in CVD risk, which goes against traditional views of HDL-C having a causal relationship with CVD [25]. In epidemiological studies, HDL-C has been shown to be inversely related to CVD risk, which suggests that it may have an athero-protective effect. However, HDL-C as a metric is measuring a complex heterogeneous mix of lipoprotein particles and may not be adequately representing the various athero-protective, antioxidant, anti-inflammatory, and cholesterol efflux properties of the underlying lipoprotein particles [26–28].

Individuals with the same total cholesterol levels can have vastly different lipoprotein particle patterns that confer different disease risk. Atherogenic dyslipidemia—the triad of elevated small, dense LDL-C, decreased HDL-C, and increased triglycerides—is a risk factor for CVD and myocardial infarction. Not surprisingly, this atherogenic dyslipidemia pattern is a typical feature of obesity, metabolic syndrome, and type 2 diabetes [18]. As evidence of the complexity of this relationship, 80% of participants in the Framingham study who developed CAD had the same total cholesterol as those that did not develop CAD [29]. Recent dietary studies have demonstrated that total or saturated dietary fat has minimal effect on lipoprotein profile; however, high carbohydrate diets have been shown to promote the development of atherogenic dyslipidemia [18, 30–32].

Understanding the History of Current Dietary Guidelines: What Is a Healthy Diet?

The original USDA dietary guidelines were introduced in 1894 followed by the first USDA food guide in 1916. Early in the twentieth century, the main focus of dietary guidelines was to avoid vitamin deficiencies and malnutrition. Following the Great Depression and close of World War II, better socioeconomic, sanitation, and nutrition conditions led to an epidemiologic transition. As chronic diseases became more prevalent, a paradigm shift in nutritional recommendations was promoted based on a growing interest in the relationship between diet and CVD. By the 1940s, cardiovascular disease (CVD) had become the leading cause of mortality in the USA with little known about its natural history, prevention, or treatment. After President Roosevelt's death secondary to CVD, President Truman signed the National Heart Act to devote resources to understanding the nationwide epidemic. In 1948, the Framingham Heart Study was initiated to investigate the relationship between cardiac health and environmental and lifestyle factors. The first reference to this notion was in the 1957 American Heart Association guidelines that said, "Diet may play an important role in the pathogenesis of atherosclerosis" [33, 34].

Early ecological, epidemiological, and short-term intervention studies were conducted to evaluate the link between diet and non-communicable chronic diseases. Ancel Keys, Frederick Stare, and Mark Hegsted were at the helm of the ship promoting the connection between dietary fat and heart

disease. Contemporaneously, John Yudkin had identified sugar as a major contributor to CAD, high triglycerides, cancer, and dental caries [35]. Keys and colleagues began the Seven Countries' study [36], which looked at the epidemiological association between saturated fat intake and heart disease mortality in over 12,000 men from seven countries. Unfortunately, while they did identify a potential association, their methodology was limited by data collection issues, and they did not control for all confounders like smoking, sugar intake, or exercise. Keys acknowledged these limitations by saying, "There is no guaranty that the main points of this discussion are actually about arteriosclerosis or the particular variety labeled atherosclerosis" [37]. Ultimately, this correlative relationship became fodder for much of the support of eliminating fat from our diet.

Based on the work by Keys, in 1977, the US Senate Committee led by Senator George McGovern released *Dietary Goals for the United States*, which concluded that "the overconsumption of foods high in fat, generally, and saturated fat in particular, as well as cholesterol, refined and processed sugars, salt and/or alcohol has been associated with the development of one or more of six to ten leading causes of death: heart disease, some cancers, stroke and hypertension, diabetes, arteriosclerosis and cirrhosis of the liver." In this report, they made seven specific recommendations, including reduction of overall fat consumption from 40 to 30% and reduction of saturated fat from 16 to 10% [38]. Despite this low-fat, low cholesterol diet now being accepted, there was opposition within the science community. In 1980, the US National Academy of Sciences Food and Nutrition Board argued that there was insufficient evidence to support limiting total fat, saturated fat, or dietary cholesterol in our dietary guidelines [35, 39].

In 1988, the *Surgeon General's Report* supported the notion that in order to decrease consumption of "bad fat," the public should decrease consumption of all fat. With this, the "low-fat" craze was started, heralding in the creation of the low-fat and non-fat food market. Despite the expansion of low- and non-fat food products and an overall decrease in fat consumption, there has been a parallel surge in overweight and obesity. In the last 30 years, Americans have decreased their fat intake by 10%, but the obesity rate has doubled [40]. By focusing on limiting a single dietary macronutrient, the food guidelines failed to underscore the importance of a balanced intake of calories and the contextual importance of dietary fat within a well-formulated diet [33].

Interestingly, however, the official listed sources of saturated fat are essentially lists of processed foods that include baked goods, candies/sweets, desserts, snacks, and packaged meals. Thus, it is even more unclear whether the ecological and epidemiological associations seen between SFA intake and CVD are due to the actual SFA content or secondary to the processed nature of the foods that are listed under this category. After all, pizza, potato chips, biscuits, and candy are not only high in SFA but also contain plenty of simple sugars, carbs, and preservatives [41]. Saturated fat in the context of a highly processed diet full of simple sugars and processed starches (i.e., a Western diet) is not a healthy diet. In the USA, saturated fats makeup approximately 10% of calories in the standard high sugar, highly processed diet.

Issued, and presumably updated, every 5 years, the US Dietary Guidelines for Americans impact the nutrition recommendations and diet for the US population. The guidelines dictate nutrition education, food labeling, food stamp programs and public assistance, and government-funded research programs at the National Institutes of Health (NIH). These guidelines extend beyond the US and guide most Western nations as they adopt similar nutrition policy globally. As brilliantly outlined by Teicholz in her critique of the 2015 dietary guidelines, the committee did not adequately surveil the scientific literature when preparing the newest update [42]. Rather, it relied primarily on recommendations from professional associations, including the American Heart Association (AHA) and the American College of Cardiology (ACC), and did not include systematic criteria for rigorous review of the updated literature. On the topic of saturated fats, specifically, the committee failed to conduct a formal review of newly published literature over the prior 5 years. Multiple meta-analyses and systematic reviews [43–45] that did not support the association between saturated fats and heart disease have been published since the 2010 dietary guidelines, but these were not reviewed by the committee. While there was movement away from the original recommendation of the 30% upper limit on dietary fat intake, the SFA guideline did not change, and recommendation to consume < 10% of daily calories from SFA remains [46].

Understanding the Research: What Evidence Exists?

The existence of an ecological association between CHD and elevated serum cholesterol does not translate to causation. Multiple large trials involving interventions to reduce total cholesterol have not been able to show a reduction in total mortality [1, 47–49]. The Honolulu Heart Study [50] contradicts this dictum further by demonstrating increased all-cause mortality among participants with lowered cholesterol levels. In a 30-year follow-up of the Framingham Heart Study, researchers found a direct association between decreased cholesterol levels over the first half of the study and higher mortality during the second half of the study [49]. Other studies found no correlation between dietary fat, serum cholesterol, and CHD mortality [51–53].

The traditional diet-heart hypothesis predicts that by reducing dietary intake of SFA, the compensatory decrease in serum

cholesterol would translate to a lower risk of CVD and death. However, upon re-analysis of data from the Minnesota Coronary Experiment [54], a long-term, double blind RCT that drastically decreased SFA in favor of "heart healthy" linoleic acid (omega 6 PUFA from corn oil), Ramsden and colleagues revealed that despite an average 30 g/dL decrease in serum cholesterol, the risk and incidence of all-cause mortality increased by 22% in the PUFA intervention group (based on a Cox model adjusted for baseline serum cholesterol, age, sex, adherence to diet, BMI, and SBP). For those who started the study aged > 65, they had a 35% higher risk of death associated with a 30 mg/dL decrease in serum cholesterol. Even more intriguing, this re-evaluation of the data from this trial recovered autopsy results, which enabled them to assess incidence of atherosclerosis and myocardial infarction. In the PUFA intervention group, 41% of participants had at least one MI vs. only 22% of the SFA control group. Likewise, the intervention group did not have less coronary or aortic atherosclerosis. The assumption that dietary cholesterol and saturated fats accumulate in the arteries is in opposition with the actual composition of arterial plaques. Felton et al. found that the arterial plaques within the aorta are primarily composed of unsaturated fats and concluded that this implies "a direct influence of dietary polyunsaturated fatty acids and not of saturated fats on aortic plaque formation and suggest that current trends favoring increased intake of polyunsaturated fatty acids should be reconsidered" [55]. This may have something to do with the pro-inflammatory mediators produced by omega 6 PUFA.

Ramsden et al. also evaluated recovered unpublished data from the Sydney Diet Heart Study [56], a single-blinded, randomized controlled trial from 1966 to 73. Again, they found that the advice to replace SFA with omega 6 PUFA for coronary heart disease reduction may be misguided. In this cohort, they found increasing rates of death from all causes, CHD, and CVD when SFA was replaced by linoleic acid. In conjunction with the re-analysis of both sets of primary data, the authors performed systematic reviews and meta-analyses and failed to find significant beneficial cardiovascular impact for use of omega 6 PUFA in place of SFA [56]. Likewise, on meta-analysis, they found that a mean decrease in serum cholesterol (7.8–13.8%) was not associated with decreased incidence of MI or any benefit on mortality from CHD [54].

The results of these meta-analyses of previously unpublished data challenge the proposition that decreased SFA lowers plasma cholesterol levels and thereby decreases risk of CAD. Despite lowering plasma lipid levels, there was no clinical benefit to the participants but rather increased risk of CAD [54]. Of course, it is prudent to remember that these detrimental effects may be due to increased linoleic acid (omega 6 PUFA) as opposed to decreasing SFA. But, in the context of dietary recommendations to decrease SFA in favor of linoleic acid-rich vegetable oils (omega 6 PUFA), these results are striking and relevant.

According to the few clinical studies that have looked at SFA and risk factors, the relationship between SFA intake and CVD risk varies depending on chain length. The Nurse's Health Study (NHS) was unable to demonstrate an increased risk of coronary heart disease with consumption of short- to medium-chain SFA ($p > 0.6$). However, when comparing the highest intake to lowest intake of long chain SFA, there was a slightly increased risk of CHD among the highest intake group after adjustment (RR 1.14, 95% CI 0.93, 1.39, $p = 0.03$) [57].

In the Women's Health Initiative Dietary Modification (WHI DM) trial, which compared decreased saturated fat intake with controls over a mean of 8.1 years in a large, controlled clinical trial of over 48,800 women, there were no observed statistically significant differences associated with lower saturated fat intake compared to usual diet in terms of lipoprotein profiles (LDL-C or HDL-C particle size or number), metabolic syndrome, incidence of fatal or non-fatal cardiac events, stroke, or CVD [58, 59]. Furthermore, the PREDIMED trial looked at a low-fat diet compared to a Mediterranean diet supplemented with olive oil or nuts, and found approximately 30% decrease in cardiovascular events over 4.8 years despite increased fat intake [60, 61].

In a landmark systematic review and meta-analysis published in 2015, de Souza et al. corroborated previous systematic reviews that found no discernible association between SFA intake and all-cause mortality, CVD [62], CHD incidence [43, 62–64] or mortality[43, 62, 63], ischemic stroke [43], or type 2 diabetes in healthy adults [10••]. Dietary fatty acids were further exonerated in a different systematic review, meta-analysis, and meta-regression that assessed the role of dietary fat in the secondary prevention of CHD and found that there was no benefit from reduction of total dietary fat or SFA in decreasing myocardial infarction, CVD, or all-cause mortality. Further, recommending PUFA to replace SFA conferred no improvement in risk reduction [65]. In a 2017 meta-analysis of randomized controlled trials, Hamley et al. found that after controlling for confounders, replacing SFA with mostly omega 6 PUFA is unlikely to reduce CHD events, CHD mortality, or total mortality. Harcombe and colleagues published multiple reviews, including currently available RCT evidence (over 62,000 participants), that do not support the current dietary guidelines to restrict dietary fat. Again, despite reductions in cholesterol, there were no significant differences in CHD or all-cause mortality [41, 66, 67, 68••]. These findings reinforced the conclusions of multiple other recent systematic reviews that have challenged the traditional diet-heart hypothesis (see Table 1) [43, 70, 71, 74–77].

In a randomized trial conducted from June to July 2017, healthy adults between 50 and 75 years old were placed on one of three different diets that differed by fat content. Participants were instructed to consume 50 g of either extra virgin coconut oil (SFA), olive oil (MUFA), or unsalted butter (SFA) daily for 4 weeks in addition to their usual diet. When

Table 1 Significant systematic reviews and meta-analyses on saturated fat consumption (2008–2018)

Author/year	Title	Main findings
Hamley, 2017 [69•]**	The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials	After adequately controlling for confounders, the available evidence from RCTs suggest that replacing SFA with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality or total mortality
Harcombe, 2016 [68••]**	Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis	Currently available RCT evidence (62,421 participants) does not support the current dietary guidelines to restrict dietary fat. Despite reductions in mean serum cholesterol levels, there were no significant differences in CHD or all-cause mortality
Hooper, 2015 [70]	Reduction in saturated fat intake for cardiovascular disease (Cochrane Database Systematic Review)	No significant difference for total mortality or cardiovascular mortality secondary to modified dietary fat intake, reduced dietary fat intake, or combined modified and reduced dietary fat intake. Small suggestion of benefit for CVD event risk in modifying dietary fat intake toward PUFA over SFA, however unclear what PUFA would be beneficial
Harcombe, 2015 [71]*	Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis	No differences in all-cause mortality and non-significant differences in CHD mortality resulted from the dietary interventions (decrease in total fat, saturated fat, or replacement with vegetable oil). Intervention groups had significant reductions in mean serum cholesterol levels; however, this did not result in significant differences in CHD or all-cause mortality. Original government dietary fat recommendations (US in 1977 and UK in 1983) were untested in any RCT prior to being introduced
de Souza, 2015 [10••]**	Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies	No discernable association was found between SFA intake and all-cause mortality, CVD, CHD incidence or mortality [43, 62, 63], ischemic stroke, or type 2 diabetes in healthy adults
Schwingshackl, 2014 [65]	Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression	No evidence for benefit of reduced/modified fat diets with regard to all-cause mortality, CVD mortality, or CVD events in the secondary prevention of CHD based on evidence from RCTs in patients with established CHD
Chowdhury, 2014 [62]	Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis	No association of dietary SFA intake, nor circulating SFA, with CHD
Ramsden, 2013 [56]	Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis	Failed to find significant beneficial cardiovascular impact for use of omega 6 PUFA in place of SFA. Substituting dietary linoleic acid (PUFA) in place of SFA increased rates of death from all causes, CHD, and CVD
de Oliveira Otto, 2012 [72]	Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis	Differential impact of SFA on CVD risk depending on source: higher dairy SFA associated with lower CVD risk, higher intake of meat SFA associated with greater CVD risk
Hoenselaar, 2011 [73]	Saturated fat and cardiovascular disease: the discrepancy between the scientific literature and dietary advice	Results and conclusions about saturated fat intake in relation to cardiovascular disease, from leading advisory committees, do not reflect the available scientific literature
Micha, 2010 [74]	Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence	In a systematic review of RCTs of disease endpoints for cardiometabolic effects of SFA consumption in humans, replacing SFA with PUFA modestly lowered CHD risk (10% RR for 5% energy substitution), whereas replacing SFA with carbohydrate had no benefit and replacing SFA with monounsaturated fat had uncertain effects
Mozaffarian, 2010	Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials	Evidence from RCTs suggests that replacing SFA with PUFAs reduced CHD events but did not reduce mortality
Siri-Tarino, 2010 [43]	Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease	No significant association between dietary saturated fat and increased risk of CHD or CVD
Skeaff, 2009 [63]	Fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials	"The available evidence from cohort and randomised controlled trials is unsatisfactory and unreliable to make judgment about and substantiate the effects of dietary fat on risk of CHD"

assessing for LDL-C (primary outcome), butter was found to significantly increase LDL-C compared to coconut oil (+ 0.42, $p < 0.0001$) or olive oil (+ 0.38, $p < 0.0001$). No difference was found between the saturated coconut oil and the monounsaturated olive oil. Further, coconut oil was found to significantly increase beneficial HDL compared with both butter and olive oil (+ 0.18 and + 0.16, respectively). There were no significant changes in weight, blood sugar, or blood pressure between the groups. This study highlighted the importance of assessing fatty acid profiles and processing methods in determining differential effects of saturated fatty acids [11, 78]. Despite containing approximately 90% saturated fat, coconut oil had more beneficial effects than butter (which has approximately 50–66% saturated fat). This may be secondary to a different fatty acid profile; coconut oil is composed of 48% lauric acid with myristic acid [79, 80]. Conversely, butter is composed of 40% palmitic and stearic acids. Interestingly, within butter, the LCFA palmitic and stearic acid may have opposing physiological effects. In a study looking at healthy males, the consumption of 19 g/day dietary stearic acid compared to dietary palmitic acid for 4 weeks was associated with improved thrombogenic and atherogenic risk factors, including plasma lipid concentrations [81].

Mozaffarian and colleagues performed a systematic review and meta-analysis looking at the association of butter consumption with all-cause mortality, CVD, and diabetes in the general population. Their analysis included 9 publications with 15 country-specific cohorts (over 636,000 participants) and included over 6.5 million person-years in follow-up with over 28,000 deaths. They found a weak and minimal association of butter with all-cause mortality (RR = 1.01, 95%CI 1.00, 1.03, $p = 0.045$), no significant association with any cardiovascular disease, coronary heart disease, or stroke. They did, however, find a modest inverse association with SFA consumption and the incidence of type 2 diabetes (RR = 0.96, 95%CI 0.93, 0.99, $p = 0.021$) [82]. Similarly, the WHI DM failed to show benefit in reducing SFA intake on type 2 diabetes incidence [83, 84]. Rather, there is evidence to support an inverse relationship between the intake of dairy products that are typically high in SFA and type 2 diabetes, which furthers brings current dietary recommendations to decrease SFA into question [85–87].

Diet and the Microbiome

In recent years, it has become increasingly apparent that the gut microbiota-host relationship is incredibly important for interfacing with our diet and modulating human metabolism. The microbiome—composed of the bacteria that live in our gut, their DNA, and the metabolites they produce—affects our health and metabolism on a daily basis [88, 89]. The standard Western diet that is high in fat, high in sugar, and low in fiber, is associated with a shift in the population of the gut flora toward one that is rich in Firmicutes and deficient in Bacteroidetes. This altered Firmicutes/Bacteroidetes ratio is associated with obesity, inflammation, and chronic diseases, including CVD. Landmark studies by Hazen and colleagues, identified a bacterially derived metabolite, trimethylamine (TMA) that is converted by the human liver into the atherogenic molecule, trimethylamine *N*-oxide (TMAO). This atherogenic metabolite is generated from phosphatidylcholine (lecithin), choline, and carnitine in the diet [90–93]. While these molecules are components of red meat and shellfish, they are also components of highly processed food, especially lecithin. One of the common uses for soy lecithin is as an emulsifier in processed foods to improve texture and miscibility of the ingredients. While it is important to isolate nutrients for experimental design, it can be difficult when translating findings for human diet development to know what component is contributing the most to disease phenotype.

The development of atherosclerosis is impacted by multiple factors, including genetics, lifestyle, and diet-microbiota interactions. It is the modifiable nature of diet that lends itself to the possibility of intervention. By minimizing processed foods and choosing well-sourced protein as part of a complex, plant-based diet with minimally processed fats, we can try to minimize the risk of CVD promoting factors. Fiber, specifically SCFA, can support the maintenance of a healthy microbiome that can minimize inflammation and protect against microbiota-mediated disease [9, 94–96]. Data from both human and animal studies implicate processed food additives (i.e., emulsifiers) in promoting obesity, metabolic syndrome, and inflammation via gut-mediated interactions [97–99]. When considering the role of saturated fat, it may be prudent to think about the foods that saturated fat are traditionally found in meats, shellfish, and processed food and consider that perhaps SFA may not be the ultimate causal factor for CVD but rather, an innocent bystander. As our understanding of the relationship between diet and the microbiome evolves, we are sure to uncover more about the complex and nuanced role of our diet and the development or prevention of disease.

Understanding How to Incorporate Saturated Fat: What Is a Balanced Diet?

Traditionally, nutritional advice and the research community have focused on single macro- or micro-nutrients; while this strategy worked to prevent nutritional deficiencies, it does not work for health promotion and prevention of non-communicable diseases. We now recognize that the interdependent relationship between different dietary components is more important to overall health than a single component [100].

The Framingham Heart Study, which has been highly influential in this arena, demonstrated a link between participants with high TG (> 1.7 mmol/L) and low HDL (aka "good cholesterol" < 1.03) levels and increased rates of CAD as opposed to those with low TG and higher HDL cholesterol [101]. While this correlation remains true, the particular benefits of a low-fat diet in altering this relationship have not been evaluated long-term and have had inconsistent results. In a cross-over dietary intervention study that compared different fat to carbohydrate macronutrient ratios using iso-caloric diets (60% carb, 25% fat, 15% protein vs. 40% carb, 45% fat, and 15% protein), they found higher plasma TG and lower HDL levels with no LDL effect when participants were assigned the higher carbohydrate diet despite lower fat intake [102]. Rather than focus on total cholesterol, or even LDL cholesterol, it is more important to evaluate the contribution of the more atherogenic lipoprotein particles. The discrimination among these different particle sizes and densities has not been adequately used as a measure of CAD risk in the majority of the epidemiological studies upon which we have based our dogma. None of these lipoprotein molecules exist in a vacuum; rather, it is the complex interplay between HDL, LDL, VLDL, and triglycerides that impact CAD risk [25].

When reducing one macronutrient component from the diet, like SFA, we replace it with another. This replacement can have different impacts on host physiological response. Both the AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk [103] and the National Lipid Association Expert Panel [104] have stated that replacing SFA with unsaturated fat (PUFA followed by MUFA) or protein has more favorable impacts on lipid profiles than replacement with carbohydrates [35]. This also appears to be supported in the multiple meta-analyses and Cochrane reviews on the topic; modifying fat intake by switching from SFA to an alternative source of fat appears to be more beneficial than increasing carbohydrate intake [45, 70]. However, there is evidence (see earlier sections) that large amounts of omega 6 PUFA may be contributing to the development of CVD. These factors may account for the increased incidence of obesity and CVD after the introduction of dietary guidelines geared at increasing carbohydrate intake in favor of lowering total fat.

Sadly, it is not as straightforward as removing or embracing all saturated fat. As demonstrated, saturated fat comes in many different types with unique physiological roles and consequences. Further, our food system today is not the same as it was pre-industrial and -agricultural revolutions. This pre-agricultural hunter-gatherer population subsisted on 45–65% of intake from animal-based food [105]. Despite their high intake of saturated animal fat, this population did not have the risk or incidence of CHD that we see now in Western populations [106]. This makes sense when considering that our paleolithic ancestors consumed wild game and ruminants that were closer in fatty acid composition to grass-fed cattle with higher levels of omega-3 fatty acids than the over-consumed and cheaply produced grain-fed beef that we now find on our supermarket shelves. Historically, most of the beef produced in the USA until the 1940s was from cattle finished on grass with use of the feedlot starting in the 1950s. Just as our health is driven by our diet, so is the health, nutrient content, and fat composition of the animals we eat. The conventional beef available today is not the same beef that our ancestors ate.

To make these findings actionable, perhaps the best dietary advice has been given by author Michael Pollan, "Eat food. Not too much. Mostly plants." Within that simple statement, he encompasses the need to eliminate "edible food-like substances" and focus on real, whole food, like fresh vegetables, pastured meat and dairy, and whole grains as they are found in nature. By eliminating the highly processed flours, sugars, and factory-farmed meat, we will likely improve our health by drastically cutting out chemical additives, antibiotics, high-glycemic carbohydrates, and industrial forms of omega-6 laden vegetable oil. After all, the list of "saturated fat" that is often used to quantify intake of SFA includes pastries, pizza, and confectionaries. These foods not only have SFA, but they have excessive amounts of sugar and salt. Decreasing the processed food will not only decrease the potential for poor quality oxidized fat, but it will also decrease our intake of the insulin-spiking carbohydrates that have supplanted the natural sources of saturated fat that are beneficial to our overall health.

Conclusions

The relationship between what we eat and our health is complex. To focus on simplistic associations between single dietary components as opposed to our diet composition and food sourcing on the whole is equivalent to not being able to see the forest for the trees. We need to examine foods and dietary patterns as a whole to fully understand their implications for human health and prevention of disease. The existing evidence does not support the notion that dietary SFA causes heart disease. There is no demonstrable benefit for reducing SFA to < 10% dietary fat. We have eschewed the naturally formed saturated fats found in plant and animal products and replaced them with highly processed and chemically extracted linoleic acid-rich vegetable oils (i.e., corn oil, soybean oil, etc.) that are now found in our food supply at alarming rates. In return, we have rising rates of obesity, metabolic syndrome, and cardiovascular disease. Based on the existing evidence, saturated fats are a vital component of a healthy diet when they are naturally occurring and eaten in the context of a minimally processed diet.

Acknowledgements I wish to acknowledge the guidance provided by Dr. Charlene Compher and thank her for critical analysis and feedback on the manuscript. Additionally, I am particularly grateful for the editing assistance from Candi Parks Gershuni.

Compliance with Ethical Standards

Conflict of Interest Victoria M. Gershuni declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Volk MG. An examination of the evidence supporting the association of dietary cholesterol and saturated fats with serum cholesterol and development of coronary heart disease. Altern Med Rev. 2007;12:228–45.
2. Kasai M, Nosaka N, Maki H, Negishi S, Aoyama T, Nakamura M, et al. Effect of dietary medium- and long-chain triacylglycerols (MLCT) on accumulation of body fat in healthy humans. Asia Pac J Clin Nutr. 2003;12:151–60.
3. Schonfeld P, Wojtczak L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. J Lipid Res. 2016;57:943–54.
4. Rowland I, et al. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr. 2017.
5. Wu GD, Compher C, Chen EZ, Smith SA, Shah RD, Bittinger K, et al. Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. Gut. 2016;65:63–72.
6. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54:2325–40.
7. Remely M, Aumueller E, Merold C, Dworzak S, Hippe B, Zanner J, et al. Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene. 2014;537:85–92.
8. Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. Cell Metab. 2014;20:779–86.
9. Sonnenburg JL, Backhed F. Diet-microbiota interactions as moderators of human metabolism. Nature. 2016;535:56–64.
10. •• de Souza RJ, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015;351:h3978. **Great review on the lack of evidence to support an association between SFA intake and the incidence of cardiovascular disease or diabetes.**
11. Khaw KT, Sharp SJ, Finikarides L, Afzal I, Lentjes M, Luben R, et al. Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. BMJ Open. 2018;8:e020167.
12. Khaw KT, Friesen MD, Riboli E, Luben R, Wareham N. Plasma phospholipid fatty acid concentration and incident coronary heart disease in men and women: the EPIC-Norfolk prospective study. PLoS Med. 2012;9:e1001255.
13. Forouhi NG, Koulman A, Sharp SJ, Imamura F, Kröger J, Schulze MB, et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. Lancet Diabetes Endocrinol. 2014;2:810–8.
14. Praagman J, Beulens JWJ, Alssema M, Zock PL, Wanders AJ, Sluijs I, et al. The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort. Am J Clin Nutr. 2016;103:356–65.
15. Daley CA, Abbott A, Doyle PS, Nader GA, Larson S. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. Nutr J. 2010;9:10.
16. Kubeck R, et al. Dietary fat and gut microbiota interactions determine diet-induced obesity in mice. Mol Metab. 2016;5:1162–74.
17. Carta G, Murru E, Banni S, Manca C. Palmitic acid: physiological role, metabolism and nutritional implications. Front Physiol. 2017;8:902.
18. Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids. 2010;45:907–14.
19. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006;83:1025–31. quiz 1205
20. Kratz M, Gülbahçe E, von Eckardstein A, Cullen P, Cignarella A, Assmann G, et al. Dietary mono- and polyunsaturated fatty acids similarly affect LDL size in healthy men and women. J Nutr. 2002;132:715–8.
21. Moreno JA, Pérez-Jiménez F, Marín C, Gómez Ṕ, Pérez-Martínez P, Moreno R, et al. The effect of dietary fat on LDL size is influenced by apolipoprotein E genotype in healthy subjects. J Nutr. 2004;134:2517–22.
22. Rivellese AA, Maffettone A, Vessby B, Uusitupa M, Hermansen K, Berglund L, et al. Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. Atherosclerosis. 2003;167:149–58.
23. Lai CQ, Corella D, Demissie S, Cupples LA, Adiconis X, Zhu Y, et al. Dietary intake of n-6 fatty acids modulates effect of apolipoprotein A5 gene on plasma fasting triglycerides, remnant lipoprotein concentrations, and lipoprotein particle size: the Framingham Heart Study. Circulation. 2006;113:2062–70.
24. Guyton JR, Slee AE, Anderson T, Fleg JL, Goldberg RB, Kashyap ML, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). J Am Coll Cardiol. 2013;62:1580–4.
25. Albers JJ, Slee A, Fleg JL, O'Brien KD, Marcovina SM. Relationship of baseline HDL subclasses, small dense LDL and LDL triglyceride to cardiovascular events in the AIM-HIGH clinical trial. Atherosclerosis. 2016;251:454–9.
26. Du XM, et al. HDL particle size is a critical determinant of ABCA1-mediated macrophage cellular cholesterol export. Circ Res. 2015;116:1133–42.
27. Camont L, Lhomme M, Rached F, le Goff W, Negre-Salvayre A, Salvayre R, et al. Small, dense high-density lipoprotein-3 particles are enriched in negatively charged phospholipids: relevance to cellular cholesterol efflux, antioxidative, antithrombotic, anti-inflammatory, and antiapoptotic functionalities. Arterioscler Thromb Vasc Biol. 2013;33:2715–23.

28. Hovingh GK, Rader DJ, Hegele RA. HDL re-examined. Curr Opin Lipidol. 2015;26:127–32.
29. Superko HR, Nejedly M, Garrett B. Small LDL and its clinical importance as a new CAD risk factor: a female case study. Prog Cardiovasc Nurs. 2002;17:167–73.
30. Dreon DM, Fernstrom HA, Williams PT, Krauss RM. A very low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. Am J Clin Nutr. 1999;69:411–8.
31. Krauss RM, Dreon DM. Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. Am J Clin Nutr. 1995;62:478S–87S.
32. Dreon DM, Fernstrom HA, Williams PT, Krauss RM. LDL subclass patterns and lipoprotein response to a low-fat, high-carbohydrate diet in women. Arterioscler Thromb Vasc Biol. 1997;17:707–14.
33. Gifford KD. Dietary fats, eating guides, and public policy: history, critique, and recommendations. Am J Med. 2002;113(Suppl 9B): 89S–106S.
34. Kritchevsky D. History of recommendations to the public about dietary fat. J Nutr. 1998;128:449S–52S.
35. Mozaffarian D, Rosenberg I, Uauy R. History of modern nutrition science-implications for current research, dietary guidelines, and food policy. BMJ. 2018;361:k2392.
36. Keys A, Aravanis C, Blackburn HW, van Buchem F, Buzina R, Djordjević BD, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl. 1966;460:1–392.
37. Keys A. Atherosclerosis: a problem in newer public health. J Mt Sinai Hosp N Y. 1953;20:118–39.
38. Dietary goals for the United States: statement of The American Medical Association to the Select Committee on Nutrition and Human Needs, United States Senate. R I Med J. 1977;60, 576–581.
39. Heyden S, Williams RS. Cholesterol controversy—where do we go from here? 'Toward healthful diets' reevaluated. Cardiology. 1982;69:110–22.
40. Kochanek KD, Murphy S, Xu J & Arias E. Mortality in the United States, 2016. NCHS Data Brief. 2017;1–8.
41. Harcombe Z. Dietary fat guidelines have no evidence base: where next for public health nutritional advice? Br J Sports Med. 2017;51:769–74.
42. Teicholz N. The scientific report guiding the US dietary guidelines: is it scientific? BMJ. 2015;351:h4962.
43. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. Am J Clin Nutr. 2010;91:535–46.
44. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. Am J Clin Nutr. 2010;91:502–9.
45. Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore HJ, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Sao Paulo Med J. 2016;134:182–3.
46. Mozaffarian D, Ludwig DS. The 2015 US dietary guidelines: lifting the ban on total dietary fat. JAMA. 2015;313:2421–2.
47. Borhani NO. Coronary heart disease prevention: the multiple risk factor intervention trial (MRFIT). West J Med. 1974;121:418.
48. Stamler J, Neaton JD. The multiple risk factor intervention trial (MRFIT)—importance then and now. JAMA. 2008;300:1343–5.
49. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA. 1987;257: 2176–80.
50. Yano K, Reed DM, McGee DL. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to biologic and lifestyle characteristics. Am J Epidemiol. 1984;119: 653–66.
51. Carman WJ, Barrett-Connor E, Sowers M, Khaw KT. Higher risk of cardiovascular mortality among lean hypertensive individuals in Tecumseh, Michigan. Circulation. 1994;89:703–11.
52. Nichols AB, Ravenscroft C, Lamphiear DE, Ostrander LD Jr. Daily nutritional intake and serum lipid levels. The Tecumseh study. Am J Clin Nutr. 1976;29:1384–92.
53. Goldbourt U, Yaari S. Cholesterol and coronary heart disease mortality. A 23-year follow-up study of 9902 men in Israel. Arteriosclerosis. 1990;10:512–9.
54. Ramsden CE, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota coronary experiment (1968-73). BMJ. 2016;353:i1246.
55. Felton CV, Crook D, Davies MJ, Oliver MF. Dietary polyunsaturated fatty acids and composition of human aortic plaques. Lancet. 1994;344:1195–6.
56. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ. 2013;346:e8707.
57. Hu FB, Stampfer MJ, Manson JAE, Ascherio A, Colditz GA, Speizer FE, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr. 1999;70:1001–8.
58. Howard BV, van Horn L, Hsia J, Manson JAE, Stefanick ML, Wassertheil-Smoller S, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative randomized controlled dietary modification trial. JAMA. 2006;295:655–66.
59. Howard BV, Curb JD, Eaton CB, Kooperberg C, Ockene J, Kostis JB, et al. Low-fat dietary pattern and lipoprotein risk factors: the Women's Health Initiative dietary modification trial. Am J Clin Nutr. 2010;91:860–74.
60. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–90.
61. Estruch R, et al. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013. 2018;368:1279–90. N Engl J Med
62. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398–406.
63. Skeaff CM, Miller J. Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. Ann Nutr Metab. 2009;55:173–201.
64. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169:659–69.
65. Schwingshackl L, Hoffmann G. Dietary fatty acids in the secondary prevention of coronary heart disease: a systematic review, meta-analysis and meta-regression. BMJ Open. 2014;4:e004487.
66. Harcombe Z, Baker JS, Davies B. Evidence from prospective cohort studies does not support current dietary fat guidelines: a systematic review and meta-analysis. Br J Sports Med. 2017;51:1743–9.
67. Harcombe Z, Baker JS, Davies B. Evidence from prospective cohort studies did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review. Br J Sports Med. 2017;51:1737–42.
68.•• Harcombe Z, Baker JS, DiNicolantonio JJ, Grace F, Davies B. Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis. Open Heart. 2016;3:e000409. **Excellent review showing that the current dietary guidelines to restrict dietary fat are not evidence based and adherence to these guidelines have not improved outcomes. Nice accompaniment to previous review showing that the original dietary guidelines were not evidence based either.**

69.• Hamley S. The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials. Nutr J. 2017;16(30):30. **Meta-analysis of available evidence from RCTs evaluating effect of replacing SFA with n-6 PUFA on CHD events, CHD mortality, and total mortality. Reveals that recommendations to replace SFA to n-6 PUFA (vegetable oils) are not supported by the literature.**

70. Hooper L, Martin N, Abdelhamid A & Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev. 2015;CD011737.

71. Harcombe Z, Baker JS, Cooper SM, Davies B, Sculthorpe N, DiNicolantonio JJ, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart. 2015;2:e000196.

72. de Oliveira Otto MC, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. Am J Clin Nutr. 2012;96:397–404.

73. Hoenselaar R. Saturated fat and cardiovascular disease: the discrepancy between the scientific literature and dietary advice. Nutrition. 2012;28:118–23.

74. Micha R, Mozaffarian D. Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids. 2010;45:893–905.

75. Malhotra A. Saturated fat is not the major issue. BMJ. 2013;347: f6340.

76. Malhotra A, Redberg RF, Meier P. Saturated fat does not clog the arteries: coronary heart disease is a chronic inflammatory condition, the risk of which can be effectively reduced from healthy lifestyle interventions. Br J Sports Med. 2017;51:1111–2.

77. Hooper L, Summerbell CD, Higgins JP, Thompson RL, Capps NE, Smith GD, et al. Dietary fat intake and prevention of cardiovascular disease: systematic review. BMJ. 2001;322:757–63.

78. German JB, Dillard CJ. Saturated fats: what dietary intake? Am J Clin Nutr. 2004;80:550–9.

79. Eyres L, Eyres MF, Chisholm A, Brown RC. Coconut oil consumption and cardiovascular risk factors in humans. Nutr Rev. 2016;74:267–80.

80. Valente FX, Cândido FG, Lopes LL, Dias DM, Carvalho SDL, Pereira PF, 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: 1627–37.

81. Kelly FD, Sinclair AJ, Mann NJ, Turner AH, Abedin L, Li D. A stearic acid-rich diet improves thrombogenic and atherogenic risk factor profiles in healthy males. Eur J Clin Nutr. 2001;55:88–96.

82. Pimpin L, Wu JH, Haskelberg H, Del Gobbo L, Mozaffarian D. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and Total mortality. PLoS One. 2016;11:e0158118.

83. Neuhouser ML, Howard B, Lu J, Tinker LF, van Horn L, Caan B, et al. A low-fat dietary pattern and risk of metabolic syndrome in postmenopausal women: the Women's Health Initiative. Metabolism. 2012;61:1572–81.

84. Alhazmi A, Stojanovski E, McEvoy M, Garg ML. Macronutrient intakes and development of type 2 diabetes: a systematic review and meta-analysis of cohort studies. J Am Coll Nutr. 2012;31: 243–58.

85. Tinker LF, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med. 2008;168:1500–11.

86. Sluijs I, et al. The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct study. Am J Clin Nutr. 2012;96:382–90.

87. O'Connor LM, et al. Dietary dairy product intake and incident type 2 diabetes: a prospective study using dietary data from a 7-day food diary. Diabetologia. 2014;57:909–17.

88. Zou J, et al. Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health. Cell Host Microbe. 2018;23:41–53 e44.

89. Donovan SM. Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health. Gut Microbes. 2017;8:75–81.

90. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120:1183–96.

91. Tang WH, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013;368:1575–84.

92. Wang Z, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472:57–63.

93. Koeth RA, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19: 576–85.

94. Jonsson AL, Backhed F. Role of gut microbiota in atherosclerosis. Nat Rev Cardiol. 2017;14:79–87.

95. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016;165:1332–45.

96. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Backhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab. 2015;22:658–68.

97. Chassaing B, Raja SM, Lewis JD, Srinivasan S, Gewirtz AT. Colonic microbiota encroachment correlates with dysglycemia in humans. Cell Mol Gastroenterol Hepatol. 2017;4:205–21.

98. Chassaing B, Van de Wiele T, De Bodt J, Marzorati M, Gewirtz AT. Dietary emulsifiers directly alter human microbiota composition and gene expression ex vivo potentiating intestinal inflammation. Gut. 2017;66:1414–27.

99. Chassaing B, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature. 2015;519:92–6.

100. Tapsell LC, Neale EP, Satija A, Hu FB. Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. Adv Nutr. 2016;7:445–54.

101. Castelli WP. Epidemiology of triglycerides: a view from Framingham. Am J Cardiol. 1992;70:3H–9H.

102. Abbasi F, et al. High carbohydrate diets, triglyceride-rich lipoproteins, and coronary heart disease risk. Am J Cardiol. 2000;85:45–8.

103. Torres J, et al. The features of mucosa-associated microbiota in primary sclerosing cholangitis. Aliment Pharmacol Ther. 2016;43: 790–801.

104. Jacobson TA, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol. 2015;9:S1–122 e121.

105. Cordain L, Miller JB, Eaton SB, Mann N. Macronutrient estimations in hunter-gatherer diets. Am J Clin Nutr. 2000;72:1589–92.

106. Cordain L, Eaton SB, Miller JB, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. Eur J Clin Nutr. 2002;56(Suppl 1):S42–52.