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Saturated Fats and Health: A Reassessment and Proposal for Food-based Recommendations: JACC State-of -the-Art Review

Brief title: Saturated fat stigma

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Abstract: The recommendation to limit dietary saturated fatty acid (SFA) intake has persisted despite mounting evidence to the contrary. Most recent meta-analyses of randomized trials and observational studies found no beneficial effects of reducing SFA intake on cardiovascular disease (CVD) and total mortality, and instead found protective effects against stroke. Although SFAs increase low-density lipoprotein (LDL)-cholesterol, in most individuals, this is not due to increasing levels of small, dense LDL particles, but rather larger LDL which are much less strongly related to CVD risk. It is also apparent that the health effects of foods cannot be predicted by their content in any nutrient group, without considering the overall macronutrient distribution. Whole-fat dairy, unprocessed meat, eggs and dark chocolate are SFA-rich foods with a complex matrix that are not associated with increased risk of CVD. The totality of available evidence does not support further limiting the intake of such foods.

Condensed Abstract: Overall, the results of randomized clinical trials and observational cohort studies do not support a rationale for population-wide restriction of dietary saturated fat to a target below current intake levels. Furthermore, lower cardiovascular disease risk cannot be confidently inferred from reduction in plasma low-density lipoprotein cholesterol concentrations induced by such a dietary restriction. Conversely, a reciprocal increase in carbohydrate intake can lead to unfavorable changes in cardiometabolic risk factors. A food-based approach to guiding saturated fat intake is warranted particularly since foods have a complex matrix, and their health effects cannot be predicted by the content of any individual nutrient.

Key Words: cardiovascular disease, diet, saturated fat, food matrix

Abbreviations
Apo = apolipoprotein
CHD = coronary heart disease
CVD = cardiovascular disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MCPD = monochloropropandiol
PURE study = Prospective Urban Rural Epidemiological study
SFA(s) = saturated fatty acid(s).

Introduction

Lowering the consumption of saturated fat has been a central theme of US dietary goals and recommendations since the late 1970s (1). Since 1980, it has been recommended that saturated fatty acid (SFA) intake be limited to less than 10% of total calories as a means of reducing risk for cardiovascular disease (CVD) (1). In 2018, the US Departments of Agriculture and Health and Human Services asked for public comments in response to the following question: "What is the relationship between saturated fat consumption (types and amounts) and risk of CVD in adults?" (2). This review aims to address this important question by examining available evidence on the effects of saturated fats on health outcomes, risk factors and potential mechanisms underlying cardiovascular and metabolic outcomes, which will have implications for the 2020 Dietary Guidelines for Americans.

The relationship between dietary SFAs and heart disease has been studied in more than 75,000 people and summarized in a number of systematic reviews of observational studies and randomized controlled trials. Some meta-analyses find no evidence that reduction in saturated fat consumption may reduce CVD incidence or mortality (3-6), whereas others report a significant – albeit mild – beneficial effect (7,8). Therefore, the basis for consistently recommending a diet low in saturated fat is unclear. The purpose of this review is to critically evaluate the health effects of dietary SFAs and to propose an evidence-based recommendation for a healthy intake of different SFA food sources.

Saturated fatty acids in foods and heterogeneity in their biologic effects

SFAs comprise a heterogeneous group of fatty acids that contain only carbon-to-carbon single bonds (**Table 1**). SFAs differ on the basis of their carbon chain length, and are categorized as short (4–6 carbon atoms), medium (8–12 carbons), long (14–20 carbon atoms) and very-long

(22 or more carbon atoms) chain fatty acids, although these definitions are not standardized. The melting point of individual SFAs increases with increasing chain length. SFAs of ≥10 carbon atoms are solid at room temperature (9). The primary food contributors of individual SFAs in the diet also differ by SFA chain length. For example, the major food sources of short-chain SFAs are dairy fats, while medium and long-chain SFAs are predominantly found in red meat, dairy fats and plant oils (9,10). Notably, food sources of SFAs contain different proportions of various fatty acids (Figure 1) in addition to other nutrients that, as described below, can substantially influence their observed physiological and biologic effects (9,11,12).

SFAs are also classified on the basis of the presence or absence of methyl branches on the carbon chain. For example, fatty acids with no methyl branch (e.g., palmitic, stearic) are classified as straight-chain fatty acids, while those with one or more methyl branches are termed branched-chain fatty acids (e.g., iso-pentadecanoic). Branched-chain SFAs are found primarily in dairy, beef, and other ruminant-derived foods (13), and have similar physicochemical properties as unsaturated fatty acids, in particular lower melting point (or more accurately, phase transition temperature). In experimental animal studies, branched-chain fatty acids alter the microbiota composition in the direction of microorganisms that use these fatty acids in cellular membranes (14), and since they are normal constituents of the healthy human infant gut (15), these fatty acids could play a role in normal colonization.

Circulating SFAs can also be classified based on their origin as exogenous or endogenous. Specifically, circulating levels of even-number chain SFAs such as myristic, palmitic and stearic acid are influenced by dietary intakes (i.e., exogenous sources). Still, they are also endogenously synthesized via *de novo* lipogenesis, a process whereby excess carbohydrate and protein are converted to fatty acids (16). Also, odd-number chain SFAs such as

pentadecanoic and heptadecanoic acids are primarily synthesized by the bacterial flora in the rumen, although animal studies do suggest a potential role of endogenous synthesis through elongation of propionic and heptanoic acids (17). Circulating pentadecanoic and heptadecanoic acid levels correlate with self-reported dairy food intake and have thus been used as objective markers of dairy fat consumption (18-24). Evidence from large observational studies indicates different associations for SFAs of varying physical, chemical and metabolic structures, thereby supporting divergent effects of different SFAs on blood lipids, glucose-insulin homeostasis, insulin resistance and diabetes (25-27).

In discussions of foods, it is useful to distinguish between "fat" and "fatty acids." Saturated fat can be defined as foods that are primarily lipid and solid at temperatures at which they are customarily stored and consumed. Examples are butter and butter-fat, dairy-derived fats contained in cheese, animal fats such as tallow and lard, and plant oils such as cocoa butter (chocolate), coconut oil, palm and palm kernel oils. These fats are solid because they are comprised primarily of "saturated fatty acids," where the term "saturated" designates a specific chemical structural property of fatty acids, specifically a reduced ability to chemically react with I_2 or H_2. The major SFAs in most natural human diets are stearic, palmitic, myristic, and lauric acids with linear chains of 18, 16, 14, and 12 carbon atoms, respectively. Foods from which saturated fats can be derived, such as full-fat dairy, yogurt, and cheese, are usually said to contain saturated fats although, in fact, they contain SFAs. SFAs are chemically defined structures, whereas saturated fats are complex chemical mixtures of all major SFAs in differing proportions, along with many other fatty acids (odd-numbered chain and branched chain SFAs, and unsaturated fatty acids with typically from 1 to 6 double bonds). Other components are present in saturated fats that are not fatty acids at all (e.g., glycerol). The vast majority of human

studies on saturated fats have used foods containing SFA and have compared these to diets with liquid oils, typically of vegetable origin. These, too, contain SFAs but in lower proportions.

Evidence on the health effects of saturated fat

In the 1950s, with the increase in coronary heart disease (CHD) in Western countries, research on nutrition and health has focused on a range of "diet-heart" hypotheses. These included the putative harmful effects of dietary fats (particularly saturated fat) and the lower risk associated with the Mediterranean diet to explain why individuals in the US, Northern Europe and the UK were more prone to CHD. In contrast, those in European countries around the Mediterranean had a lower risk. These ideas were fueled by ecologic studies such as the Seven Countries Study. In recent decades, however, diets have changed substantially in several regions of the world. For example, the very high intake of saturated fat in Finland has decreased considerably, with per capita butter consumption decreasing from ~16 kg/year in 1955 to ~3 kg/year in 2005, and the percent energy from saturated fat decreasing from ~20% in 1982 to ~12% in 2007 (28). Therefore, the dietary guidelines that were developed based on information from several decades ago may no longer be applicable.

A few large and well-designed prospective cohort studies, which used validated questionnaires to assess diet and recorded endpoints in a systematic manner, were initiated recently. They demonstrated that replacement of fat with carbohydrate was not associated with lower risk of CHD and may even be associated with increased total mortality (29-31). Furthermore, a number of systematic reviews of cohort studies have shown no significant association between saturated fat intake and coronary artery disease or mortality, and some even suggested a lower risk of stroke with higher consumption of saturated fat (3,6,32,33). These studies were conducted predominantly in high-income countries (US and Europe) but few were

conducted in other regions of the world, overall representing ~80% of the global population. Likewise, data from the Fatty Acids and Outcomes Research Consortium consisting of 15 prospective cohorts worldwide (33,083 adults who were free of CVD) demonstrated that biomarkers of very long-chain SFA (20:0, 22:0, 24:0) were not associated with total CHD (associations for fatal and non-fatal CHD were similar) and, if anything, levels in plasma/serum (but not phospholipids) may be inversely associated with CHD (34).

Recently, in a large and the most diverse study addressing this question, the PURE (Prospective Urban Rural Epidemiological) study (35) in 135,000 people mostly without CVD from 18 countries on five continents (80% low- and middle-income countries), increased consumption of all types of fat (saturated, monounsaturated and polyunsaturated) was associated with lower risk of death and had a neutral association with CVD. By contrast, a diet high in carbohydrate was associated with higher risk of death, but not with risk of CVD. This study also demonstrated that individuals in the quintile with the highest saturated fat intake (about ~14% of total daily calories) had lower risk of stroke, consistent with the results from meta-analyses of previous cohort studies (36). Furthermore, in a newly-published study of 195,658 participants from the UK Biobank who were followed up for 10.6 years, there was no evidence that saturated fat intake was associated with incident CVD. In contrast, the substitution of polyunsaturated for saturated fat was associated with higher CVD risk. While there was also a positive relation of saturated fat intake with all-cause mortality, this became significant only with intakes well above average consumption (37). Notably, the diet with the lowest hazard ratio for all-cause mortality comprised high fiber (10–30 g/day), protein (14–30%), and monounsaturated fat (10–25%) intakes and moderate polyunsaturated fat (5% to <7%) and starch (20% to <30%) intakes (37). For dietary carbohydrate, as also shown in the PURE study, higher consumption (mainly from

starchy carbohydrates and sugar) was associated with a higher risk of CVD and mortality (37). In the context of contemporary diets, therefore, these observations would suggest there is little need to further limit the intakes of total or saturated fat for most populations. By contrast, restricting carbohydrate intake, particularly refined carbohydrates, may be more relevant today for decreasing the risk of mortality in some individuals, e.g., those with insulin resistance and type 2 diabetes.

Most randomized trials of nutrient intake and clinical events have been relatively small in size. Those that comprise the basis of dietary recommendations to limit dietary saturated fat were conducted some 40 to 50 years ago (38), and have important methodological flaws, as described further below. By far, the largest contemporary study is the WHI (Women's Health Initiative) trial in nearly 49,000 women, which demonstrated that risk for heart attack and stroke was unaffected after 8 years on a low-fat diet in which saturated fat provided 9.5% of total daily energy intake (39). The PREDIMED (Prevención con Dieta Mediterránea) trial compared a standard low-fat diet to a Mediterranean diet supplemented with nuts or olive oil. Despite an increase in total fat intake by 4.5% of total energy (including slightly higher saturated fat consumption), major cardiovascular events and death were significantly reduced compared to the control group (40). Furthermore, in the six most recent systematic reviews and meta-analyses of randomized trials (many of which were small and conducted more than 40 years ago but still comprise the core of current dietary recommendations), results showed that replacing saturated fat with polyunsaturated fat has no significant effect on coronary outcomes (the primary outcome of these trials) or on total mortality (5,7,41). Even if these analyses were to be challenged, for example, based on the criteria for study selection or other lines of evidence (42), an important possibility to consider is that an apparently lower risk of CVD with substitution of SFA by

polyunsaturated fatty acids could be attributed to a possible beneficial effect of polyunsaturated fatty acids and not necessarily to an adverse effect of SFAs.

There is, therefore, a large body of information that raises questions regarding conventional beliefs about SFAs and clinical outcomes. Taken together, the evidence from both cohort studies and randomized trials does not support the assertion that further restriction of dietary saturated fat will reduce clinical events.

Low-density lipoprotein-cholesterol and other biomarkers for assessing the effects of dietary saturated fat on cardiovascular risk

Plasma low-density lipoprotein (LDL)-cholesterol concentration has traditionally been used to assess risk for CVD and to monitor the effects of lifestyle and pharmacological interventions (43). However, there are weaknesses in the argument that a reduction in CVD risk with saturated fat restriction can be inferred from the well-documented capacity of SFAs to increase LDL-cholesterol when substituted for carbohydrate or *cis*-unsaturated fatty acids (12). First, while it is evident that LDL particles play a causal role in the development of CVD (44,45) and that, in general, there is an inverse relationship between change in LDL-cholesterol and CVD benefit (45), a diet-induced reduction of LDL-cholesterol cannot be inferred to result in CVD benefit without having the means for a comprehensive assessment of other biologic effects that may accompany this reduction. In this regard, it is notable that post-menopausal estrogen plus progestin therapy (46) and treatment with several cholesteryl ester transport protein inhibitors (47) result in no CVD benefit despite substantial LDL-cholesterol lowering. In contrast, Mediterranean-style dietary interventions reduce CVD risk without significantly reducing LDL-cholesterol (48,49). Moreover, inhibition of sodium-glucose cotransporter type 2 reduces CVD events despite an increase in LDL-cholesterol levels (50).

A second reason that a reduction in LDL-cholesterol induced by dietary saturated fat restriction cannot be inferred to yield a proportional reduction in CVD risk is the observation that the lower LDL-cholesterol concentration primarily reflects reduced levels of large LDL particle subspecies (51) which are more cholesterol-enriched but have much weaker associations with CVD risk than smaller LDL particles (44,52) and are not reduced by saturated fat restriction in the majority of individuals (51). Moreover, decreasing saturated fat intake also lowers the levels of high-density lipoprotein (HDL)-cholesterol, and hence has a relatively small effect on the ratio of total to HDL-cholesterol (12), which is a robust marker of CVD risk (53). Thus, the potential benefit of dietary restriction of saturated fat could be substantially overestimated by reliance on the change in LDL-cholesterol levels alone. This concern is highlighted in several randomized trials where changes in total and LDL-cholesterol did not inform the impact of changes in dietary SFAs on CVD risk (5,39,40). Likewise, the PURE study reported that the observed hazard ratio for the association between saturated fat and CVD events does not fit a relation with plasma LDL-cholesterol, but rather, is related to the ratio of apolipoprotein B (ApoB) to ApoA1, which is a measure related to atherogenic particle concentration (ApoB is found in LDL and very low-density lipoprotein particles, and ApoA1 is found in HDL particles); in fact, this ratio is lower in those with higher saturated fat intake (35). For these reasons, dietary effects on CVD risk may not be reliably reflected by changes in LDL-cholesterol levels, and it is, therefore, imperative to develop and implement more valid surrogate markers for assessing CVD risk and monitoring diet-induced effects in research and clinical practice.

Modulation of the health effects of saturated fat by dietary carbohydrate intake and insulin resistance

Insulin-resistant states like the metabolic syndrome, prediabetes, and type 2 diabetes affect over 100 million people in the US (54). Insulin resistance manifests functionally as carbohydrate intolerance. For example, insulin-resistant lean subjects demonstrate impaired skeletal muscle glucose oxidation, increased hepatic *de novo* lipogenesis, and atherogenic dyslipidemia after a high-carbohydrate meal (55). Therefore, an individual with insulin resistance has a higher propensity to convert carbohydrate to fat, which will further exacerbate the insulin-resistant phenotype. In addition to standard risk factors (e.g., high triglyceride and low HDL-cholesterol concentrations, increased central adiposity, hypertension, hyperglycemia, hyperinsulinemia), this phenotype also includes increased circulating levels of SFAs and lipogenic fatty acids, such as palmitoleic acid (C16:1).

It is important to distinguish between dietary saturated fat and circulating SFAs. Whereas several reports show no association between increased intake of SFAs and risk for chronic disease (6,29), individuals with higher circulating levels of even-chain SFA (particularly palmitate, C16:0) have increased risk of developing metabolic syndrome (56), diabetes (57-59), CVD (59), heart failure (60), and mortality (61). Notably, however, the amount of circulating SFAs in blood is not related to saturated fat intake from the diet but instead tends to track more closely with dietary carbohydrate intake. For example, an increase in saturated fat consumption by 2–3-fold either has no effect or decreases serum levels of SFA in the context of lower carbohydrate intake (62-65). Decreased accumulation of circulating SFA in response to diets lower in carbohydrate and higher in saturated fat is partially mediated by lower production (through *de novo* lipogenesis), but also increased clearance. Low-carbohydrate diets consistently increase rates of whole-body fat oxidation, which includes the preferred use of SFA for fuel. Thus, the combination of greater fat oxidation and attenuation of hepatic lipogenesis could

explain why a higher dietary saturated fat intake is associated with lower circulating SFA in the context of low carbohydrate intake.

Although palmitic acid is the primary fatty acid product of *de novo* lipogenesis, serum palmitoleic acid (*cis*-C16:1n7), a product of stearoyl CoA desaturase-1 activity, is a better proxy of lipogenesis because of its low content in the diet and the fact that it increases proportionally more than any other fatty acid when carbohydrate is converted to fat (66). Several studies support a close link between increased dietary carbohydrate intake and increased palmitoleic acid levels, an effect that is independent of changes in weight and saturated fat intake (62,63,65). Beyond its importance as a surrogate for *de novo* lipogenesis, palmitoleic acid levels in blood and adipose tissue are consistently and strongly linked to obesity and hypertriglyceridemia (67), hyperglycemia and type 2 diabetes (59,68,69), heart failure (60,70), and CVD mortality (61,70). Furthermore, in non-diabetic men, higher proportions of palmitoleic acid in erythrocyte membranes were significantly associated with worsening of hyperglycemia (68) and development of metabolic syndrome (56,71). In the ARIC (Atherosclerosis Risk in Communities) study, the highest quintile of plasma phospholipid palmitoleic acid was associated with a 67% greater risk of incident heart failure (60) and 52% greater risk of incident ischemic stroke (72) compared with the lowest quintile. Furthermore, in the Physician's Health Study, an increase in plasma palmitoleic acid concentration by 1 standard deviation was associated with a 19% greater odds ratio for coronary artery disease (73) and a 17% greater odds ratio for congestive heart failure (70). Clearly, the impact of dietary SFA on health must consider the important role of carbohydrate intake and the underlying degree of insulin resistance, both of which significantly affect how the body processes saturated fat. This intertwining aspect of

macronutrient physiology and metabolism has been consistently over-looked in previous dietary recommendations.

Tailoring dietary saturated fat intake to cardiometabolic risk

Despite many decades of nutrition research in humans and animal models, the scientific community has not yet reached a consensus on "the one diet" (i.e., low-fat, Mediterranean) that achieves optimal metabolic health for all. The highly heterogeneous outcomes of dietary intervention studies suggest that some individuals have better outcomes for specific diets than others. Therefore, the objective should be to match each person to their individual best diet, which is culturally appropriate (74). Conversely, as discussed above, the once apparently tight link between dietary SFAs and CVD appears to be loosening as a result of mounting evidence that casts doubt on previously established beliefs. Part of the debate relates to the role of variation in specific food sources of SFAs, and part to inter-individual variation in the biologic and clinical effects of these SFAs. Some research over the last two decades has shifted towards the identification of genetic factors underlying the inter-individual differences in response to different dietary fats. The information emerging from these studies suggests that genetic variants may modulate the relationship between dietary SFAs and CVD-related biomarkers (75). In some cases, dietary SFAs enhance the association of genetic variants predisposing to increased CVD risk. This has been shown for the apolipoprotein E (APOE) gene, one of the most extensively researched loci in relation to CVD risk. Specifically, carriers of the less common APOE4 allele have repeatedly shown greater fasting plasma lipid responses to saturated fat in the diet than non-APOE4 carriers (76,77) and similar findings have been reported in the postprandial state (78). These gene by diet interactions have been demonstrated for other CVD risk factors as well, such as obesity. For example, by using a weighted genetic risk score calculated on the basis of 63

obesity-associated variants in two populations, the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) and the Multi-Ethnic Study of Atherosclerosis (MESA), it was shown that dietary SFA intake interacts with the genetic risk score to modulate body mass index (79). In brief, the association between high SFA intake and obesity was apparent only in subjects in the upper tertile of the GRS, i.e. those with stronger genetic predisposition to obesity may be more sensitive to dietary SFA (79). In terms of single locus by diet interactions, one of the most studied ones is the APOA2. A putative functional variant -265T>C (rs5082) within the ApoA2 promoter gene has shown consistent interactions with saturated fat intake to influence the risk of obesity. Specifically, saturated fat intake is associated with higher average body mass index exclusively in subjects who are homozygotes for the less common T allele, but not in those who are heterozygotes for the T allele or homozygotes for the most common C allele (80,81). The potential mechanism for this ApoA2 by saturated fat interaction has been elucidated recently (82). Nevertheless, based on current evidence, and in the absence of randomized dietary intervention studies, the effects of this and other gene-diet interactions (79,83,84) cannot be attributed specifically to SFAs; it is equally likely that the observed effects are related to the overall influence of foods or dietary patterns containing the SFAs. The current information suggests that genetic predisposition modulates the association between saturated fat intake and cardiovascular risk. It is this segment of the population (the SFA-sensitive) where the reduction in SFA may be beneficial and could therefore be recommended.

Obesity and type 2 diabetes are major contributors to the risk of CVD, and recent evidence suggests that the optimal diet for weight control and glycemic control depends in part on the individual's "carbohydrate tolerance" (85), which in turn is determined by insulin resistance and insulin secretion capacity. Carbohydrate tolerance may also vary with level of

exercise/fitness of the individual. Whereas diets lower in total and saturated fat may be optimal for carbohydrate tolerant (i.e. insulin sensitive) individuals, a diet lower in carbohydrates and higher in fiber and fat seems to be optimal for patients with type 2 diabetes (86). In the US, the prevalence of prediabetes among adults was 37 % in 2012 and is projected to rise to 40 % in 2030 (87), accompanied by slight increases in the prevalence of type 2 diabetes. This novel information emphasizes the need for a more personalized and food-based approach in recommending levels of total and saturated fat in the diet.

From single nutrients to whole foods: lessons from ancestral diets, food processing, and the food matrix

The overall health effect of fats and oils depends on the content of SFAs and unsaturated fatty acids but is not merely the sum of the effects of the individual lipid components. Rather, it depends on the interacting effects from naturally occurring components and from unhealthy compounds introduced by processing. These compounds are often overlooked in the assessment of health effects of oils and fats, and the risk of this is illustrated by the "*trans*-fat" story. The substitution of traditional dairy fats with vegetable oils has a long history, dating back at least to the 1870s US legislation, and has driven the saturated *vs* unsaturated fat debate (88). By the 1950s, the major component of 20th-century vegetable oils, dietary polyunsaturated linoleic acid, was widely recognized to decrease plasma cholesterol concentrations, and hence surmised to have a more favorable effect on atherosclerosis than saturated fat, which could raise cholesterol. However, despite its high content of SFAs, dairy fat does not promote atherogenesis (89). The ability of adult humans to digest the sugar unique to milk, lactose, evolved separately numerous times (90,91), demonstrating unequivocally that the ancestors of many modern humans required continuous dairy consumption for survival to reproductive age. Bovine (92), goat (93) and sheep

(94) domestication started around the same time, about 10,000 years ago, coinciding with the emergence of lactase persistence, i.e., the ability to digest lactose. The saturated fat of the meat of these species was likely a major contributor to human diets, along with fruit oils – where available – such as olive, avocado, and palm, all low in polyunsaturated fat, with the latter also being high in saturated fat. Coconut fat would have been the only abundant lipid-rich seed, and that too is highly saturated. Seed oil consumption, which now dominates the food supply, would have been negligible back then and until the advent of industrialized fat extraction in recent centuries. These historical facts demonstrate that saturated fats were an abundant, key part of the ancient human diet.

By the 1970s, many experimental studies in animal models were conducted with dietary coconut oil of unspecified origin, which reliably caused dramatic increases in hepatic and blood cholesterol in rodents; this was taken as evidence that dietary SFAs are inherently atherogenic (95,96). However, coconut oils of the era were usually highly processed and often fully hydrogenated. Recent gentle preparation methods yield “virgin” coconut oils (97) that do not raise LDL-cholesterol compared to customary diets and have similar effects compared to olive oil in humans (98). Studies in rodents demonstrated that while highly processed (“refined-bleached-deodorized”) coconut oil raises serum cholesterol, virgin coconut oil does not (99,100).

In the last decade, the concept of process contaminants generated from high-temperature treatment of oils in the presence of trace metals has come to the fore. The triglyceride derivatives glycidyl and monochloropropandiol (MCPD) esters are common contaminants, well-studied for their carcinogenic properties in rodents (101). Recently, the metabolic effects of virgin coconut oil and of oil processing on human liver cells were investigated. A method was developed to enable cells to take up whole oil, including process contaminants. Oil was passed through

successive stages of processing, starting with (a) virgin oil, which was then subjected to (b) free fatty acid removal, (c) bleaching, and (d) deodorization. With increasing processing, cellular cholesterol increased, HMGCoA reductase expression increased and the activity of the cholesterol oxidation enzyme CYP7A1 decreased. A major chemical alteration in the oil was the increase in both glycidyl and MCPD esters. Remarkably, addition of either glycidol or MCPD to virgin coconut oil partially recapitulated the effects on cellular cholesterol metabolism (102). Experimental rodent studies using oxidation-resistant linoleic acid, dideuterated in the *bis* allylic position, support the hypothesis that oxidation products and not specific fatty acids cause plaque formation in transgenic mouse models (103).

Human studies that assume all foods high in saturated fats are similarly atherogenic come, in many cases, from an era prior to the recognition of process contaminants. The American Heart Association recently issued a Presidential Recommendation to avoid saturated fats, based on studies conducted in the 1960s and the 1970s (38). Three studies conducted in Europe (Oslo, Norway (104); London, UK (105); and Helsinki, Finland (106)) and one study conducted in the US (Los Angeles (107)) comprised the core evidence chosen on the basis of the quality of study design, execution, and adherence. These studies were purported to have compared high saturated with high polyunsaturated fat diets over at least a 2-year period, and to have included biomarkers of adherence and collection of CVD events. Key quality parameters were that the diets did not include *trans* unsaturated fats as a major component and that the dietary intake of the comparison groups was controlled. However, careful inspection of the diets indicates that this was not the case. First, partially hydrogenated fish oils were major constituents of European (and Canadian) margarines and shortenings of this era (88). Hydrogenated fish oils are rich in a wide array of *trans* monoenes and polyenes not present in partially hydrogenated

vegetable oils (108). The Oslo study, for instance, explicitly estimated intake of partially hydrogenated fish oil at 40–50 g per day (109). Secondly, the three European studies all used customary diets as comparisons (105-107,110), which were substituted for experimental diets. One can thus infer that the European diets are tests of polyunsaturated fats against *trans*-plus-saturated fats, which means that any effects described cannot be assigned to saturated fats alone. Dropping these three studies from a meta-analysis leaves the US trial, which did not find a significant difference between groups for its primary CVD outcome (38). We consider this to be the proper interpretation of these studies.

Taken together, these observations strongly support the conclusion that the healthfulness of fats is not a simple function of their content in SFA but a result of the various components in the food, often referred to as the "food matrix". While the various SFAs have distinct metabolic roles (9,11,12), ample evidence is available from research on specific foods that other food components and the food matrix likely dominate over saturated fat content, as discussed in the following section. Recommendations should, therefore, emphasize food-based strategies that translate for the public into understandable, consistent and robust recommendations for healthy dietary patterns.

Health effects of differing food sources of saturated fatty acids

Yogurt and cheese

Dairy is the major source of SFA in most diets, and major dietary guidelines recommend low-fat or fat-free versions of dairy foods to limit SFA intake. However, food-based meta-analyses consistently find that cheese and yogurt intakes are inversely associated with CVD risk (11,111-113). Whole-fat dairy may also be protective against type 2 diabetes (3,114,115). Using circulating biomarkers of dairy intake i.e., plasma levels of C17:0, an inverse association with

CHD was found (116); whereas for other biomarkers (15:0 and 17:0, but also the natural ruminant *trans*-16:1n7), a neutral association was found with total mortality (11). Moreover, a pooled individual-level analysis of nearly 65,000 participants across international cohorts found that plasma and tissue levels of odd-chain SFA (15:0, 17:0) and natural ruminant *trans* fatty acids (*trans*-16:1n7), all of which reflect dairy fat consumption, were associated with lower risk of diabetes (117). Cheeses and yogurts consist of complex food matrices and major components include different fatty acids, proteins (whey and casein), minerals (calcium, magnesium, phosphate), sodium, and phospholipid components of milk fat globule membrane (115). Yogurt and cheese also contain probiotics and bacterially-produced bioactive peptides, short-chain fatty acids, and vitamins such as vitamin K2. The complex matrix and components of dairy may explain why the effect of dairy food consumption on CVD cannot be explained and predicted by its content in SFA.

Eggs

Eggs can be a significant contributor to total SFA intake. However, eggs are also nutrient-dense, providing important nutrients that are not widely available in other foods. Well-designed prospective, population-based studies have provided conflicting evidence on the relationship between egg consumption and CVD (118,119), but a number of meta-analyses have found that higher egg consumption is not associated with risk of CHD and may be associated with lower risk of stroke (120,121). Moreover, randomized controlled trials have found neutral or beneficial effects on cardiometabolic risk markers in people with prediabetes and type 2 diabetes (122).

Dark chocolate

Dark chocolate contains stearic acid (C18:0), which has a neutral effect on CVD risk. However, chocolate contains other nutrients that may be more important for CVD and type 2 diabetes than its SFA content. Experimental and observational studies suggest that dark chocolate has multiple beneficial health effects, including potential anti-oxidative, anti-hypertensive, anti-inflammatory, anti-atherogenic, and anti-thrombotic properties, as well as preventive effects against CVD and type 2 diabetes (123-125).

Meat

Although intake of processed meat has been associated with increased risk of CHD, intake of unprocessed red meat is not, which indicates that the SFA content of meat is unlikely to be responsible for this association (126). A meta-analysis found no differences in cardiometabolic risk factors between groups of individuals consuming more *vs* fewer than 0.5 daily servings of meat (127). Prospective cohort studies also depict stronger associations of processed meat consumption, compared to unprocessed red meat consumption, in relation to type 2 diabetes. Another meta-analysis found that processed meat gave rise to a 19% higher risk of type 2 diabetes but red meat consumption was not significantly associated with diabetes (127). The collective evidence from randomized controlled trials suggests there is low- to very-low-certainty evidence supporting that diets restricted in red meat have a significant effect on major cardiometabolic outcomes (128). However, one analysis found a small but significant association of processed meat, unprocessed red meat, and poultry consumption with a higher risk of incident CVD, and a mild association of processed or unprocessed red meat with a higher risk of all-cause mortality (129). Nevertheless, meat is a major source of protein, bioavailable iron, minerals and vitamins. In modest amounts, unprocessed red meat constitutes an important part of the diet for the elderly and low-income populations in many developing countries (130).

Research gaps and directions

The dietary recommendation to reduce intake of SFAs without considering specific fatty acids and food sources is not aligned with the current evidence base. As such, it may distract from other more effective food-based recommendations, and may also cause a reduction in the intake of nutrient-dense foods (such as eggs, dairy, and unprocessed meat) that may help decrease the risk of CVD, type 2 diabetes, and other non-communicable diseases, but also malnutrition, deficiency diseases and frailty, particularly among "at-risk" groups. Furthermore, based on several decades of experience, a focus on total SFA has had the unintended effect of misleadingly guiding governments, consumers, and industry toward foods low in SFA but rich in refined starch and sugar. All guidelines should consider the types of fatty acids and, more importantly, the diverse foods containing SFA, which may possess harmful, neutral, or even beneficial effects in relation to major health outcomes (Figure 2). We strongly recommend a more food-based translation of how to achieve a healthy diet and reconsidering the guidelines on reduction in total SFA. Indeed, a focus on gently processed foods is more likely to emerge as a key factor until much more is known about the health effects of specific process contaminants so that their levels can be minimized.

Conclusions

The long-standing bias against foods rich in saturated fats should be replaced with a view towards recommending diets consisting of healthy foods. What steps could shift the bias? We suggest the following measures: 1) Enhance the public's understanding that many foods (e.g., whole-fat dairy) that play an important role in meeting dietary and nutritional recommendations may also be rich in saturated fats. 2) Make the public aware that low-carbohydrate diets high in saturated fat, which are popular for managing body weight, may also improve metabolic disease

endpoints in some individuals, but emphasize that health effects of dietary carbohydrate – just like those of saturated fat – depend on the amount, type and quality of carbohydrate, food sources, degree of processing, etc. 3) Shift focus from the current paradigm that emphasizes the saturated fat content of foods as key for health, to one that centers on specific traditional foods, so that nutritionists, dietitians, and the public can easily identify healthful sources of saturated fats. 4) Encourage committees in charge of making macronutrient-based recommendations to translate those recommendations into appropriate, culturally sensitive dietary patterns tailored to different populations.

Highlights

- The US Dietary Guidelines recommend the restriction of saturated fatty acid (SFA) intake to less than 10% of calories to reduce cardiovascular disease (CVD).
- Different SFAs have different biologic effects, which are further modified by the food matrix and the carbohydrate content of the diet.
- Several foods relatively rich in SFAs, such as whole-fat dairy, dark chocolate and unprocessed meat, are not associated with increased CVD or diabetes risk.
- There is no robust evidence that current population-wide arbitrary upper limits on saturated fat consumption in the US will prevent CVD or reduce mortality.

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Figure Legends

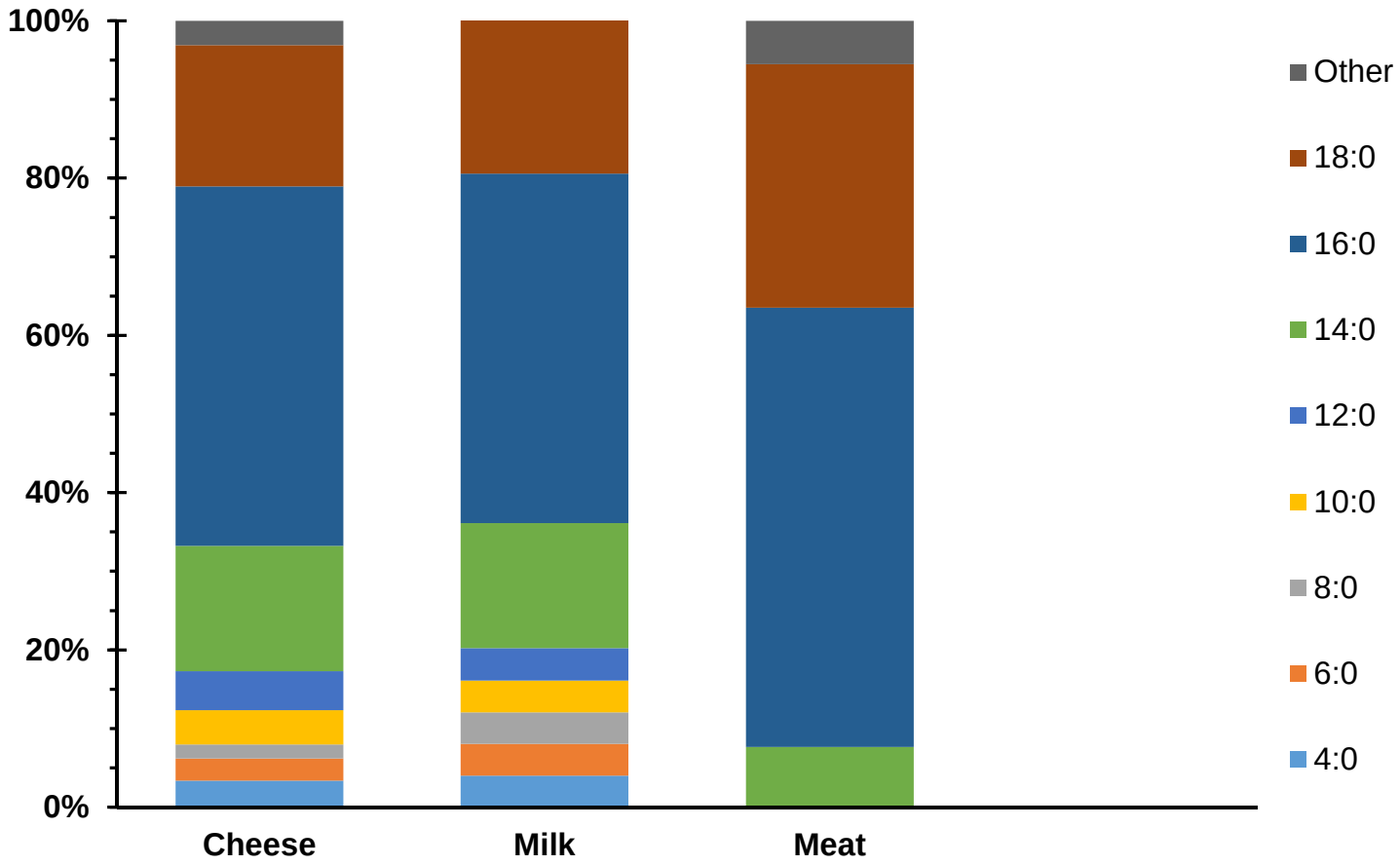
Figure 1. Saturated fatty acid profiles of major food sources, i.e., whole-fat cheese, whole-fat milk, and red meat. These data indicate that food sources of saturated fat contain different proportions of short-, medium-, and long-chain saturated fatty acids; these fatty acids have diverse physical and chemical characteristics, and differing effects on various blood lipids and lipoproteins (9,11,12). Data from the US Department of Agriculture, FoodData Central (https://fdc.nal.usda.gov/).

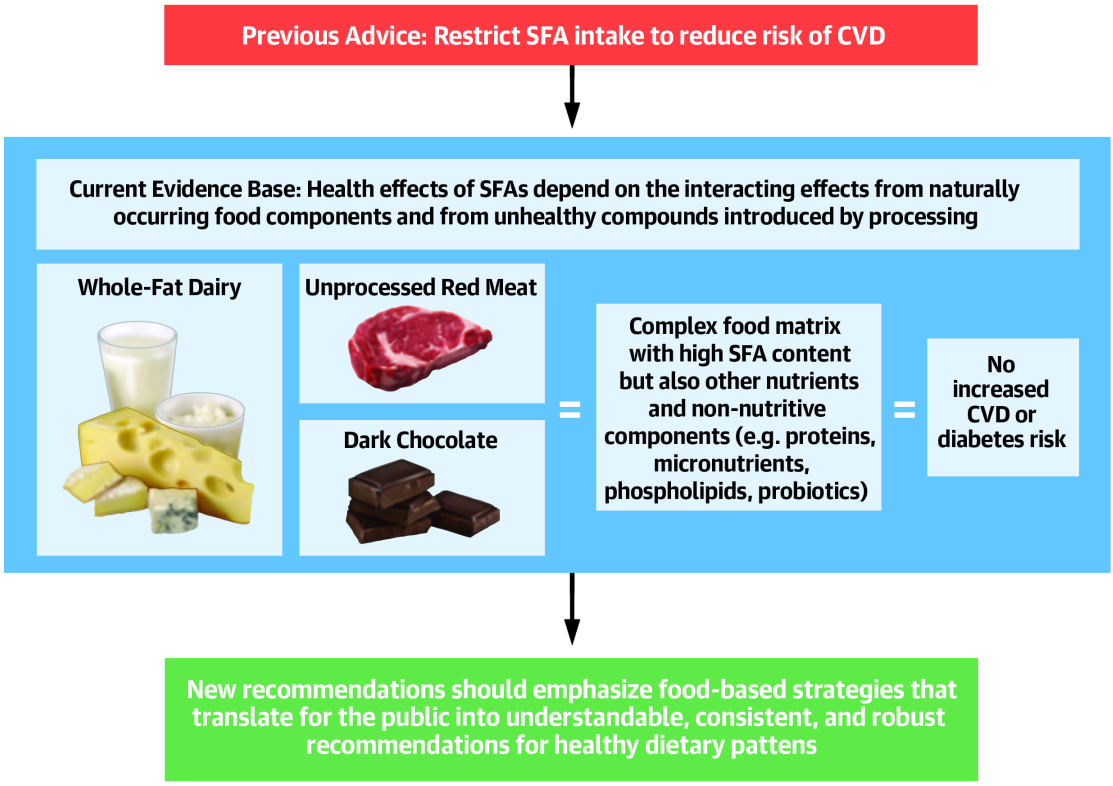
Central illustration: Available evidence discussed in this manuscript supports the rationale for replacing dietary saturated fat targets with food-based guidelines for saturated fat intake.

Table 1. Major naturally occurring saturated fatty acids.

Abbreviation	Common or systematic name	Carbon chain length	Major dietary sources
4:0	Butyric	Short	Dairy foods
6:0	Caproic	Short	Dairy foods
8:0	Caprylic	Medium	Dairy foods, coconut and palm kernel oils
10:0	Capric	Medium	Dairy foods
12:0	Lauric	Medium	Coconut milk and oil
14:0	Myristic	Long	Dairy foods
15:0	Pentadecanoic	Long	Red meat, dairy foods, oils
16:0	Palmitic	Long	Red meat, dairy foods, palm oil
17:0	Heptadecanoic	Long	Red meat, dairy foods
18:0	Stearic	Long	Dairy foods, meat, chocolate

C15:0 and C17:0 are predominantly obtained from foods sources, whereas circulating levels of all other saturated fatty acids are influenced by both dietary intake and endogenous metabolism.




Previous Advice: Restrict SFA intake to reduce risk of CVD
Current Evidence Base: Health effects of SFAs depend on the interacting effects from naturally occurring food components and from unhealthy compounds introduced by processing
Whole-Fat Dairy
Unprocessed Red Meat
Dark Chocolate
=
Complex food matrix with high SFA content but also other nutrients and non-nutritive components (e.g. proteins, micronutrients, phospholipids, probiotics)
=
No increased CVD or diabetes risk
New recommendations should emphasize food-based strategies that translate for the public into understandable, consistent, and robust recommendations for healthy dietary pattens