

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Saturated Fats and Health: A Reassessment and Proposal for Food-Based Recommendations



JACC State-of-the-Art Review

Arne Astrup, MD, DMSc,^a Faidon Magkos, PhD,^a Dennis M. Bier, MD,^b J. Thomas Brenna, PhD,^{c,d,e}
Marcia C. de Oliveira Otto, PhD,^f James O. Hill, PhD,^g Janet C. King, PhD,^h Andrew Mente, PhD,ⁱ Jose M. Ordovas, PhD,^j
Jeff S. Volek, PhD, RD,^k Salim Yusuf, DPHIL,^l Ronald M. Krauss, MD^{l,m}

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 particles, 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, 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. (J Am Coll Cardiol 2020;76:844-57) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

From the ^aDepartment of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark; ^bChildren's Nutrition Research Center, Baylor College of Medicine, Houston, Texas; ^cDepartment of Pediatrics, Dell Pediatric Research Institute, University of Texas at Austin, Austin, Texas; ^dDepartment of Chemistry, Dell Pediatric Research Institute, University of Texas at Austin, Austin, Texas; ^eDepartment of Nutrition, Dell Pediatric Research Institute, University of Texas at Austin, Austin, Texas; ^fDepartment of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center at Houston, Houston, Texas; ^gDepartment of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, Alabama; ^hDepartment of Nutritional Sciences and Toxicology, University of California-Berkeley, Berkeley, California; ⁱPopulation Health Research Institute; McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; ^jDepartment of Nutrition and Genomics, Human Nutrition Research Center of Aging, Tufts University, Boston, Massachusetts; ^kDepartment of Human Sciences, Ohio State University, Columbus, Ohio; ^lDepartment of Pediatrics, University of California-San Francisco, San Francisco, California; and the ^mDepartment of Medicine, University of California-San Francisco, San Francisco, California. The evidence discussed in this paper has been presented by the authors during the Expert Workshop "Saturated Fat and Health: A Nutrient or Food Approach?" held in February 2020 in Washington, DC. The workshop was funded by the Nutrition Coalition—a nonprofit nonpartisan educational organization whose primary goal is ensuring that U.S. nutrition policy is based on rigorous scientific evidence—in part with a generous grant from philanthropists Robert G. and Sue Douthit O'Donnell, of California. The sponsors had no role in preparing or reviewing the manuscript before submission. Dr. Astrup has received research funding from Danish Dairy Foundation, Arla Foods Amba, and the European Milk Foundation; has received speaker honoraria for the Expert Symposium on the Dairy Matrix 2016 sponsored by the European Milk Foundation; and has served on the advisory board and as a consultant for McCain Foods Limited and Weight Watchers. Dr. Bier has served as a consultant and/or received lecture fees and/or reimbursements for travel, hotel and other expenses from the International Life Sciences Institute, the International Council on Amino Acid Science, Nutrition and Growth Solutions, Ajinomoto, the Lorenzini Foundation, the CrossFit Foundation, the International Glutamate Technical Committee, Nestlé S.A., Ferrero SpA, Indiana University, Mallinckrodt Pharmaceuticals, the Infant Nutrition Council of America, and the Israel Institute. Dr. Brenna has received research funding from the National



Listen to this manuscript's
audio summary by
Editor-in-Chief
Dr. Valentin Fuster on
JACC.org.

Lowering the consumption of saturated fat has been a central theme of U.S. dietary goals and recommendations since the late 1970s (1). Since 1980, it has been recommended that saturated fatty acid (SFA) intake be limited to <10% of total calories as a means of reducing risk for cardiovascular disease (CVD) (1). In 2018, the U.S. 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 about 400,000 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.

SFAs 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-chain (4 to 6 carbon atoms), medium-chain (8 to 12 carbon atoms), long-chain (14 to 20 carbon atoms), and very long-chain (22 or more carbon atoms) 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 subsequently, 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 1 or more methyl branches are termed branched-chain fatty acids (e.g., isopentadecanoic). Branched-chain SFAs are found primarily in dairy, beef, and other ruminant-derived

ABBREVIATIONS AND ACRONYMS

apo	= apolipoprotein
APOE	= apolipoprotein E
CHD	= coronary heart disease
CVD	= cardiovascular disease
HDL	= high-density lipoprotein
LDL	= low-density lipoprotein
MCPD	= monochloropropanediol
SFA	= saturated fatty acid

Cattlemen's Beef Association/North Dakota Beef Council; has received panel participation honorarium from Dairy Management (2017); and is a shareholder in Retrope. Dr. Hill has received research funding from the National Cattlemen's Beef Association; has served as a member of the scientific advisory committee of the Milk Producers Education Program (Milk PEP) and the health and wellness advisory board for General Mills; and is a trustee of the International Life Science Institute. Drs. Mente and Yusuf have received research funding from the Dairy Farmers of Canada and the National Dairy Council to analyze data on dairy consumption and health outcomes in the PURE study, which is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute, and more than 70 other sources (government and pharmaceutical). Dr. Ordovas has received research funding from the U.S. Department of Agriculture on personalized nutrition, and Archer Daniels Midland on probiotics; and has served on the scientific advisory board or as a consultant for Nutrigenomix, the Predict Study, GNC, and Weight Watchers. Dr. Volek has received research funding from the Lotte and John Hecht Memorial Foundation, Metagenics, National Dairy Council/Dutch Dairy Organization, Malaysian Palm Board, and Pruvit Ventures; has received royalties for books on ketogenic diets; has served on the scientific advisory board for Virta Health, UCAN, Advancing Ketogenic Therapies, Cook Keto, Axxcess Global, and Atkins Nutritionals; owns equity in PangeaKeto and Virta Health; and is founder of and chief science officer for Virta Health. Dr. Krauss has received research funding from Dairy Management; has served on the scientific advisory board for Virta Health and Day Two; and has a licensed patent for a method of lipoprotein particle measurement. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [JACC author instructions page](#).

HIGHLIGHTS

- The U.S. Dietary Guidelines recommend the restriction of SFA intake to <10% of calories to reduce 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 United States will prevent CVD or reduce mortality.

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 because 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 fats can be defined as foods that are primarily lipids, and solid at temperatures at which they are customarily stored and consumed. Examples are butter and butterfat, dairy-derived fats contained in cheese, animal fats such as tallow and lard, and plant oils such as cocoa butter (chocolate), coconut oil, and palm and palm kernel oils. These fats are solid because they comprise primarily SFAs, in which the term *saturated* designates a specific chemical structural property of fatty acids, specifically a reduced ability to chemically react with I₂ or H₂. 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 number-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 SFAs and have compared these with 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 focused on a range of “diet-

TABLE 1 Major Naturally Occurring Saturated Fatty Acids

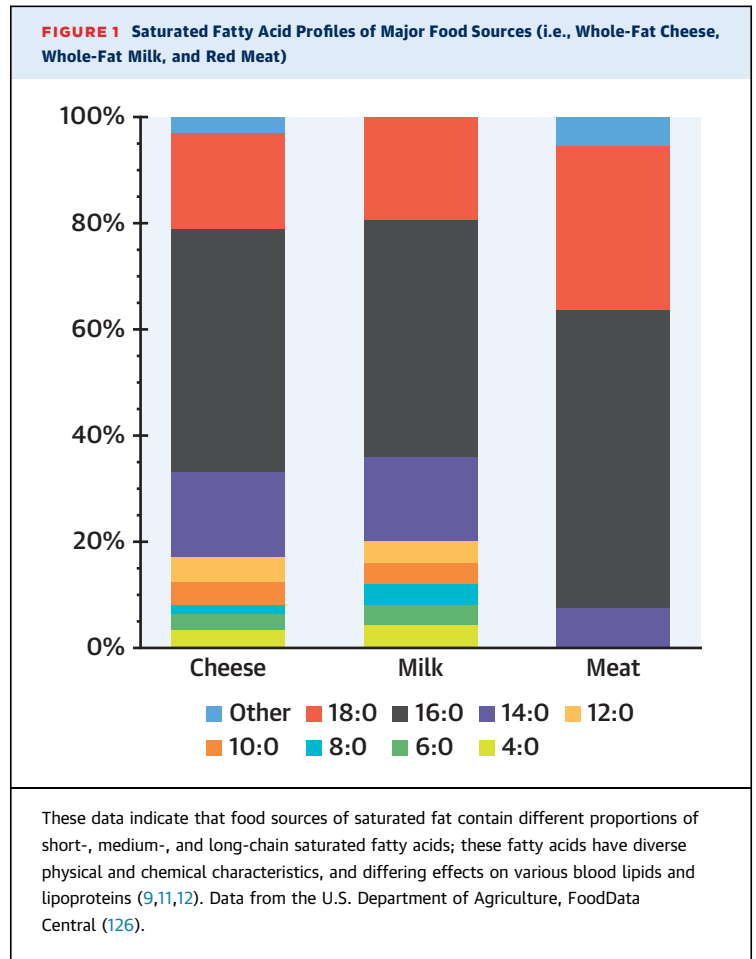
Abbreviation	Common or Systematic Name	Carbon Chain Length	Major Dietary Sources
4:0	Butyric	Short	Dairy foods
6:0	Caproic	Short	Dairy foods
8:0	Caprylic	Medium	Dairy foods, coconut and palm kernel oils
10:0	Capric	Medium	Dairy foods
12:0	Lauric	Medium	Coconut milk and oil
14:0	Myristic	Long	Dairy foods
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 food sources, whereas circulating levels of all other saturated fatty acids are influenced by both dietary intake and endogenous metabolism.

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 United States, Northern Europe, and the United Kingdom 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 (United States 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 nonfatal CHD were similar), and if anything, levels in plasma or 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 5 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. Although 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 to 30 g/day), protein (14% to 30%), and monounsaturated fat (10% to 25%) intakes and moderate polyunsaturated fat (5% to <7%) and starch (20% to <30%) intakes (37).

For dietary carbohydrate, 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 subsequently. 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 PRE-DIMED (Prevención con Dieta Mediterránea) trial compared a standard low-fat diet with 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 with the control group (40). Furthermore, in the 6 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 SFAs 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, although it is evident that LDL particles play a causal role in the development of CVD (44,45) and that, in general, there is a relationship between lowering of 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 postmenopausal estrogen plus progestin therapy (46) and treatment with several cholesterol 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). Large LDLs are more cholesterol-enriched but have much weaker associations with CVD risk than do smaller LDL particles (44,52), which 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 in which 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 (apo B) to apo A1, which is a measure related to atherogenic particle concentration (apo B is found in LDL and very-low-density lipoprotein particles, and apo A1 is found in HDL particles); in fact, this ratio was 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 therefore it is 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, pre-diabetes, and type 2 diabetes affect >100 million people in the United States (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 SFAs (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- to 3-fold

either has no effect or decreases serum levels of SFAs in the context of lower carbohydrate intake (62-65). Decreased accumulation of circulating SFAs 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 SFAs 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 SFAs 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 body 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 nondiabetic 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 SD 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 SFAs 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 overlooked 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 from specific diets than do others. Therefore, the objective should be to match each person to their individual best diet, which is culturally appropriate (74). Conversely, as discussed previously, 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 relates to interindividual variation in the biologic and clinical effects of these SFAs. Some research over the last 2 decades has shifted toward the identification of genetic factors underlying the interindividual 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 apo 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 do 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 2 populations, the GOLDN (Genetics of Lipid Lowering Drugs and Diet Network) and the MESA (Multi-Ethnic Study of Atherosclerosis), 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 genetic risk score (i.e., those with stronger genetic pre-disposition to obesity may be more sensitive to dietary SFAs) (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 apo A2 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 apo A2 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 pre-disposition modulates the association between saturated fat intake and cardiovascular risk. It is this segment of the population (the SFA-sensitive) in which the reduction in SFA intake 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 or 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 United States, the prevalence of pre-diabetes 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 U.S. legislation, and has driven the saturated versus 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 with customary diets and have similar effects compared with 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 monochloropropanediol (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: 1) virgin oil; which was then subjected to 2) free fatty acid removal; 3) bleaching; and 4) 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, di-deuterated 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; London, United Kingdom; and Helsinki, Finland) (104-106) and 1 study conducted in the United States (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 to 50 g/day (109). Second, the 3 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*-

CENTRAL ILLUSTRATION Shifting From Saturated Fatty Acid-Based to Food-Based Dietary Guidelines for Cardiovascular Health

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 patterns

Astrup, A. et al. *J Am Coll Cardiol.* 2020;76(7):844-57.

Available evidence discussed in this paper supports the rationale for replacing dietary saturated fat targets with food-based guidelines for saturated fat intake. CVD = cardiovascular disease; SFA = saturated fatty acid.

plus-saturated fats, which means that any effects described cannot be assigned to saturated fats alone. Dropping these 3 studies from a meta-analysis leaves the U.S. 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 SFA content, but rather is a result of the various components in the food, often referred to as the “food matrix.” Although 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 SFAs 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 SFAs (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 the 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 SFAs.

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, antihypertensive, anti-inflammatory, antiatherogenic, and antithrombotic properties, as well as preventive effects against CVD and type 2 diabetes (118-120).

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 (121). A meta-analysis found no differences in cardiometabolic risk factors between groups of individuals consuming more versus fewer than 0.5 daily servings of meat (122). Prospective cohort studies also depict stronger associations of processed meat consumption, compared with 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 (122). 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 (123). 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 (124). 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 (125).

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 (e.g., dairy, unprocessed meat) that may help decrease not only the risk of CVD, type 2 diabetes, and other noncommunicable diseases, but also malnutrition, deficiency diseases, and frailty, particularly among “at-risk” groups. Furthermore, based on several decades of experience, a focus on total SFAs has had the unintended effect of misleadingly guiding governments, consumers, and industry toward foods low in SFAs but rich in refined starch and sugar. All guidelines should consider the types of fatty acids and, more importantly, the diverse foods containing SFAs, which may possess harmful, neutral, or even beneficial effects in relation to major health outcomes (Central Illustration). We strongly recommend a more food-based translation of how to achieve a healthy diet and reconsidering the guidelines on reduction in total SFAs. 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 toward 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; and 4) encourage committees in charge of making macronutrient-based recommendations to translate those recommendations into appropriate, culturally sensitive dietary patterns tailored to different populations.

ADDRESS FOR CORRESPONDENCE: Dr. Arne Astrup, Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Rolighedsvej 26, 1958 Frederiksberg C, Denmark. E-mail: ast@nexs.ku.dk. Twitter: [@romax43](https://twitter.com/romax43).

REFERENCES

- Mozaffarian D, Rosenberg I, Uauy R. History of modern nutrition science—implications for current research, dietary guidelines, and food policy. *BMJ* 2018;361:k2392.
- Harcombe Z. US dietary guidelines: is saturated fat a nutrient of concern? *Br J Sports Med* 2019;53:1393-6.
- de Souza RJ, Mente A, Maroleanu A, 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.
- 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.
- Ramsden CE, Zamora D, Majchrzak-Hong S, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). *BMJ* 2016;353:i1246.
- 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.
- Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* 2015;6:CD011737.
- Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010;7:e1000252.
- Ratnayake WM, Galli C. Fat and fatty acid terminology, methods of analysis and fat digestion and metabolism: a background review paper. *Ann Nutr Metab* 2009;55:8-43.
- Hu FB, Stampfer MJ, Manson JE, 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.
- de Oliveira Otto MC, Mozaffarian D, Kromhout D, 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.
- Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;77:1146-55.
- Ran-Ressler RR, Bae S, Lawrence P, Wang DH, Brenna JT. Branched-chain fatty acid content of foods and estimated intake in the USA. *Br J Nutr* 2014;112:565-72.
- Ran-Ressler RR, Khailova L, Arganbright KM, et al. Branched chain fatty acids reduce the incidence of necrotizing enterocolitis and alter gastrointestinal microbial ecology in a neonatal rat model. *PLoS One* 2011;6:e29032.
- Ran-Ressler RR, Devapatla S, Lawrence P, Brenna JT. Branched chain fatty acids are constituents of the normal healthy newborn gastrointestinal tract. *Pediatr Res* 2008;64:605-9.
- Wu JH, Lemaitre RN, Imamura F, et al. Fatty acids in the de novo lipogenesis pathway and risk of coronary heart disease: the Cardiovascular Health Study. *Am J Clin Nutr* 2011;94:431-8.
- Pfeuffer M, Jaudszus A. Pentadecanoic and heptadecanoic acids: Multifaceted odd-chain fatty acids. *Adv Nutr* 2016;7:730-4.
- Baylin A, Kabagambe EK, Siles X, Campos H. Adipose tissue biomarkers of fatty acid intake. *Am J Clin Nutr* 2002;76:750-7.
- Brevik A, Veierod MB, Drevon CA, Andersen LF. Evaluation of the odd fatty acids 15:0 and 17:0 in serum and adipose tissue as markers of intake of milk and dairy fat. *Eur J Clin Nutr* 2005;59:1417-22.
- de Oliveira Otto MC, Nettleton JA, Lemaitre RN, et al. Biomarkers of dairy fatty acids and risk of cardiovascular disease in the Multi-ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2013;2:e000092.
- Smedman AE, Gustafsson IB, Berglund LG, Vessby BO. Pentadecanoic acid in serum as a marker for intake of milk fat: relations between intake of milk fat and metabolic risk factors. *Am J Clin Nutr* 1999;69:22-9.
- Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr* 2007;86:929-37.
- Warensjo E, Jansson JH, Cederholm T, et al. Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study. *Am J Clin Nutr* 2010;92:194-202.
- Wolk A, Vessby B, Ljung H, Barrefors P. Evaluation of a biological marker of dairy fat intake. *Am J Clin Nutr* 1998;68:291-5.
- Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler Thromb* 1992;12:911-9.
- 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.
- Zhu Y, Tsai MY, Sun Q, et al. A prospective and longitudinal study of plasma phospholipid saturated fatty acid profile in relation to cardiometabolic biomarkers and the risk of gestational diabetes. *Am J Clin Nutr* 2018;107:1017-26.
- Puska P. Fat and heart disease: yes we can make a change—the case of North Karelia (Finland). *Ann Nutr Metab* 2009;54 Suppl 1:33-8.
- Jakobsen MU, O'Reilly EJ, Heitmann BL, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009;89:1425-32.
- Hu FB. Are refined carbohydrates worse than saturated fat? *Am J Clin Nutr* 2010;91:1541-2.
- Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr* 2000;71:1455-61.
- Kang ZQ, Yang Y, Xiao B. Dietary saturated fat intake and risk of stroke: Systematic review and dose-response meta-analysis of prospective

cohort studies. *Nutr Metab Cardiovasc Dis* 2020; 30:179-89.

33. Zhu Y, Bo Y, Liu Y. Dietary total fat, fatty acids intake, and risk of cardiovascular disease: a dose-response meta-analysis of cohort studies. *Lipids Health Dis* 2019;18:191.

34. Korat AVA, Qian F, Imamura F, et al. Biomarkers of very long-chain saturated fatty acids and incident coronary heart disease: Prospective evidence from 15 cohorts in the Fatty Acids and Outcomes Research Consortium (Abstract P414). *Circulation* 2020;141:AP414.

35. Mente A, Dehghan M, Rangarajan S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol* 2017;5:774-87.

36. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 2017;390:2050-62.

37. Ho FK, Gray SR, Welsh P, et al. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. *BMJ* 2020;368:m688.

38. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: A presidential advisory from the American Heart Association. *Circulation* 2017;136:e1-23.

39. Howard BV, Van Horn L, Hsia J, 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.

40. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378: e34.

41. 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.

42. Forouhi NG, Krauss RM, Taubes G, Willett W. Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. *BMJ* 2018;361:k2139.

43. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2960-84.

44. Boren J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2020;41: 2313-30.

45. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic,

epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;38: 2459-72.

46. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2002;349:523-34.

47. Armitage J, Holmes MV, Preiss D. Cholesteryl ester transfer protein inhibition for preventing cardiovascular events: JACC review topic of the week. *J Am Coll Cardiol* 2019;73: 477-87.

48. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.

49. Fito M, Guxens M, Corella D, et al. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med* 2007;167:1195-203.

50. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. *Circ Res* 2018;122:1439-59.

51. Bergeron N, Chiu S, Williams PT, S MK, Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. *Am J Clin Nutr* 2019;110:24-33 [erratum in: *Am J Clin Nutr* 2019;110:783].

52. Krauss RM. All low-density lipoprotein particles are not created equal. *Arterioscler Thromb Vasc Biol* 2014;34:959-61.

53. Lemieux I, Lamarche B, Couillard C, et al. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. *Arch Intern Med* 2001;161:2685-92.

54. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* 2015;314: 1021-9.

55. Petersen KF, Dufour S, Savage DB, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc Natl Acad Sci U S A* 2007;104:12587-94.

56. Warensjo E, Riserus U, Vessby B. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. *Diabetologia* 2005;48:1999-2005.

57. Forouhi NG, Koulman A, Sharp SJ, 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.

58. Patel PS, Sharp SJ, Jansen E, et al. Fatty acids measured in plasma and erythrocyte-membrane phospholipids and derived by food-frequency questionnaire and the risk of new-onset type 2 diabetes: a pilot study in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort. *Am J Clin Nutr* 2010;92:1214-22.

59. Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH, ARIC Study Investigators. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2003; 78:91-8.

60. Yamagishi K, Nettleton JA, Folsom AR, ARIC Study Investigators. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2008;156:965-74.

61. Warensjo E, Sundstrom J, Vessby B, Cederholm T, Riserus U. Markers of dietary fat quality and fatty acid desaturation of diabetes in total and cardiovascular mortality: a population-based prospective study. *Am J Clin Nutr* 2008; 88:203-9.

62. Forsythe CE, Phinney SD, Fernandez ML, et al. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. *Lipids* 2008;43:65-77.

63. Hyde PN, Sapper TN, Crabtree CD, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. *JCI Insight* 2019;4:e128308.

64. King IB, Lemaitre RN, Kestin M. Effect of a low-fat diet on fatty acid composition in red cells, plasma phospholipids, and cholesterol esters: investigation of a biomarker of total fat intake. *Am J Clin Nutr* 2006;83:227-36.

65. Volk BM, Kunces LJ, Freidenreich DJ, et al. Effects of step-wise increases in dietary carbohydrate on circulating saturated fatty acids and palmitoleic acid in adults with metabolic syndrome. *PLoS One* 2014;9:e113605.

66. Aarsland A, Wolfe RR. Hepatic secretion of VLDL fatty acids during stimulated lipogenesis in men. *J Lipid Res* 1998;39:1280-6.

67. Paillard F, Catheline D, Duff FL, et al. Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity. *Nutr Metab Cardiovasc Dis* 2008;18:436-40.

68. Mahendran Y, Agren J, Uusitupa M, et al. Association of erythrocyte membrane fatty acids with changes in glycemia and risk of type 2 diabetes. *Am J Clin Nutr* 2014;99:79-85.

69. Vessby B, Aro A, Skarfors E, Berglund L, Salminen I, Lithell H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. *Diabetes* 1994;43:1353-7.

70. Djousse L, Weir NL, Hanson NQ, Tsai MY, Gaziano JM. Plasma phospholipid concentration of cis-palmitoleic acid and risk of heart failure. *Circ Heart Fail* 2012;5:703-9.

71. Ni Y, Zhao L, Yu H, et al. Circulating unsaturated fatty acids delineate the metabolic status of obese individuals. *EBioMedicine* 2015;2:1513-22.

72. Yamagishi K, Folsom AR, Steffen LM, ARIC Study Investigators. Plasma fatty acid composition and incident ischemic stroke in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Cerebrovasc Dis* 2013;36:38-46.

73. Djousse L, Matthan NR, Lichtenstein AH, Gaziano JM. Red blood cell membrane concentration of cis-palmitoleic and cis-vaccenic acids and risk of coronary heart disease. *Am J Cardiol* 2012;110:539-44.
74. Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. *BMJ* 2018;361:k2173.
75. Corella D, Coltell O, Mattingley G, Sorli JV, Ordovas JM. Utilizing nutritional genomics to tailor diets for the prevention of cardiovascular disease: a guide for upcoming studies and implementations. *Expert Rev Mol Diagn* 2017;17:495-513.
76. Lopez-Miranda J, Ordovas JM, Mata P, et al. Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *J Lipid Res* 1994;35:1965-75.
77. Weggemans RM, Zock PL, Ordovas JM, Pedro-Botet J, Katan MB. Apoprotein E genotype and the response of serum cholesterol to dietary fat, cholesterol and cafestol. *Atherosclerosis* 2001;154:547-55.
78. Jackson KG, Lockyer S, Carvalho-Wells AL, Williams CM, Minihane AM, Lovegrove JA. Dietary fat manipulation has a greater impact on postprandial lipid metabolism than the apolipoprotein E (epsilon) genotype-insights from the SATgenepilon study. *Mol Nutr Food Res* 2012;56:1761-70.
79. Casas-Agustench P, Arnett DK, Smith CE, et al. Saturated fat intake modulates the association between an obesity genetic risk score and body mass index in two US populations. *J Acad Nutr Diet* 2014;114:1954-66.
80. Corella D, Peloso G, Arnett DK, et al. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. *Arch Intern Med* 2009;169:1897-906.
81. Corella D, Tai ES, Sorli JV, et al. Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene-saturated fat interaction. *Int J Obes (Lond)* 2011;35:666-75.
82. Lai CQ, Smith CE, Parnell LD, et al. Epigenomics and metabolomics reveal the mechanism of the APOA2-saturated fat intake interaction affecting obesity. *Am J Clin Nutr* 2018;108:188-200.
83. Brown S, Ordovas JM, Campos H. Interaction between the APOC3 gene promoter polymorphisms, saturated fat intake and plasma lipoproteins. *Atherosclerosis* 2003;170:307-13.
84. Garaulet M, Lee YC, Shen J, et al. CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am J Clin Nutr* 2009;90:1466-75.
85. Hjorth MF, Zohar Y, Hill JO, Astrup A. Personalized dietary management of overweight and obesity based on measures of insulin and glucose. *Annu Rev Nutr* 2018;38:245-72.
86. Skytte MJ, Samkani A, Petersen AD, et al. A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. *Diabetologia* 2019;62:2066-78.
87. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: Insights from yesterday, today, and future trends. *Popul Health Manag* 2017;20:6-12.
88. Riepmma SF. *The Story of Margarine*. Washington, DC: Public Affairs Press, 1970.
89. Chen M, Li Y, Sun Q, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr* 2016;104:1209-17.
90. Segurel L, Bon C. On the evolution of lactase persistence in humans. *Annu Rev Genomics Hum Genet* 2017;18:297-319.
91. Hawks J. Still evolving (after all these years). *Sci Am* 2014;311:86-91.
92. Beja-Pereira A, Caramelli D, Lalueza-Fox C, et al. The origin of European cattle: evidence from modern and ancient DNA. *Proc Natl Acad Sci U S A* 2006;103:8113-8.
93. Naderi S, Rezaei HR, Pompanon F, et al. The goat domestication process inferred from large-scale mitochondrial DNA analysis of wild and domestic individuals. *Proc Natl Acad Sci U S A* 2008;105:17659-64.
94. Stiner MC, Buitenhuis H, Duru G, et al. A forager-herder trade-off, from broad-spectrum hunting to sheep management at Asikli Hoyuk, Turkey. *Proc Natl Acad Sci U S A* 2014;111:8404-9.
95. Kritchevsky D, Tepper SA, Kim HK, Story JA, Vesselinovitch D, Wissler RW. Experimental atherosclerosis in rabbits fed cholesterol-free diets. 5. Comparison of peanut, corn, butter, and coconut oils. *Exp Mol Pathol* 1976;24:375-91.
96. Kritchevsky D, Tepper SA, Bises G, Klurfeld DM. Experimental atherosclerosis in rabbits fed cholesterol-free diets. *Atherosclerosis* 1982;41:279-84.
97. Marina AM, Man YB, Nazimah SA, Amin I. Antioxidant capacity and phenolic acids of virgin coconut oil. *Int J Food Sci Nutr* 2009;60 Suppl 2:114-23.
98. Khaw KT, Sharp SJ, Finikarides L, 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.
99. Arunima S, Rajamohan T. Influence of virgin coconut oil-enriched diet on the transcriptional regulation of fatty acid synthesis and oxidation in rats - a comparative study. *Br J Nutr* 2014;111:1782-90.
100. Brenna JT, Kothapalli KS. Commentary on 'Influence of virgin coconut oil-enriched diet on the transcriptional regulation of fatty acid synthesis and oxidation in rats-a comparative study' by Sakunthala Arunima and Thankappan Rajamohan. *Br J Nutr* 2014;112:1425-6.
101. Jedrkiewicz R, Kupska M, Glowacz A, Gromadzka J, Namiesnik J. 3-MCPD: A worldwide problem of food chemistry. *Crit Rev Food Sci Nutr* 2016;56:2268-77.
102. Liu R, Cheng M, Kothapalli KSD, et al. Glycerol derived process contaminants in refined coconut oil induce cholesterol synthesis in HepG2 cells. *Food Chem Toxicol* 2019;127:135-42.
103. Berbee JFP, Mol IM, Milne GL, et al. Deuterium-reinforced polyunsaturated fatty acids protect against atherosclerosis by lowering lipid peroxidation and hypercholesterolemia. *Atherosclerosis* 2017;264:100-7.
104. Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation* 1970;42:935-42.
105. Morris JN, Ball KP, Antonis A, et al. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 1968;2:693-9.
106. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol* 1979;8:99-118.
107. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation* 1969;40:111-63.
108. Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and LP [a] in men. *J Lipid Res* 1995;36:1370-84.
109. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Med Scand Suppl* 1966;466:1-92.
110. Turpeinen O, Miettinen M, Karvonen MJ, et al. Dietary prevention of coronary heart disease: long-term experiment. I. Observations on male subjects. *Am J Clin Nutr* 1968;21:255-76.
111. Astrup A. Yogurt and dairy product consumption to prevent cardiometabolic diseases: epidemiologic and experimental studies. *Am J Clin Nutr* 2014;99:1235S-42S.
112. Ibsen DB, Laursen ASD, Lauritzen L, Tjonneland A, Overvad K, Jakobsen MU. Substitutions between dairy product subgroups and risk of type 2 diabetes: the Danish Diet, Cancer and Health cohort. *Br J Nutr* 2017;118:989-97.
113. Guo J, Astrup A, Lovegrove JA, Gijsbers L, Givens DI, Soedamah-Muthu SS. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol* 2017;32:269-87.
114. Thorning TK, Bertram HC, Bonjour JP, et al. Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. *Am J Clin Nutr* 2017;105:1033-45.
115. Thorning TK, Raben A, Tholstrup T, Soedamah-Muthu SS, Givens I, Astrup A. Milk and dairy products: good or bad for human health? An assessment of the totality of scientific evidence. *Food Nutr Res* 2016;60:32527.
116. Chowdhury R, Warnakula S, Kunutsor S, 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.

117. Imamura F, Fretts A, Marklund M, et al. Fatty acid biomarkers of dairy fat consumption and incidence of type 2 diabetes: a pooled analysis of prospective cohort studies. *PLoS Med* 2018;15:e1002670.

118. Yuan S, Li X, Jin Y, Lu J. Chocolate consumption and risk of coronary heart disease, stroke, and diabetes: a meta-analysis of prospective studies. *Nutrients* 2017;9:688.

119. Larsson SC, Akesson A, Gigante B, Wolk A. Chocolate consumption and risk of myocardial infarction: a prospective study and meta-analysis. *Heart* 2016;102:1017-22.

120. Gianfredi V, Salvatori T, Nucci D, Villarini M, Moretti M. Can chocolate consumption reduce cardio-cerebrovascular risk? A systematic review and meta-analysis. *Nutrition* 2018;46:103-14.

121. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation* 2010;121:2271-83.

122. O'Connor LE, Kim JE, Campbell WW. Total red meat intake of ≥ 0.5 servings/d does not negatively influence cardiovascular disease risk factors: a systemically searched meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2017;105:57-69.

123. Zeraatkar D, Johnston BC, Bartoszko J, et al. Effect of lower versus higher red meat intake on cardiometabolic and cancer outcomes: a systematic review of randomized trials. *Ann Intern Med* 2019;171:721-31.

124. Zhong VW, Van Horn L, Greenland P, et al. Associations of processed meat, unprocessed red meat, poultry, or fish intake with incident cardiovascular disease and all-

cause mortality. *JAMA Intern Med* 2020;180:503-12.

125. Sandoval-Insausti H, Perez-Tasigchana RF, Lopez-Garcia E, Garcia-Esquinas E, Rodriguez-Artalejo F, Guallar-Castillon P. Macronutrients intake and incident frailty in older adults: a prospective cohort study. *J Gerontol A Biol Sci Med Sci* 2016;71:1329-34.

126. U.S. Department of Agriculture. FoodData Central. Available at: <https://fdc.nal.usda.gov>. Accessed March 24, 2020.

KEY WORDS cardiovascular disease, diet, food matrix, saturated fat



Go to <http://www.acc.org/jacc-journals-cme> to take the CME/MOC/ECME quiz for this article.