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Fats in Foods: Current Evidence for Dietary Advice

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Abstract
Current discussion of the importance of food fats in the risk of coronary heart disease (CHD) often suffers from preconceptions, misunderstandings, insufficient knowledge, and selective reasoning. As a result, the sustained controversy about dietary fat recommendations can be contradictory and confusing. To clarify some of these issues, the International Expert Movement to Improve Dietary Fat Quality in cooperation with the International Union of Nutritional Sciences (IUNS) organized a symposium at the 21st meeting of the IUNS, October 17, 2017, Buenos Aires, Argentina, to summarize the key scientific evidence underlying the controversy on the relationship between the saturated and unsaturated fat consumption and CHD risk. Presenters also discussed, using examples, the rationale for and implications of the partial replacement of foods rich in saturated fats by those rich in unsaturated fats. Presentations included strategies to fit healthier fats into meals. This report summarizes the symposium presentations.

Consumption of Saturated Fatty Acids and Coronary Heart Disease Risk

Whether dietary saturated fatty acids (SAFA) significantly increase the risk of coronary heart disease (CHD) is arguably the most controversial aspect of food fats and CHD [1, 2]. After briefly reviewing the structural differences between saturated and unsaturated fatty acids, Ingeborg Brouwer, Vrije Universiteit, Amsterdam, showed

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evidence from intervention trials as well as observational studies and discussed the difficulties and limitations of the different studies. By doing that she emphasized the importance of taking all available evidence from human studies into account when recommendations and guidelines on SAFA and CHD are discussed.

Brouwer focused on 3 key systematic reviews and meta-analyses of dietary SAFA and the risk of CHD [3–5]. She pointed out that nutritional studies are not the same as nor equivalent to medical or pharmaceutical studies. In a sense, they are more complex due to well-known dietary variables that are difficult, if not impossible, to control [2, 6]. Nearly everyone in a population is exposed continuously, nutrition variables may be interrelated, eating patterns change over time, there is no placebo, and macronutrients provide energy. In pharmaceutical trials, 1 group is given the treatment and the other is not, but exposure in both groups is otherwise similar. The control group may be given a placebo, which should be indistinguishable from the treatment. In studies of dietary fat, the replacement macronutrient may be carbohydrates, proteins, other fatty acids or a combination of these possibilities. In addition, macronutrient replacement may be partial, for example, 5% energy (En), so that both groups may still be exposed to the experimental variable. Weight change/loss may occur depending on the participant's behavior. Further, individuals have limited awareness of their dietary habits, making the measurement of dietary intake a crucial, often limiting, feature of observational nutrition research among free living participants.

In the evaluation of dietary SAFA studies, meta-analyses and systematic reviews constitute the strongest type of evidence, but they may be of varying quality [7, 8]. They have received recent criticism for various methodological issues that can affect the conclusions [9, 10]. The next strongest evidence comes from double blind, randomized controlled trials (RCT) where the actual effect of a treatment is compared with a placebo. These studies are of a shorter term than observational studies, may not reflect real-life experience, can have compliance difficulties, and usually involve a smaller number of participants. Their advantage is being able to demonstrate cause. Next in the hierarchy of evidence are observational cohort studies, which reflect the natural environment, can be of long-term duration, have large study groups, and are complex but lack a control. Observational studies cannot establish cause but may show association. Both types of studies require choices about disease endpoints versus intermediate endpoints and have drawbacks [6, 11]. Weaker study designs include case-control studies, case series, and reports and finally, opinions and editorials.

These issues demand caution when drawing conclusions on the basis of only one kind of evidence. For example, several meta-analyses of RCTs on the replacement of SAFA with mostly n-6 PUFA have been published. They are all more or less based on the same studies because more meta-analyses do not necessarily mean that new studies have been published. For example, in the review of Hooper et al. [3], the partial replacement of SAFA by PUFA caused a 27% reduction in cardiovascular disease (CVD) events but did not affect mortality. The latter is not surprising, as the duration of the RCTs is limited. Hamley came to a different conclusion when he grouped relevant trials as adequately or inadequately controlled, depending on whether there were substantial dietary or non-dietary differences between the experimental and control groups [9]. Based on his grouping of the trials, he concluded that adequately controlled trials showed no association between partial replacement of SAFA with PUFA and risk of total CHD events, major CHD events and CHD mortality, while inadequately controlled trials found significant reductions in these risks [9]. Considered together, the trials showed no effect on CHD mortality, but they pointed toward a protective effect of replacement of SAFA with PUFA on cardiovascular events.

An extremely important issue when judging observational studies is whether the replacement nutrient has been taken into account. For example, in a meta-analysis of 16 prospective cohort studies on SAFA and risk of CHD, Siri-Tarino et al. [12] concluded that there was no significant evidence that dietary SAFA were associated with risk of CHD. However, the study did not account for the replacement nutrient for SAFA, which affects the CHD risk assessment [5].

However, data from the Nurses' Health Study and the Health Professionals Follow-up Study showed that isocaloric substitution of 5%En from SAFA by PUFA was associated with a 25% reduction in CHD risk [4]. Similarly, Mozaffarian et al. [5] estimated that the replacement of 5%En from SAFA with the equivalent energy from PUFA was associated with a 17% lower risk of CHD. In these large analyses, the reduction in SAFA consumption along with an equivalent replacement by PUFA was associated with a marked reduction in CHD risk.

Finally, Brouwer commented on the recently published results of the PURE study [13]. This was an 18-country, 7-year, prospective, cohort study that examined the associations of dietary fats and carbohydrates with risk of CVD and mortality. The investigators reported a lower risk overall of total mortality with the highest intakes of total, SAFA, MUFA, and PUFA, but no single

type of fat was related to CVD mortality, CVD, or myocardial infarction. Important features of this study were the preponderance of observations from Asian and other countries with habitually low total and SAFA fat consumption, high carbohydrate intakes (≥60%En), especially of refined carbohydrates such as white rice and white bread, and mortality mainly from non-CVD causes. Under these circumstances, estimates of different types of fat intakes by food frequency questionnaire and relationships between dietary fat variables and CVD/CHD events and mortality will be more difficult to detect. Dehghan et al. [13] question the current dietary guidelines of the WHO, claiming that the study shows that people with a high intake of saturated fat are better off. In fact, the study shows that people in the low intake categories have a higher risk of dying early, which is not surprising, as these people have such low fat intakes that it is virtually impossible to choose a wholesome, complete diet. The main problems in these cohorts are in the lowest categories where the intakes of fat and saturated fat were so low that it was virtually impossible to choose a wholesome, complete diet. Such intakes cannot be recommended. The findings of the PURE study are not in contrast with the recommendation of the WHO to replace saturated fat by unsaturated fat and strive for a SAFA intake below 10%En.

Given the strength of all available evidence, Brouwer endorsed recommendations for the partial replacement of SAFA by unsaturated fatty acids to reduce CHD risk, despite the limitations she described. She also noted that it is not only impossible, but undesirable, to replace all SAFA, and that striving for 10%En from dietary SAFA is a "good guideline."

Evidence Relating Dietary PUFA to CHD Risk

Joyce Nettleton, Denver, CO, USA, reviewed the evidence on PUFA and CHD. She noted that nearly half (45.4%) of cardiometabolic deaths in the United States were attributed to unhealthy diet, specifically low intakes of nuts, seeds, and n-3 long-chain (LC) PUFA from seafood [14]. Studies conducted in the 1950s linked dietary fat and cholesterol with serum cholesterol (serum-C) levels and the development of atherosclerosis [15, 16]. Kinsell et al. [17] reported that participants who were fed on large amounts of vegetable fats experienced a major fall in serum-C levels, even with high dietary cholesterol intake. But it was Ancel Keys' publication of the relationship between total dietary fat energy and serum-C levels, as observed in the Seven Countries study [18] that cemented the relationship between dietary fat, serum-C and risk of CHD. That led the American Heart Association (AHA) in 1961 to declare that serum-C could be reduced by "eating less foods containing cholesterol," decreasing total fat intake, and replacing a substantial portion of (SAFA)-rich foods with vegetable oils and fish fat [19]. By 2000, the emphasis on lowering total fat intake shifted to moderate fat consumption and diets low in saturated fat and cholesterol [20]. Reducing serum-C levels through diet, lifestyle, and drugs remains the cornerstone of managing CHD risk. The replacement of SAFA-rich foods with those rich in unsaturated fatty acids, especially PUFA, is the key dietary fat recommendation of the World Health Organization [21], AHA [10], European Society of Cardiologists [22], the United States [23], the Netherlands [24], Nordic countries [25], Germany [26], and several other countries.

The scientific basis and clinical effectiveness of these dietary fat recommendations are not without dispute [9, 27, 28]. Critics contend that insufficient evidence of benefit supports limiting SAFA intake to ≤10%En [29, 30]; partial replacement of dietary SAFA with PUFA does not affect the risk of CHD, CVD, or CVD mortality in some studies [9, 27], and increased linoleic acid intake (LA) does not affect CHD mortality [28]. It is critical that any reduction in or replacement of SAFA consider the macronutrient that replaces it [31].

Many observational studies have reported significant risk reductions for CHD or CVD mortality based on the estimated effects of the substitution of PUFA for SAFA [32–34], high compared with low dietary or circulating LA [35, 36] or observed a reduction in low-density lipoprotein cholesterol (LDL-C) and the ratio of total to high-density lipoprotein cholesterol (total-C:HDL-C), markers of CHD risk [31]. However, others have estimated that the replacement of SAFA with PUFA or LA is not significantly associated with CHD risk or mortality [13, 37, 38]. One study reported an increased risk of mortality with cholesterol lowering from a high-LA diet [28].

Meta-analyses of RCTs on dietary PUFA and CHD mortality have reported a significant decrease in the risk of CHD events [3, 5, 38] but no effect on CHD mortality. However, disagreement with the studies included in these analyses and others prompted Al-Khudairy et al. [39] and Hamley [9] to conclude that replacing SAFA with mostly n-6 PUFA is unlikely to reduce CHD events or mortality. In contrast, Sacks et al. [10], on behalf of AHA, concluded from 4 well-controlled RCTs that lowering the intake of SAFA and replacing it with unsaturated fats, especially PUFA, reduced CHD by about 30% and would lower the incidence of CVD.

Partial replacement of SAFA with mainly vegetable unsaturated fatty acids may overlook the specific contributions of omega-3 (n-3) PUFA to CHD risk reduction. n-3 PUFAs include the short-chain (18:3n-3), plant-based n-3 PUFA, alpha-linolenic acid (ALA), and LC forms, mainly eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), found predominantly in seafood. ALA is the most common dietary n-3 PUFA and occurs in some seeds and nuts and their oils, while n-3 LCPUFA occur in fish, especially fatty fish, fish oil/algal oil capsules, eggs, poultry and some genetically modified plants [40]. Controversy also plagues clear dietary guidance on the consumption of n-3 PUFA.

Although ALA accounts for the greatest intake of n-3 PUFA, it is less biologically potent than n-3 LC-PUFA and generally thought to require conversion to its LC derivative, EPA, for CVD benefits [40, 41]. Recent reviews of n-3 LCPUFA in reducing the risk of CHD disease and mortality have supported modest CVD benefits [1, 42, 43], with some questions about the strength of the evidence and effect sizes [44]. Benefits and CHD risk reduction are most often observed among individuals at high risk of CHD, that is, those with high triglyceride levels, high total cholesterol or LDL-C, and prevalent heart failure [43–45] and in studies of secondary rather than primary prevention. Doses of n-3 LCPUFA of 1 g/day or more are more likely to be associated with reduced CHD risk than lower amounts.

In summary, CHD risk is affected more by the type of dietary fat than the total amount of fat consumed [1]. Reducing the intake of 1 type of fat must also consider the replacement macronutrient. RCTs of the partial replacement of SAFA with PUFA [5] and observational studies comparing high versus low intakes of whole grains on the risk of CHD [46–48] were associated with significantly lower CHD risk, whereas refined carbohydrates were associated with slightly increased risk and protein with no effect on risk [3, 4]. Total PUFA intake may not distinguish between n-6 and n-3 PUFA, which may act by different mechanisms, but consumption of both classes is associated with lower CHD risk [1, 36].

Replacement of Dietary SAFA with Unsaturated Fatty Acids

Ronald Mensink, Maastricht University, the Netherlands, delved into the rationale for replacing SAFA with unsaturated fatty acids. He noted that dietary recommendations often suggest consuming no more than 10%En from SAFA [23, 25], yet SAFA intakes exceed 10%En in many countries [49]. The logic behind such a recommendation derives from the risk factor model for CHD causality, in which LDL-C is a causal risk factor for CHD [50] and a mixture of dietary SAFA increases LDL-C compared with other macronutrients [31]. A fatty acid is considered hypercholesterolemic when it replaces an equivalent amount of energy from dietary carbohydrates and the exchange increases the total cholesterol. Carbohydrates have arbitrarily been considered neutral with regard to serum cholesterol.

Different classes of fatty acids have different effects on LDL-C relative to carbohydrates. Thus, SAFA and *trans* monounsaturated fatty acids (MUFA) raise LDL-C levels, while *cis*-MUFA and *cis*-PUFA lower them [4, 51]. The effects of *trans*-MUFA are the most unfavorable and those of *cis*-PUFA are the most favorable. Compared with *cis*-PUFA, SAFA, *trans*-MUFA, and carbohydrates significantly increase LDL-C. Further, the type of carbohydrate that replaces SAFA makes a difference. Carbohydrates from refined starches and sugars do not affect CHD risk, but those from whole grains are associated with a significantly lower CHD risk [4].

In addition to the type of macronutrient exchange, which biomarker or combination of biomarkers is used to assess CHD risk affects the estimate. Potential biomarkers include LDL-C, apolipoprotein B, small dense LDL, HDL-C, apolipoprotein A1, total-C:HDL-C ratio, and others. For example, replacement of dietary SAFA by carbohydrate, especially refined carbohydrate, is associated with increased small dense LDL particles and CHD risk [52] and may not improve the serum lipoprotein profile [51].

Would it be appropriate for diets to distinguish among the different SAFA? When evaluated individually relative to carbohydrates, lauric, myristic, and palmitic acids (C12–C16) each raise LDL-C concentrations significantly, but stearic acid (C18) does not [51]. Mensink noted that intakes of SAFA with fewer than 12 carbons are low and their effects on serum lipids not assessed in many studies. Tholstrup et al. [53] compared the effects on plasma lipids of 3-week diets containing 25%En from medium-chain triglycerides (MCT) containing C8 and C10 SAFA or high-oleic acid sunflower oil with habitual dietary fat in the Danish diet and reported that MCT diets increased plasma LDL-C and triglycerides compared with a high-oleic acid diet, but did not raise HDL-C concentrations.

An additional consideration is the multifactorial nature of CHD: diet, genes, environment, co-existing clinical conditions, such as dyslipidemia, and type 2 diabetes,

hemostatic function, blood pressure, immune function, smoking, and many other factors that affect CHD risk. Many of these are affected by dietary fatty acids. For example, in a controlled study of the effects of *trans* fatty acids, C12-C16 SAFA, stearic acid, oleic acid, and carbohydrate on plasma markers of inflammation and endothelial function, *trans* fatty acid consumption raised the levels of C-reactive protein, interleukin-6, and E-selectin compared with oleic acid or carbohydrate, but these effects were modified in the presence of stearic acid. Only stearic acid increased plasma fibrinogen levels, while interleukin-6 levels rose with stearic acid, C12-C16 SAFA, and *trans* fatty acids [54]. The effects of dietary fatty acids on other non-lipoprotein-related pathways, such as blood pressure, hemostatic function, postprandial metabolism, are mixed [55].

We consume fatty acids in fats and oils, which contain a variety of SAFA in different proportions. The predominant SAFA in western diets are palmitic (C16) and stearic (C18) acids, which comprise most of the SAFA in butter, palm oil, and cocoa butter [56]. Lauric acid (C12) is a major SAFA in coconut and palm kernel oils. Various fats and oils have different effects on LDL-C, with those rich in SAFA increasing LDL-C concentrations and those rich in MUFA and PUFA reducing LDL-C. However, the food matrix also influences the effect of fat-rich foods on LDL-C as illustrated in studies comparing the cholesterolemic effects of cheese consumption with those of butter [57, 58]. This topic is under active investigation.

Mensink concluded that we should not give the impression that SAFA need to be abandoned from the diet. A food or food pattern is more than a single nutrient. However, their intake should not be unlimited. The focus on limiting dietary SAFA consumption requires consideration of the replacement macronutrient. Although individual SAFA behave metabolically differently, it is not known whether they affect health differently.

Fitting Healthier Fats into Meals

It is now recognized in recent dietary guidelines from the United States [20], Nordic countries [26], the Netherlands [24], Public Health England [59] and in healthy eating patterns, such as the Mediterranean [60] and Dietary Approaches to Stop Hypertension Diets [61], the general public needs food-based recommendations rather than nutrient-based guidelines. As Connie Diekman, Washington University, St. Louis, MO, USA, put it, consumers want to know what to eat. They want to trust the science and dietary guidelines and they need simple tips, tools, and advice. Diekman cited AHA's "Facts on Fats," which groups food fats into 3 groups to love (e.g., vegetable oils, fish), limit (e.g., butter, cheese, heavy cream), or lose (donuts, cakes, coconut oil) [62]. Shifting to healthier fats means eating more plant oils such as canola, avocado, or soy instead of animal fats such as lard, butter, and cream, using fat-free plain yogurt instead of sour cream, fat-free, or low fat milk instead of whole milk and eating seeds, fatty fish, and nuts regularly.

A healthy eating pattern includes more plant-based foods, for example, vegetables, fruits, whole grains, legumes, and nuts, fish, and less red and processed meat, sugar-sweetened foods and drinks, and refined or highly processed grains [63]. Diekman noted several key steps in developing a healthier eating pattern: be mindful that taste drives food choices, practical and easy always wins, begin with the current eating pattern rather than an ideal, emphasize lifestyle over short-term changes, allow for slow, easy change, and recognize that dietitians can help clients and patients make the changes.

The translation of science for consumers links greater SAFA intakes to higher LDL-C levels and hence, higher risk of CHD. Thus, dietary guidelines focus on choices among food fats, suggesting some limitations. Choosing more plant foods is advantageous for CHD and overall health [61, 63]. Recognizing that fats and fatty acids are not the enemy, the focus must be on adopting a healthy eating plan that provides a balance among different types of fats. In conclusion, Diekman observed that where controversy divides, science can unite.

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Author Contribution

The principal author was J.A.N. In addition I.A.B., R.M., C.D., and G.H. made substantial written contributions, edits, and reviews and assisted in revisions. All authors approved of the final version and have agreed to be accountable for all aspects of the work described.

References

1 Wang DD, Hu FB: Dietary fat and risk of cardiovascular disease: recent controversies and advances. Annu Rev Nutr 2017;37:423–446.
2 Svendsen K, Arnesen E, Retterstol K: Saturated fat – a never ending story? Food Nutr Res 2017;61:1377572.
3 Hooper L, Martin N, Abdelhamid A, Davey Smith G: Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev 2015;6:CD011737.
4 Li Y, Hruby A, Bernstein AM, Ley SH, et al: Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. J Am Coll Cardiol 2015;66:1538–1548.
5 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.
6 James MJ, Sullivan TR, Metcalf RG, Cleland LG: Pitfalls in the use of randomised controlled trials for fish oil studies with cardiac patients. Br J Nutr 2014;112:812–820.
7 Huedo-Medina TB, Garcia M, Bihuniak JD, Kenny A, et al: Methodologic quality of meta-analyses and systematic reviews on the Mediterranean diet and cardiovascular disease outcomes: a review. Am J Clin Nutr 2016;103:841–850.
8 Barnard ND, Willett WC, Ding EL: The misuse of meta-analysis in nutrition research. JAMA 2017;318:1435–1436.
9 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.
10 Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, et al: Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136:e1–e23.
11 Cobb LK, Anderson CA, Elliott P, Hu FB, et al: Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. Circulation 2014;129:1173–1186.
12 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;91:535–546.
13 Dehghan M, Mente A, Zhang X, Swaminathan S, 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;390:2050–2062.
14 Micha R, Penalvo JL, Cudhea F, Imamura F, et al: Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA 2017;317:912–924.
15 Keys A: Human atherosclerosis and the diet. Circulation 1952;5:115–118.
16 Mayer GA, Connell WF, Dewolfe MS, Beveridge JM: Diet and plasma cholesterol levels. Am J Clin Nutr 1954;2:316–322.
17 Kinsell LW, Michaels GD, Partridge FW, Boling LA, et al: Effect upon serum cholesterol and phospholipids of diets containing large amounts of vegetable fat. J Clin Nutr 1953;1:224–231.
18 Keys A, Grande F: Role of dietary fat in human nutrition. III. Diet and the epidemiology of coronary heart disease. Am J Public Health Nations Health 1957;47:1520–1530.
19 Dietary fat and its relation to heart attacks and strokes. Report by the Central Committee for Medical and Community Program of the American Heart Association. JAMA 1961;175:389–391.
20 USDA: Nutrition and Your Health. Dietary Guidelines for Americans. Bethesda, MD, 2000.
21 Joint FAO/WHO Expert Consultation: Fats and Fatty Acids in Human Nutrition. Geneva, FAO/WHO, 2010.
22 Piepoli MF, Hoes AW, Agewall S, Albus C, et al: 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–2381.
23 U.S. Department of Health and Human Services and U.S. Department of Agriculture: 2015–2020 Dietary Guidelines for Americans. Washington, 2015.
24 Kromhout D, Spaaij CJ, de Goede J, Weggemans RM: The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 2016;70:869–878.
25 Nordic Council of Ministers: Nordic Nutrition Recommendations 2012. Integrating Nutrition and Physical Activity. Copenhagen, Denmark; Nordic Council of Ministers, 2014.
26 Wolfram G, Bechthold A, Boeing H, Ellinger S, et al: Evidence-based guideline of the German Nutrition Society: fat intake and prevention of selected nutrition-related diseases. Ann Nutr Metab 2015;67:141–204.
27 Harcombe Z, Baker JS, DiNicolantonio JJ, Grace F, et al: Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis. Open Heart 2016;3:e000409.
28 Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, et al: Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968–1973). BMJ 2016;353:i1246.
29 Harcombe Z: Dietary fat guidelines have no evidence base: where next for public health nutritional advice? Br J Sports Med 2017;51:769–774.
30 Dinicolantonio JJ, Harcombe Z, O'Keefe JH: Problems with the 2015 Dietary Guidelines for Americans. An alternative. Minn Med 2016;99:40–43.
31 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;77:1146–1155.
32 Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, 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;89:1425–1432.
33 Guasch-Ferre M, Babio N, Martinez-Gonzalez MA, Corella D, et al: Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. Am J Clin Nutr 2015;102:1563–1573.
34 Wang DD, Li Y, Chiuve SE, Stampfer MJ, et al: Association of specific dietary fats with total and cause-specific mortality. JAMA Intern Med 2016;176:1134–1145.
35 Farvid MS, Ding M, Pan A, Sun Q, et al: Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. Circulation 2014;130:1568–1578.
36 Wu JH, Lemaitre RN, King IB, Song X, et al: Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality: the Cardiovascular Health Study. Circulation 2014;130:1245–1253.
37 Chowdhury R, Warnakula S, Kunutsor S, Crowe F, 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.
38 Skeaff CM, Miller J: Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. Ann Nutr Metab 2009;55:173–201.
39 Al-Khudairy L, Hartley L, Clar C, Flowers N, et al: Omega 6 fatty acids for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2015;11:CD011094.
40 Baker EJ, Miles EA, Burdge GC, Yaqoob P, et al: Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res 2016;64:30–56.
41 Sanders TA: Plant compared with marine n-3 fatty acid effects on cardiovascular risk factors and outcomes: what is the verdict? Am J Clin Nutr 2014;100(suppl 1):453S–458S.
42 Mori TA: Marine omega-3 fatty acids in the prevention of cardiovascular disease. Fitoterapia 2017;123:51–58.
43 Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, et al: A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. Mayo Clin Proc 2017;92:15–29.

44 Maki KC, Palacios OM, Bell M, Toth PP: Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: an updated meta-analysis and review of research gaps. J Clin Lipidol 2017;11:1152–1160.e1152.
45 Wang C, Xiong B, Huang J: The role of omega-3 polyunsaturated fatty acids in heart failure: a meta-analysis of randomised controlled trials. Nutrients 2016;9:18–34.
46 Aune D, Keum N, Giovannucci E, Fadnes LT, et al: Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. BMJ 2016;353:i2716.
47 Helnaes A, Kyro C, Andersen I, Lacoppidan S, et al: Intake of whole grains is associated with lower risk of myocardial infarction: the Danish Diet, Cancer and Health Cohort. Am J Clin Nutr 2016;103:999–1007.
48 Li B, Zhang G, Tan M, Zhao L, et al: Consumption of whole grains in relation to mortality from all causes, cardiovascular disease, and diabetes: dose-response meta-analysis of prospective cohort studies. Medicine (Baltimore) 2016;95:e4229.
49 Harika RK, Eilander A, Alssema M, Osendarp SJ, et al: Intake of fatty acids in general populations worldwide does not meet dietary recommendations to prevent coronary heart disease: a systematic review of data from 40 countries. Ann Nutr Metab 2013;63:229–238.
50 Lowering blood cholesterol to prevent heart disease. NIH Consensus Development Conference statement. Arteriosclerosis 1985;5:404–412.
51 Mensink RP: Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis. Geneva, World Health Organization, 2016.
52 Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM: Saturated fats versus polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. Annu Rev Nutr 2015;35:517–543.
53 Tholstrup T, Ehnholm C, Jauhiainen M, Petersen M, et al: Effects of medium-chain fatty acids and oleic acid on blood lipids, lipoproteins, glucose, insulin, and lipid transfer protein activities. Am J Clin Nutr 2004;79:564–569.
54 Baer DJ, Judd JT, Clevidence BA, Tracy RP: Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr 2004;79:969–973.
55 Nettleton JA, Brouwer IA, Geleijnse JM, Hornstra G: Saturated fat consumption and risk of coronary heart disease and ischemic stroke: a science update. Ann Nutr Metab 2017;70:26–33.
56 Zong G, Li Y, Wanders AJ, Alssema M, et al: Intake of individual saturated fatty acids and risk of coronary heart disease in US men and women: two prospective longitudinal cohort studies. BMJ 2016;355:i5796.
57 de Goede J, Geleijnse JM, Ding EL, Soedamah-Muthu SS: Effect of cheese consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2015;73:259–275.
58 Chen M, Li Y, Sun Q, Pan A, et al: Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr 2016;104:1209–1217.
59 Public Health England: The Eatwell Guide. London, Public Health England, 2016.
60 Stradling C, Hamid M, Taheri S, Thomas GN: A review of dietary influences on cardiovascular health: part 2: dietary patterns. Cardiovasc Hematol Disord Drug Targets 2014;14:50–63.
61 Mertens E, Markey O, Geleijnse JM, Lovegrove JA, et al: Adherence to a healthy diet in relation to cardiovascular incidence and risk markers: evidence from the Caerphilly Prospective Study. Eur J Nutr 2017, March 14, Epub ahead of print.
62 American Heart Association: The Facts on Fat: Eat Smart. Dallas, TX, American Heart Association, 2017.
63 Mozaffarian D: Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. Circulation 2016;133:187–225.