The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010?[1–4]

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ABSTRACT

Current dietary recommendations advise reducing the intake of saturated fatty acids (SFAs) to reduce coronary heart disease (CHD) risk, but recent findings question the role of SFAs. This expert panel reviewed the evidence and reached the following conclusions: the evidence from epidemiologic, clinical, and mechanistic studies is consistent in finding that the risk of CHD is reduced when SFAs are replaced with polyunsaturated fatty acids (PUFAs). In populations who consume a Western diet, the replacement of 1% of energy from SFAs with PUFAs lowers LDL cholesterol and is likely to produce a reduction in CHD incidence of $\geq$2–3%. No clear benefit of substituting carbohydrates for SFAs has been shown, although there might be a benefit if the carbohydrate is unrefined and has a low glycemic index. Insufficient evidence exists to judge the effect on CHD risk of replacing SFAs with MUFAs. No clear association between SFA intake relative to refined carbohydrates and the risk of insulin resistance and diabetes has been shown. The effect of diet on a single biomarker is insufficient evidence to assess CHD risk. The combination of multiple biomarkers and the use of clinical endpoints could help substantiate the effects on CHD. Furthermore, the effect of particular foods on CHD cannot be predicted solely by their content of total SFAs because individual SFAs may have different cardiovascular effects and major SFA food sources contain other constituents that could influence CHD risk. Research is needed to clarify the role of SFAs compared with specific forms of carbohydrates in CHD risk and to compare specific foods with appropriate alternatives. *Am J Clin Nutr* 2011;93:684–8.

INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of death in Western countries, despite the halving of age-specific mortality rates in the past 20 y (1); the prevalence of CVD is increasing because of an aging population (2). Saturated fatty acids (SFAs) have played a key role in hypotheses relating diet to the risk of coronary heart disease (CHD), and early evidence based on animal studies, international comparisons, and controlled feeding trials with total cholesterol as the endpoint support a major adverse effect. Thus, a reduction of SFA intakes has been at the heart of most dietary recommendations to reduce the risk of CHD (3). However, more recently, important issues have emerged about the role of SFAs. These issues include the following:

1) The specific macronutrient sources of energy to which SFAs are compared and the possibility that the replacement of SFAs with *trans* fats or highly processed refined carbohydrates could have little positive effect or even an adverse effect
2) Whether specific SFAs have different relations with CHD risk
3) Whether advice should focus more on the major food sources of SFAs because they may contain high amounts of protein, calcium, and other components that also influence the risk of CHD, so the effect of particular foods on CHD cannot be predicted solely by their content of SFAs
4) Whether the effect of replacing SFAs with carbohydrate has changed over time as populations have become more obese

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5) Whether important relations exist between intake of SFAs or its major food sources and risks of other diseases, including stroke and cancer, which should be considered in making dietary recommendations

In addressing these issues, a key consideration is the type of evidence that is sufficient to guide dietary recommendations. Ideally, these issues would be addressed by conducting randomized trials with CVD and total mortality as the endpoints. However, this is rarely possible for practical reasons, and decisions will usually need to be made on a combination of animal experiments, observational studies, and intervention studies with intermediate endpoints. The definition of sufficient evidence is not always clear.

METHODS

For details about the process that led to the choice of the individual symposium participants, selection of literature to be considered, and other factors, *see* the modified PRISMA diagram as supplementary material under "Supplemental data" in the online issue.

CONCLUSIONS FROM THE SYMPOSIUM

Does evidence from observational, mechanistic, and intervention studies provide a coherent picture of the effect of SFAs on CHD?

Evidence for fat substitutions from observational studies and intervention trials

In the Seven Countries Study (4), the higher risk of CHD mortality associated with intake of SFAs may be biased because of confounding by many other factors and can only be hypothesis-generating. The evidence from cohort studies can be summarized as described below.

Individual cohorts

The data are inconsistent, but no associations were found in most cases. Associations tend to be examined in populations with a narrow range of higher SFA intakes.

Recent pooled analyses

Substituting polyunsaturated fatty acids (PUFAs) for SFAs is associated with lower CHD risk; substituting total carbohydrate for SFAs is associated with no or a moderately higher risk of CHD (5). Few studies have addressed the quality of carbohydrates, and this can be important because the association with SFAs may differ depending on the type of carbohydrate to which it is compared. For example, replacing SFAs with carbohydrate that have a low glycemic index may lower the risk of CHD (6). Carbohydrates are likely to have fewer adverse effects on blood lipids and CHD risk in healthy and physically active individuals than in overweight and inactive subjects with insulin resistance (7).

Meta-analyses of cohort studies with self-reported SFA intakes are not associated with CHD, stroke, or CVD (8–11). In these analyses, however, the replacement nutrient was not specified but will be largely carbohydrates. Although replacing carbohydrates with monounsaturated fatty acids (MUFAs) reduces LDL cholesterol (12), there is little evidence that MUFAs are associated with CHD risk (11, 13). Using experimental animal models in which the extent of atherosclerosis can be directly measured, it has been shown that MUFA-enriched diets are not atheroprotective when compared with SFA-enriched diets (14). However, in human observational studies, MUFAs are derived largely from meat and dairy products, which may partly explain the lack of association.

Industrially produced *trans* fatty acids (TFAs) are consistently associated with a higher risk of CHD (on a gram-for-gram basis), TFA intakes are associated with a higher risk than are SFAs, but the lowest risk was found for diets high in n−6 PUFAs and low in TFAs (15, 16).

When PUFAs replace SFAs, the evidence from epidemiologic, clinical, and mechanistic studies is consistent in finding that the risk of CHD is reduced. In countries following a Western diet, replacing 1% of energy intake from SFAs with PUFAs has been associated with a 2–3% reduction in the incidence of CHD (13, 17). This figure is probably an underestimate of the benefit because it is based on a single measure of diet in a prospective analysis and because of the high amount of TFA co-occurring in some PUFA food sources, such as margarines (rich in TFAs before the mid-1990s).

The fact that SFAs raise total and LDL cholesterol (lipid hypothesis) is well established by evidence from metabolic studies, but this paradigm may be too simplistic. Replacing SFAs with refined carbohydrates also decreases HDL cholesterol and LDL particle size and increases triglycerides, and highly refined carbohydrates increase plasma glucose. Beyond the lipoprotein phenotype, the whole metabolic profile is adversely affected by greater intakes of highly refined carbohydrates, eg, inflammatory markers and thrombotic factors (18). Although the direct causality of these metabolic changes remains unclear, each of these changes would predict a higher risk of CHD, which would counterbalance a reduction in LDL cholesterol by replacing SFAs with carbohydrates. Thus, mechanistic studies of blood lipids are consistent with epidemiologic studies, which suggest a lack of benefit in replacing SFAs with carbohydrates, and the type of carbohydrate (low compared with high glycemic index, refined starch and sugar-rich beverages compared with whole grains and fruit) should always be taken into account when data are interpreted. In fact, it is not very meaningful to discuss high-fat compared with low-fat or carbohydrate diets if one does not concomitantly consider the carbohydrate quality used or consumed in the population under study.

Most randomized controlled trials (RCTs) have been underpowered and not optimally designed (19), but some trials have produced supportive evidence of the benefits of substituting

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[3]This article reports consensus reached by all of the authors at a 2-d invitation-only symposium organized by AA and WCW and held in Copenhagen, Denmark, in May 2010.

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PUFAs for SFAs (20), and a meta-analysis of RCTs found a 10% reduction in CHD for each 5% of energy from SFAs substituted for PUFAs (13). No benefits have been found for substituting carbohydrates for SFAs (11, 13). However, the quality of carbohydrates was not addressed in these trials.

Many factors contribute to the decrease in CVD observed in many countries, including better treatments and changes in risk factors (21). To what extent changes in diet have contributed to the favorable changes in risk factors is uncertain, although before 1990 the declining CHD rates in the United States and Poland correlated with replacing SFAs with PUFAs (22).

The totality of evidence indicates that substituting PUFAs for SFAs is beneficial for lowering total and LDL cholesterol and for CHD prevention, but there is no evidence to support the benefit of substituting refined carbohydrates for SFAs. Insufficient evidence exists to judge the effect on CHD risk of replacing SFAs with MUFAs, mainly because the available data on MUFAs are limited and confounded by the food sources of MUFAs (eg, dairy and meats) in Western dietary patterns. No clear association was shown between intake of SFAs and insulin resistance and diabetes risk in some studies (23–25), although several controlled feeding studies and cohort studies suggest that, in comparison with n−6 PUFAs or MUFAs (from vegetable oils), independent of any body weight change, SFA intakes reduce insulin sensitivity and may increase the risk of diabetes (26).

Is there sufficient evidence for using biomarkers of CHD risk to validate the effects of diet on CHD?

Biomarkers can be useful in assessing risk, and strong evidence indicates that LDL particles are important for the development and progression of atherosclerosis and CHD. Indeed, LDL cholesterol is the most widely accepted lipid biomarker for CHD risk. However, convincing evidence from the Prospective Studies Collaboration meta-analysis supports that the ratio of total cholesterol to HDL cholesterol is a powerful predictor of CHD (27) and that this ratio is more predictive than is LDL cholesterol. Apolipoprotein B and non-HDL cholesterol are also biologically important markers and play roles in clinical risk assessment, particularly in individuals with the metabolic syndrome. There is growing evidence of the relation of specific LDL particle subclasses to CHD risk, but their levels tend to be correlated with other lipid measures (28). Triglyceride concentrations, both fasting and more importantly nonfasting (29, 30), are also relevant as indicators of CVD risk in the metabolic syndrome and insulin resistance. Lipoprotein(a) is a well-established marker of genetic predisposition to CHD, but uniform standards for clinical assays have not been established (31).

However, other biomarkers that explain CVD risk are desirable. Single risk factors have limitations when considered on their own because the effects of diet on CVD risk are mediated by many pathways, with blood lipids being only one. Although elevated LDL cholesterol is one of the major risk factors known, there is still a need for clinical endpoints for assessing the effects of diet on CVD risk. Also, we must consider the type of CVD—sudden death is different from stable plaque. A comprehensive risk score made up of multiple biomarkers of CHD risk, including total and HDL cholesterol, blood pressure, body fatness, glucose tolerance, and inflammatory markers, can substantiate the effects of diet on CHD risk, but the risk score should be consistent with other evidence. The effect of diet on a single biomarker may be insufficient evidence to assess CHD risk.

Should we distinguish between different SFAs in recommendations?

The individual SFAs have different physiologic effects. Limited epidemiologic evidence suggests that stearic acid is associated with CHD (32), but epidemiologic data cannot clearly distinguish C-18 from other SFAs in terms of CHD risk. In terms of cholesterol-raising effects, stearic acid is neutral, whereas other SFAs (12:0, 14:0, and 16:0) raise LDL and HDL cholesterol compared with carbohydrate, and it appears that C-14 has the strongest effects on LDL and HDL cholesterol (33). There is a lack of evidence on the effect of short-chain and medium-chain (4:0–10:0) SFAs on cholesterol and CHD risk. The amount of conjugated linoleic acid in the diet is generally very low and probably has negligible metabolic effects.

In terms of practical dietary recommendations, it is not feasible to separate different types of SFAs with respect to food choices, because the foods contain a combination of several SFAs. We do not yet have enough evidence to give dietary recommendations for individual SFAs, but the evidence is useful for advising food manufacturers, eg, stearic acid can be used as a replacement for *trans* fatty acids where appropriate, although the evidence is not sufficient to determine whether it is superior to other SFAs because multiple pathways may be involved and clear data on clinical endpoints are not available.

Should advice on SFA intake be based on food rather than on types of fatty acids?

Most dietary recommendations aim to reduce SFA intake to $\leq$10% of energy. Typically these recommendations do not specify the replacement macronutrient. The best evidence supports the benefits of substituting PUFAs for SFAs, but there is usually an upper limit of PUFA included in these recommendations. Any reductions in SFA intake to $<$10% of energy would require changes in dietary patterns, ie, a significant increase in intake of carbohydrates and/or MUFA-rich foods. Evidence from epidemiologic and intervention studies indicates that increasing the intake of refined (high glycemic index) carbohydrates would not be beneficial, although the quality of carbohydrates may be important (6). Although biomarker data, including the total cholesterol:HDL ratio, suggest that replacement with MUFAs would be beneficial, the evidence for the replacement in relation to clinical endpoints is currently limited (5).

Food-based recommendations are more practical for the general public than is nutrient-based dietary advice. However, the evidence linking individual foods or food patterns to CVD risk is more limited. The epidemiologic data provide strong evidence that a high intake of processed meat products, a major source of SFAs, is associated with an increased risk of CHD (32). There is no consistent evidence that a higher intake of dairy products is associated with CHD risk in epidemiologic studies (34), but data do support the beneficial effects of dairy products on type 2 diabetes risk (34, 35). However, intervention studies on the effect of dairy fat on the risk of CHD and diabetes are lacking; thus, the

role of SFAs in dairy fat still needs to be investigated. There is increasing evidence to support that the total matrix of a food is more important than just its fatty acid content when predicting the effect of a food on CHD risk, eg, the effect of SFAs from cheese on blood lipids and CHD may be counterbalanced by the content of protein, calcium, or other components in cheese. In addition, the special fatty acid profile (rumenic acid, *trans* vaccenic acid, and short-chain fatty acids) may modify the effect on CHD risk. Another example is dark chocolate, which has a high content of stearic acid, oleic acid, and polyphenols, and observational studies, mechanistic studies, and RCTs show that dark chocolate reduces risk factors of CVD (36).

Most epidemiologic studies and several intervention studies support the benefits of Mediterranean dietary pattern on CVD risk factors and hard endpoints (18, 37). Notably, the Mediterranean diet is low in SFAs and high in MUFAs. The data on the benefits of other dietary patterns, such as traditional Asian diets—which are very low in SFAs—are mainly derived from ecologic and cross-sectional studies. However, consistent evidence from epidemiologic studies and RCTs indicate that long-chain omega-3 (n−3) fatty acids are beneficial at preventing CHD.

It is quite clear that the effect of a specific food (eg, meat and dairy products) on risk of CVD cannot be determined simply on the basis of the fatty acid profile of a food. Epidemiologic studies have shown a lower risk of CVD with lower intakes of full-fat dairy products and fatty red meats and higher intakes of PUFAs from vegetable fats, which is consistent with strong evidence that replacing SFAs by PUFAs reduces the risk of CVD (38). The use of nonhydrogenated vegetable oils (including canola or olive oil rich in MUFAs) decreases the CVD risk compared with animal fats. Thus, although the evidence is stronger for PUFAs, indirect evidence suggests that SFAs could also be replaced with MUFAs as well as unrefined carbohydrates with a low glycemic index. A valuable way to communicate the message is to describe the broad dietary pattern that decreases CVD risk. Note that only a minority of different populations adhere to a healthy dietary pattern. A healthy dietary pattern is primarily plant-based and low in SFAs, but can include lean meats and low-fat dairy products in small-to-modest amounts.

Because CVD is the leading cause of death in most countries, the relation of diet to CVD should figure prominently in dietary recommendations. However, other important issues, such as obesity, and incidence of cancer and osteoporosis, should also be considered; at present there is no clear relation of SFA intake to these outcomes (39).

Gaps in our knowledge and research directions needed

1) Research is needed to clarify the role of SFAs in CVD risk compared with that of different forms of carbohydrates rather than carbohydrates as a whole (eg, carbohydrates from whole grains and refined carbohydrates).
2) Limited data have been published on the relation of specific foods to the risk of various diseases, although these data obviously have been collected and used to calculate nutrient intakes. Information about dietary patterns and risk of chronic diseases is available, but the data cannot be used to describe the role that individual foods may play in the risk of chronic disease. Thus, additional research is needed to examine individual foods (eg, cheese and red meats) and the risk of major disease (in the context of a healthy dietary pattern).
3) When specific foods are examined, are they being compared with appropriate alternatives? For example, it may not be useful, as is usually done, to compare a specific food to all other sources of energy, which are usually mainly refined starches, sugars, red meat, and fat-rich dairy products in typical Western diets. Other comparisons may be more informative, eg, cheese compared with butter compared with peanut butter compared with sausage compared with liver paste. Such analyses can be conducted on the basis of existing observational prospective studies, but can also be addressed in short-term human experimental intervention studies with surrogate endpoints.
4) The field of genomics may be important in explaining dietary responses via "Mendelian randomization" and interactions between diet and genotype. Research needs to be conducted in different parts of the world to better understand the responses of different populations to diet; eg, the role of MUFAs in CHD can be informed by studies from southern Europe, where olive oil is a major part of some diets.

Specific research issues

1) Foods and dietary patterns in relation to CVD endpoints and risk factors
2) Thorough evaluations of the effects of modified oils rich in stearic fat or other fatty acids as a replacement for cholesterol-raising SFAs
3) Intervention studies to assess the effects of short-chain and medium-chain (4:0–10:0) SFAs on CVD risk
4) Prospective cohort studies from different countries; country-specific data for making dietary recommendations
5) Pooling studies across multiple cohorts conducted in different populations
6) Biological interactions between insulin resistance, reflected by obesity and physical inactivity, and carbohydrate quality and quantity
7) The effects of early-life nutrition, especially different types of fatty acids, on developmental programming with respect to future risk of type 2 diabetes and CVD
8) Biomarkers of SFA-rich food intake (eg, 15:0, 17:0, and 14:0) for use in intervention studies to assess the effect of dairy foods on health outcomes, although there is also a need for better biomarkers that allow distinction of dairy foods from beef and lamb
9) Evaluation of the effect of dietary recommendations on eating behaviors and disease risk in the population
10) Translation of nutrient-based recommendations to food-based recommendations
11) The effects of food labeling, taxation, and global trade on diets

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