Dietary Fats and Cardiovascular Disease

A Presidential Advisory From the American Heart Association

ABSTRACT: Cardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year. Preventive treatment that reduces CVD by even a small percentage can substantially reduce, nationally and globally, the number of people who develop CVD and the costs of caring for them. This American Heart Association presidential advisory on dietary fats and CVD reviews and discusses the scientific evidence, including the most recent studies, on the effects of dietary saturated fat intake and its replacement by other types of fats and carbohydrates on CVD. In summary, randomized controlled trials that lowered intake of dietary saturated fat and replaced it with polyunsaturated vegetable oil reduced CVD by ≈30%, similar to the reduction achieved by statin treatment. Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and of other major causes of death and all-cause mortality. In contrast, replacement of saturated fat with mostly refined carbohydrates and sugars is not associated with lower rates of CVD and did not reduce CVD in clinical trials. Replacement of saturated with unsaturated fats lowers low-density lipoprotein cholesterol, a cause of atherosclerosis, linking biological evidence with incidence of CVD in populations and in clinical trials. Taking into consideration the totality of the scientific evidence, satisfying rigorous criteria for causality, we conclude strongly that lowering intake of saturated fat and replacing it with unsaturated fats, especially polyunsaturated fats, will lower the incidence of CVD. This recommended shift from saturated to unsaturated fats should occur simultaneously in an overall healthful dietary pattern such as DASH (Dietary Approaches to Stop Hypertension) or the Mediterranean diet as emphasized by the 2013 American Heart Association/American College of Cardiology lifestyle guidelines and the 2015 to 2020 Dietary Guidelines for Americans.

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Key Words: AHA Scientific Statements ■ blood cholesterol ■ cardiovascular diseases, atherosclerosis ■ cholesterol, LDL ■ dietary fats ■ fatty acids, saturated ■ fatty acids, unsaturated

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Cardiovascular disease (CVD) is the leading global cause of death, accounting for 17.3 million deaths per year, comprising 31.5% of total global deaths in 2013. Nearly 808 000 people in the United States died of heart disease, stroke, and other CVDs in 2014, translating to about 1 of every 3 deaths. The annual direct and indirect costs of these deaths total more than $316.1 billion, including health expenditures and lost productivity.[1] Preventive treatment that reduces CVD by even a small percentage can substantially reduce, nationally and globally, the number of people who develop CVD and the costs of caring for them.

Since 1961, the American Heart Association (AHA) has recommended reduction in dietary saturated fat to reduce the risk of CVD.[2,3] The purpose of this AHA presidential advisory on dietary fats and CVD is to review and discuss the scientific evidence, including the most recent studies, on the effects on CVD of dietary saturated fat and its replacement by other types of fats and carbohydrates. A presidential advisory is initiated by the AHA president to address a topic of special current importance. This report discusses the major classes of dietary fatty acids, except for the very-long-chain n-3 fatty acids in fish, which are covered by other AHA reports.

The scientific rationale for decreasing saturated fat in the diet has been and remains based on well-established effects of saturated fat to raise low-density lipoprotein (LDL) cholesterol, a leading cause of atherosclerosis[4]; to cause atherosclerosis in several animal species, especially nonhuman primates[5]; to clear the atherosclerosis in animals[6] when it is reduced in the diet; and likewise to reverse atherosclerosis in humans.[7,8] In addition, reducing saturated fat and replacing it with polyunsaturated fat in randomized controlled trials has reduced the incidence of CVD.[9,10] Populations with very low saturated fat intake such as in East Asian and Mediterranean countries have very low rates of CVD,[11] and members of many single populations who have low saturated and high unsaturated fat intake have lower future incidence of CVD compared with those with high saturated and low unsaturated fat intake.[12] The current AHA/American College of Cardiology guideline is to decrease intake of saturated fat to 5% to 6% of total daily energy (calorie) intake for individuals with elevated LDL cholesterol concentration.[3] The 2015 to 2020 Dietary Guidelines for Americans recommend consuming <10% of calories from saturated fat for the general population and replacing saturated fat with unsaturated fat.[13] The average intake of saturated fat in adults in the United States is 11% of total daily energy intake[13,14]; only about 5% of adults consume <7%, and 30% to 40% consume <10%.[14] Thus, most adults need to reduce saturated fat to reduce their risk of CVD. The implementation strategy recommended to achieve this reduction is to shift food choices from those high in saturated to those high in polyunsaturated and monounsaturated fats.[3,13]

In the past few years, meta-analyses of observational studies and randomized clinical trials have come to discordant conclusions about the relationship between dietary saturated fat and risk of CVD.[9,10,12,15–17] This has created confusion among patients, their physicians, and the public. In this article, we analyze and discuss the methodology and interpretation of results reported by these researchers and the reasons for the divergent findings.

SUMMARY OF CONCLUSIONS

Dietary saturated fat, like any macronutrient, supplies energy (calories) to the diet. In randomized clinical trials on saturated fat, the group that is assigned a diet lower in saturated fat is taught how to replace it with foods higher in ≥1 other macronutrients, typically carbohydrates or unsaturated fats, to maintain the same total energy intake. Other trials, often called controlled feeding trials, actually provide to the research participants their assigned diet high or low in saturated fat balanced with a similar amount of energy from another macronutrient. Essential to the interpretation of the results from these trials (and the reason for the divergent results in meta-analyses noted above) is the macronutrient composition of the comparator diet. Clinical trials that used polyunsaturated fat to replace saturated fat reduced the incidence of CVD.[9,10] In contrast, trials that used mainly carbohydrates to replace saturated fat did not reduce CVD. However, the types of carbohydrate-containing foods were often unspecified and typically included sugar and other refined carbohydrates to maintain energy balance. Evidence from prospective observational studies indicates that carbohydrates from whole grains reduce CVD when they replace saturated fat.[18]

Prospective observational studies, also called cohort studies, are conducted in large populations in which dietary intake is assessed at the beginning of the study and in some studies reassessed repeatedly during the follow-up periods, and CVD is assessed at various points during follow-up. In prospective observational studies, the participants eat whatever diet they themselves choose, and the researchers request that participants report their recent or past dietary history. Research participants in observational studies who eat a large amount of saturated fat eat less of various other macronutrients, usually carbohydrates, unsaturated fat, or both, to maintain energy intake. Participants who eat a comparatively small amount of saturated fat eat more carbohydrates or unsaturated fats. Because carbohydrates and unsaturated fats differ in their metabolic effects, it is necessary to evaluate the effects of low and high saturated fat intakes in the context of the replacement

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Circulation. 2017;136:e1–e23. DOI: 10.1161/CIR.0000000000000510

macronutrient. This is easier in a clinical trial because the trial controls the dietary intake but more complicated in observational studies in which the participants control their own diets.

Meta-analyses of prospective observational studies aiming to determine the effects on CVD of saturated fat that did not take into consideration the replacement macronutrient have mistakenly concluded that there was no significant effect of saturated fat intake on CVD risk.[15,16] In contrast, meta-analyses that specifically evaluated the effect of replacing saturated fat with polyunsaturated fat found significant benefit, whereas replacing saturated fat with carbohydrates, especially refined carbohydrates, yielded no significant benefit to CVD risk.[12,17,18] Thus, again, differences in the effects of the replacement or comparator nutrients, specifically carbohydrates and unsaturated fats, are at the root of the apparent discrepancies among studies and meta-analyses on whether lowering saturated fat reduces the risk of developing CVD. In fact, the evidence to recommend reduction of saturated fat and its replacement by polyunsaturated and monounsaturated fat has strengthened as better methodology is more widely adopted for the analysis of dietary intake in observational studies.

We judge the evidence to favor recommending n-6 polyunsaturated fat, that is, linoleic acid, stronger than monounsaturated fat to replace saturated fat because of the positive results of randomized clinical trials that used polyunsaturated fat compared with the paucity of trials that used monounsaturated fat[10]; the greater relative risk reduction for polyunsaturated fats in observational studies[12,17,18]; the greater reduction in LDL cholesterol with polyunsaturated fat[4]; and the regression of atherosclerosis in nonhuman primates by polyunsaturated but not monounsaturated fat.[5] However, progress in reducing CVD would be enhanced by replacing saturated fat by either type of unsaturated fat.

FATTY ACID COMPOSITION OF FATS AND OILS

The fatty acid composition of major fats and oils in the diet is shown in the Table.[19] The main sources of saturated fat to be decreased are dairy fat (butter), lard (pork), beef tallow, palm oil, palm kernel oil, and coconut oil. Polyunsaturated fats are contained in canola oil, corn oil, soybean oil, peanut oil, safflower oil, sunflower oil, and walnuts. However, original high-linoleic varieties of safflower and sunflower oils are uncommon. High-oleic varieties of safflower and sunflower oil, olive oil, avocados, and tree nuts such as almonds, cashews, hazelnuts, pistachios, and pecans have mainly monounsaturated fats and are low in saturated fat.

CVD OUTCOMES: RANDOMIZED CLINICAL TRIALS THAT LOWERED DIETARY SATURATED FAT

The randomized clinical trial, when designed appropriately to answer the research question and executed with high quality, is the cornerstone for health and medical guidelines and policy. However, a randomized trial of a food or nutrient must achieve a biologically meaningful difference in intake between treatment and control groups and sustain it for a long enough time to deliver a valid result. Participants may find it difficult to maintain intake of a diet to which they are not accustomed and may revert to their original more familiar diet. In some trials, the difference in dietary saturated fat was maintained for many years,[20–22] but in others, the difference fell well short of planned.[23–25] In addition, the comparator nutrient that replaced saturated fat, polyunsaturated fat or carbohydrates, differed among trials. Reviewers who evaluate these trials must take into account the specific nutritional experiment that was conducted and the level of its adherence throughout the follow-up period.

Low Saturated, High Polyunsaturated Fat Diets

In the mid-1950s, 4 research groups reported that replacing saturated fat from animal products with polyunsaturated fat from vegetable oils substantially reduced serum cholesterol levels.[26–29] Soon, controlled trials followed to test whether the reduction in serum cholesterol caused by substituting polyunsaturated for saturated fat prevented CVD. We examined several recent systematic reviews and meta-analyses[9,10,16] from which we identified and here discuss 4 trials[20–22,30] that make up the core evidence on this important question on the basis of quality of study design, execution, and adherence. These trials compared high saturated with high polyunsaturated fat intake; did not include *trans* unsaturated fat as a major component; controlled the dietary intake of the intervention and control groups; had at least 2 years of sustained intake of the assigned diets; proved adherence by objective biomarkers such as serum cholesterol or blood or tissue levels of polyunsaturated fatty acids; and collected and validated information on cardiovascular or coronary disease events. The reason for the 2-year minimum duration is that changes in polyunsaturated fatty acids very slowly equilibrate with tissue fatty acid levels; it takes ≈2 years to achieve 60% to 70% of the full effect.[20,30] Trials of serum cholesterol–lowering agents show that a reduction in coronary heart disease (CHD) incidence occurs with a lag of 1 to 2 years.[31] These systematic reviews[9,10,16] together found and analyzed 6 additional trials[7,23,32–35] that replaced saturated with polyunsaturated

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Table. Fatty Acid Composition of Fats and Oils

	Saturated, g/100 g			Monounsaturated, g/100 g		Polyunsaturated, g/100 g		
	Total	Lauric (12:0), Myristic (14:0), Palmitic (16:0)	Stearic (18:0)	Total	Oleic (18:1)	Total	Linoleic (18:n-6)	α-Linolenic (18:3n-3)
Canola oil	7	4	2	63	62	28	19	9
Coconut oil	82	67	3	6	6	2	2	0
Corn oil	13	11	2	28	27	55	53	1
Dairy fat (butter)	63	39	12	26	21	4	3	0
Lard (pork)	39	25	14	45	41	11	10	1
Olive oil	14	11	2	73	71	10	10	1
Palm oil	49	45	4	37	37	9	9	0
Palm kernel oil	82	72	3	11	11	2	2	0
Peanut oil	17	10	2	46	45	32	32	0
Safflower oil (high linoleic)	6	4	2	14	14	75	75	0
Safflower oil (high oleic)*	8	5	2	75	75	13	13	1
Soybean oil	16	10	4	23	23	58	50	7
Sunflower oil (high linoleic)	10	6	4	20	20	66	66	0
Sunflower oil (high oleic)*	10	5	4	84	83	4	4	0
Tallow (beef)	50	30	19	42	36	4	3	1

A zero value equals <0.5 g/100 g.
*Primary safflower and sunflower oils of commerce.
Data from US Department of Agriculture food composition tables.[19]

fat but did not have ≥1 of these characteristics crucial to testing the hypothesis. We also discuss these "noncore" trials and evaluate their potential impact on the overall result on dietary saturated and polyunsaturated fat and risk of CVD.

Core Trials on Replacing Saturated With Polyunsaturated Fat

The Wadsworth Hospital and Veterans Administration Center in Los Angeles (Dayton et al[20]) conducted a high-quality, double-blind, well-controlled trial. There were 846 men with a mean age of 65 years, and 30% had CVD. The experimental diet used corn, soybean, safflower, and cottonseed oils, all high in polyunsaturated linoleic acid, to replace saturated fat in the control diet. The participants were served their meals at the center, with each diet group in a separate dining room. Adherence was confirmed by objective measures demonstrating enrichment with linoleic acid in blood, adipose tissue, and atherosclerosis specimens in the coronary arteries and aorta. Moreover, the investigators established double-blind conditions. The average duration was 8 years. The experimental diet reduced serum cholesterol by 13%. There were 20% fewer primary events, myocardial infarction or sudden death, in the diet group than in the control group, not a statistically significant difference. The diet significantly reduced the CVD end point, definite myocardial infarction, sudden death, or ischemic stroke, by 34% (P=0.04) and total CVD events by 31% (P=0.01). There were 41% fewer men who had an ischemic stroke in the diet group than in the control group (P=0.055).

By contemporary standards, the trial needed more participants to reach a definitive conclusion. However, the strict dietary control and 8-year-long intervention period ensured both a large difference in the dietary fatty acid intakes and enough CVD events to reach a statistically significant treatment effect for the secondary CVD outcomes, which were more highly powered because of their larger numbers of events.

The Oslo Diet-Heart Study[21] assigned at random 412 men who had had a myocardial infarction to either a control group who continued their usual high-saturated fat diet or an experimental group who changed to a low saturated, high polyunsaturated fat diet. The men in the experimental group and their wives were taught in their homes how to select and prepare foods that were low in saturated fat and high in polyunsaturated vegetable oils. The polyunsaturated fat diet lowered serum cholesterol by 14% (41 mg/dL), thereby confirming adherence, and this effect was sustained throughout the 5-year trial. The polyunsaturated fat diet significantly reduced the primary outcome, recurrent myocardial infarction and new cases of angina pectoris or sudden death, significantly by 29% (P=0.011). Among the components of the primary outcome, myocardial infarction and angina pectoris were significantly reduced by 37% and 66%, respectively, whereas incidence of sudden death was the same in both groups. The end point, myocardial

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infarction or sudden death, was reduced by 25% (*P*=0.05). There were fewer cardiovascular deaths in the experimental group by 27% (*P*=0.09). The low saturated, high polyunsaturated fat group continued to experience reduced cardiovascular mortality compared with the high saturated fat control group for an additional 6 years after the trial ended.

The British Medical Research Council compared a diet containing soybean oil, 86 g/d, with a diet with saturated fat from animal products in 393 men after myocardial infarction.[22] They were instructed to drink half the soybean oil allotment with fruit juice and use half in cooking, and they were counseled on how to reduce the saturated fat in their diet so that the total fat contents of the intervention and control groups were similar. Replacing animal fat with soybean oil lowered serum cholesterol by 16%. The primary outcome was first relapse (myocardial infarction, angina, sudden death). After 4 years, 62 of 199 in the soybean oil group had had a recurrent coronary event compared with 74 of 194 in the high saturated fat group; the difference, −18% (95% CI, −38 to 7), was not statistically significant.

The Finnish Mental Hospital Study compared a diet high in polyunsaturated fat, mainly from soybean oil, with a diet high in saturated fat in 1222 patients at 2 psychiatric hospitals.[30,36,37] In 1 hospital, the high polyunsaturated fat diet was given first, followed by the saturated fat diet; in the other hospital, the diets were given in the reverse order. Each diet period lasted 6 years. There were 2 cohorts. One comprised the entire patient populations of the 2 hospitals; 25% had evidence of CHD on an ECG, and 57% were women. The other cohort included only patients who had no evidence of CHD, that is, a primary prevention cohort. Women made up 44%. Serum cholesterol was 38 mg/dL (14%) lower on the high polyunsaturated fat diet than on the high saturated fat diet. Adherence was also demonstrated by 3-fold enrichment of linoleic acid in adipose tissue. In the mixed primary and secondary prevention cohort, CHD death, the primary outcome, was significantly lower by 41% (95% CI, −26 to −53) during the polyunsaturated than the saturated fat diet (Figure 1). In the primary prevention cohort, CHD death or myocardial infarction was the primary outcome, and the incidence was significantly lower also by 41% (95% CI, −17 to −58) during the polyunsaturated than during the saturated fat periods. In each hospital, CHD events were lower during the times when the polyunsaturated fat diet was given. Results were similar in men and women.

We performed a fixed-effects meta-analysis of these 4 core trials using the primary outcome chosen by each trial (Figure 2). This approach ensures that the results of the meta-analysis are based on prospectively defined primary outcomes, thereby having more validity than an alternative approach that redefines a new common outcome for all the component trials. This alternative approach would have a serious weakness, the selection of a new outcome that is post hoc and potentially influenced by researchers' bias. We included the entire Finnish trial population, primary and secondary prevention, women and men combined.

The results showed that lowering saturated fat and replacing it with vegetable oil rich in polyunsaturated fat, primarily soybean oil, lowered CHD by 29%. This effect on CHD is consistent with the effect of the experimental diet on serum cholesterol.[31] Each trial achieved a crucial element in clinical trial execution, producing and maintaining the required difference in diets as objectively documented by blood and tissue fatty acid biomarkers and serum cholesterol, that was needed to test the study aim. However, these trials were conducted in the 1960s, before widespread use of statins, when serum cholesterol levels were higher than now, as was the saturated fat content of the diet.

In addition to replacing dietary saturated fat with polyunsaturated fat, these clinical trials lowered dietary cholesterol. The cholesterol content of the diets was listed in 3 of the core trials.[20,22,30] We used the Keys[38] equation to estimate that the decreased cholesterol intake lowered serum cholesterol by ≈5 to 8 mg/dL, making up 15% to 20% of the total reduction in serum cholesterol. For example, in the Dayton et al[20] study, cholesterol intake decreased from 653 to 365 mg/d, and serum cholesterol decreased from 233 to 203 mg/dL, a 30-mg/dL difference, of which 6 mg/dL was accounted for by reduced dietary cholesterol. Because many foods that are high in saturated fat also contain cholesterol, the benefits to serum cholesterol lowering by reducing saturated fat will be augmented by consequent reduction in dietary cholesterol.

Noncore Trials on Replacing Saturated With Polyunsaturated Fat

In addition to the 4 core trials, several other trials aimed to test the hypothesis that replacing saturated with polyunsaturated fats reduces CHD.[7,23,32–35] We did not include these trials in our core group because they had a mixed dietary intervention in which polyunsaturated and carbohydrate replaced saturated fat and had insufficient duration, low adherence, few events, and/or serious flaws in study design. STARS (Saint Thomas Atherosclerosis Regression Study) was a 3.3-year trial that achieved its primary aim of reducing the severity of stenoses (blockages) in the coronary arteries.[7] The dietary treatment lowered saturated fat intake and replaced it with carbohydrates and polyunsaturated fat. The diet lowered serum cholesterol by 11%. CVD events (fatal CHD or nonfatal myocardial infarction) occurred in 2 of 27 participants in the diet group versus 5 of 28 in the control group.

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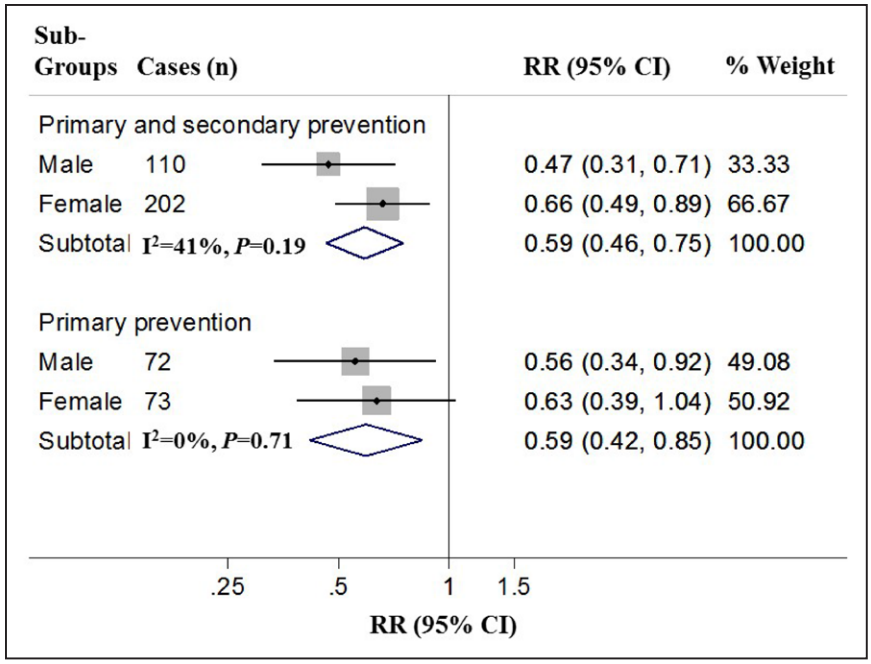

Figure 1. Finnish Mental Hospital Study.[30,36,37] Significant reduction in coronary heart disease (CHD) by replacing saturated with polyunsaturated fat. Results are shown separately for participants in the primary and secondary CHD prevention cohorts of the trial and participants who were in the primary CHD prevention cohort. Relative risks (RRs) of the primary CHD outcome, CHD death, were calculated on the basis of age-adjusted deaths rates, and results were pooled across sex by inverse-variance fixed-effects meta-analyses. CI indicates confidence interval. Meta-analysis by Drs Yanping Li and Jason H.Y. Wu.

The Welsh DART study (Diet and Reinfarction Trial)[23] compared the effect of fat advice with no fat advice on CVD during 2 years. The fat advice group reduced saturated fat from 15% to 11% of total calories, increased polyunsaturated fat from 7% to 9%, and increased carbohydrate intake from 44% to 46%. These changes fell well short of intended and produced only a 3.5% reduction in serum cholesterol. There were 8% fewer men with CHD death or nonfatal myocardial infarction in the fat advice group compared with the no-fat advice group, not statistically significant but similar to what is predicted from the small decrease in serum cholesterol.[31]

Houtsmuller et al[32] conducted a 6-year trial in patients with newly diagnosed diabetes mellitus that reduced saturated fat and replaced it with mainly polyunsaturated fat. Serum cholesterol decreased significantly by 7%. The high polyunsaturated, low saturated fat diet reduced the progression of diabetic microvascular disease, which was the primary outcome. CVD events were determined by electrocardiography; however, those reading the ECGs were not blinded to treatment assignment. For this reason, this trial was not included in the core group. The high polyunsaturated, low saturated fat group experienced significantly fewer CVD events, 8 of 51 versus 24 of 51, a 67% reduction, much greater than the 12% predicted by the modest lowering of serum cholesterol.

Rose et al[33] conducted a trial in male patients with CVD that replaced saturated fat with polyunsaturated

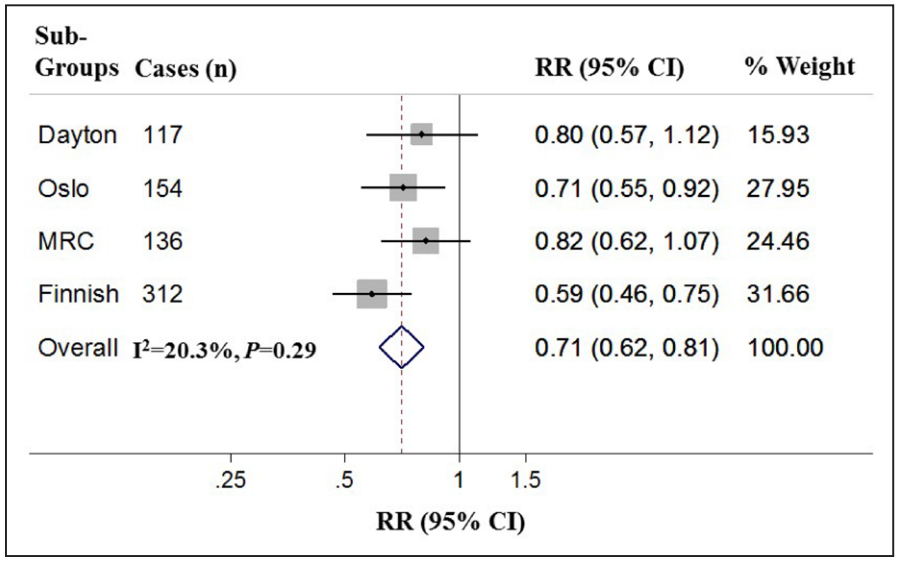

Figure 2. Meta-analysis of core trials on replacing saturated with polyunsaturated fat. Significant reduction in coronary heart disease (CHD). Relative risk (RR) of the primary CHD outcome of each trial. Findings across studies were pooled by inverse-variance fixed-effects meta-analyses. Risk reduction is the same with random-effects meta-analysis: RR, 0.71 (95% confidence interval [CI], 0.61–0.83). Data are from Dayton et al,[20] Oslo Diet-Heart Study,[21] Medical Research Council,[22] and Finnish studies.[30,36,37] Result from the Finnish trial used the total cohort (ie, patients who participated in the primary or secondary prevention cohorts). Meta-analysis by Drs Yanping Li and Jason H.Y. Wu.

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corn oil. There were 26 patients in the control group and 28 in the corn oil group. The mean duration for receiving corn oil was 1.5 years. There were 12 cardiovascular events in the corn oil group versus 6 in the control group, not a statistically significant difference. The small number of participants and short duration of the trial excluded it from the core group.

The Minnesota Coronary Survey[34] compared high polyunsaturated with high saturated fat diets in patients hospitalized for mental illness. The participants were given the assigned diets only when they were patients in the hospital. Because hospitalization for mental illness became less common and less prolonged after the study started, as a national trend, the patients received the assigned diets intermittently, contrary to the intent of the researchers, and for a much shorter time than planned. The researchers originally enrolled 9570 participants in the trial and intended to study them for at least 3.6 years to be able to adequately test the effect of the diets. However, the trend toward outpatient treatment of mental illness resulted in ≈75% of the participants being discharged from inpatient care during the first year of the study. Only about half the remaining patients stayed in the study for at least 3 years. The average duration was only 384 days. The incidence of CHD events was similar in the 2 groups, 25.7 and 27.2 per 1000 person-years in the control and polyunsaturated fat groups, respectively. A recent reanalysis of this trial restricted to the participants who remained in the trial for at least 1 year also found no significant differences in CHD events or CHD deaths.[39] We excluded this trial from the core group because of the short duration, large percentage of withdrawals from the study, and intermittent treatment, which is not relevant to clinical practice. Another concern is the use of lightly hydrogenated corn oil margarine in the polyunsaturated fat diet. This type of margarine contains *trans* linoleic acid, the type of *trans* fatty acid most strongly associated with CHD.[40]

The Sydney Heart Study[35] was unique among the diet trials on CVD because a margarine high in *trans* unsaturated fat was a major component of the diet for participants assigned to the high polyunsaturated diet. When this trial was conducted, there was little recognition of the harms of *trans* unsaturated fat in partially hydrogenated vegetable oils, so the researchers inadvertently tested substitution of saturated with an even more atherogenic *trans* fat. As predicted from current knowledge about *trans* unsaturated fat, CVD events were higher in the experimental group. If anything, this trial confirmed the results of observational studies that also report higher CVD risk from results from regression models in which *trans* unsaturated fat replaced saturated fat.[41,42] We did not include this trial in our evaluation of the effects of lowering dietary saturated fat because *trans* fats are not recommended[3,13] and are being eliminated from the food supply.[43]

Two meta-analyses[9,16] analyzed the 4 core trials plus Minnesota,[34] STARS,[7] and DART.[23] Both meta-analyses showed a significant reduction in CVD of 19% by replacing saturated with polyunsaturated fat. Another systematic review and meta-analysis[10] included the Dayton et al study,[20] the Oslo Diet-Heart Study,[21] the Medical Research Council study,[22] the study by Houtsmuller et al,[32] the Rose et al study,[33] and the Sydney Diet Heart Study[35] and excluded the Finnish trial.[30,36,37] The Finnish trial was not included because it had 2 hospitals rather than at least 6 in the cluster randomization scheme, as required by the researchers conducting this meta-analysis.[10] In this group of trials, reduced saturated fat and increased polyunsaturated fat significantly lowered CVD events by 27% (see Table 9 in Reference 10). The extent of reduction in dietary saturated fat was significantly associated with the extent of decrease in CVD events among the trials. Reduction in serum cholesterol, as a consequence of reduced saturated fat and increased polyunsaturated fat, explained virtually all the variation among the trials in CVD event reduction.

The core trials reviewed in this section were started in the late 1950s and early 1960s. Readers may wonder why at least 1 definitive clinical trial has not been completed since then. Reasons include the high cost of a trial having upward of 20 000 to 30 000 participants needed to achieve satisfactory statistical power, the feasibility of delivering the dietary intervention to such a large study population, technical difficulties in establishing food distribution centers necessary to maintain high adherence for at least 5 years, and declining CVD incidence rates caused by improved lifestyle and better medical treatment. These linked issues, which must be managed to obtain a definitive result, remain the central considerations for dietary trials on CVD and indeed are the overarching reason why few of these trials have ever been done. Finally, by the 1980s, with rising rates of breast and colon cancer, the US government committed to conducting the WHI (Women's Health Initiative),[24] a trial that studied a diet aimed at decreasing total fat in the diet to 20% with the expectation that saturated fat would likewise be substantially decreased. Consequently, carbohydrates were increased in the diet. Details are discussed subsequently.

In summary, randomized controlled trials that lowered intake of saturated fat and replaced it with polyunsaturated vegetable oil reduced CVD events by ≈30%, similar to the reduction achieved by statin treatment.[31] Adding trials weakened by a short duration, low adherence, or use of *trans* unsaturated fat partially diluted the effect of the higher-quality core trials, but the results of meta-analyses that included both core and noncore trials still showed significant and substantial reduction in CVD when saturated fat is replaced with polyunsaturated fat.[9,10,16]

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Low-Fat, High-Carbohydrate Diets

Few trials have studied the effect of reducing saturated fat and replacing it mainly with carbohydrates, without including with the diet other treatments such as antihypertensive or lipid-lowering medication. The British Medical Research Council[25] studied 252 men after myocardial infarction aiming to reduce total fat from 41% to 22% and maintaining it at 41% in the control group. The type of fat was similar in the high- and low-fat groups, mainly saturated fat from dairy products and meat. The low-fat, high-carbohydrate diet lowered serum cholesterol by 5%, less than expected from the planned reduction in saturated fat. The researchers remarked that the low-fat diet was unpleasant and difficult to tolerate. There were 48 CHD events in the control group compared with 46 in the low-fat group. The specific carbohydrate-containing foods in the low-fat diet group were not described except that sugar intake and skim milk were increased and biscuits and cakes were decreased.

DART, described previously,[23] lowered total fat from 35% to 31% by reducing saturated fat, replacing it partly with carbohydrates and partly with polyunsaturated fat. The reduction in CHD events, 8%, was not significant.

Originally designed as a diet study to prevent breast and colon cancer, the WHI tested the hypothesis that reducing all types of fats and replacing them with high-carbohydrate foods, particularly fruits and vegetables, decreases CVD.[24] Enrolled between 1993 and 1998 and conducted in postmenopausal women 50 to 79 years of age, this trial assigned 30 000 women at random to maintain their usual high-fat diet (37% of total energy intake) and 20 000 to a low-fat diet (20% of energy intake). They were followed up for 8 years. This trial was not a test of reduction purely in saturated fat because monounsaturated and polyunsaturated fats were also reduced to meet the primary dietary objective of decreasing total fat. The emphasis on reduction of all types of fat came from its primary aim to test the hypothesis that decreasing dietary fat of any kind reduces breast and colon cancer. The effect of this type of diet on CVD was a secondary aim. After 5 years, the low-fat diet group lowered LDL cholesterol by 4 mg/dL, an ≈3% reduction, similar to the British Medical Research Council trial[25] and DART.[23] Similar to those studies, the participants in the low-fat group did not achieve the goal for reducing dietary fat (24% after the first year and 29% after the eighth year compared with 35% and 37%, respectively, in the control group). Also like the earlier studies, the low-fat diet in the WHI had no significant effect on coronary events or stroke.

A systematic review and meta-analysis[10] identified 6 trials that reduced saturated fat, replacing it mainly with carbohydrates. In contrast to the favorable results of trials using polyunsaturated fat as the replacement macronutrient reported in the same article,[10] the low-fat, high-carbohydrate approach did not significantly reduce CVD events (relative risk, –7%; 95% CI, –21 to 8).

In summary, a dietary strategy of reducing intake of total dietary fat, including saturated fat, and replacing the fats mainly with unspecified carbohydrates does not prevent CHD. In contrast to trials of polyunsaturated fat, adherence to the low-fat regimen fell short of the intention, impairing the ability of the trials to test a biologically based or efficacy hypothesis. The authors of these and other dietary trials[20,23,25] remarked on the difficulty experienced by participants in adhering to and maintaining goals to reduce dietary total fat. Finally, we note that a trial has never been conducted to test the effect on CHD outcomes of a low-fat diet that increases intake of healthful nutrient-dense carbohydrates and fiber-rich foods such as whole grains, vegetables, fruits, and legumes that are now recommended in dietary guidelines.

CVD OUTCOMES: PROSPECTIVE OBSERVATIONAL STUDIES

Prospective observational studies of diet and disease refer to research in which large populations provide information on their diet, lifestyle, health, and other characteristics and behaviors at the beginning and then are followed up for many years for the occurrence of disease.[44] This research technique has several key advantages over randomized controlled trials but also important weaknesses. Compared with clinical trials, prospective observational studies include larger and potentially more representative populations and have longer durations. Most important, participants choose their own intake of foods and beverages and do not have to adapt their diet to randomized diet assignment; therefore, the problem of sustaining adherence has no relevance. Furthermore, prospective observational studies can update dietary information periodically during the follow-up period. Observational studies are much less expensive than randomized controlled trials (expressed as cost per participant or cost per hypothesis tested). However, the observational approach likewise has weaknesses. Participants who have a high intake of saturated fat may have dietary and nondietary characteristics that differ from those with low intake of saturated fat, and these differences could affect CVD, creating a confounding situation. Incomplete or inaccurate ascertainment of dietary components can affect associations with disease. Meticulous collection of diet and health information and the statistical methods used can reduce or even eliminate the influence of confounding to isolate the effect of the nutrient itself. In summary, randomized controlled trials and prospective

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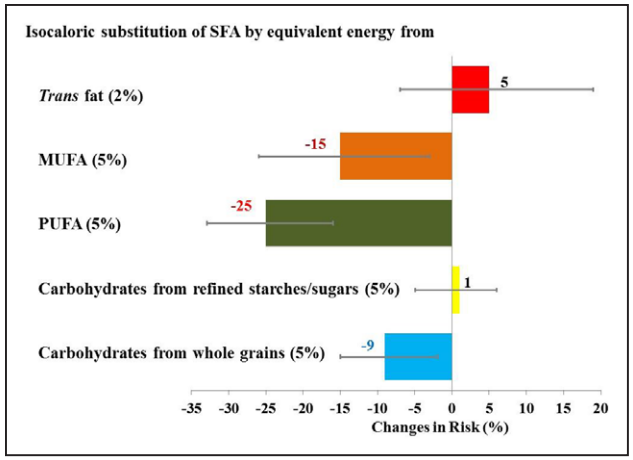

Figure 3. Replacement of saturated fat with other types of fat or carbohydrates.
Association with risk of cardiovascular disease in the Nurses' Health Study and Health Professionals Follow-Up Study. Multivariable adjustment. MUFA indicates monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; and SFA, saturated fatty acids. Modified from Li et al[18] with permission from The American College of Cardiology Foundation. Copyright © 2015, The American College of Cardiology Foundation.

observational studies are complementary research approaches. When the results are similar, the assumption of causality is strengthened between consumption of a dietary component and disease.

Fundamentally, methodology in observational analyses of diet and disease differs from that in analyses of biomarkers and genetic markers in relation to disease risk and is less familiar to scientists who work in other fields of epidemiology or in clinical trials. Observational studies in nutrition have special complexities, especially when studying foods or macronutrients such as fat and carbohydrates that make up a substantial portion of daily energy intake. For example, a low saturated fat intake occurs in the context of different dietary patterns, including low-fat, high-carbohydrate diets or Mediterranean diets high in unsaturated fat.

In North America and many European countries, the diets of people who eat a low-saturated fat diet typically are high in refined carbohydrates and low in unsaturated fats. For this reason, comparing CVD incidence in those with high and those with low saturated fat intakes primarily compares saturated fat with carbohydrates, most coming from refined grains, fruit juice, sweet desserts and snacks, sugar-sweetened beverages, and other foods. Well-publicized results of a meta-analysis reporting that saturated fat is not associated with CVD implicitly compare a high saturated fat diet with commonly eaten diets low in saturated fat and high in carbohydrate-containing foods made with refined carbohydrates and added sugars that themselves are associated with CVD.[15,16]

Further adding complexity, high-carbohydrate foods are very heterogeneous and may have beneficial or harmful associations with disease. For example, high-carbohydrate diets that include whole grains and cereal fiber are associated with lower rates of CVD, whereas refined grains and added sugars are associated with higher rates (Figure 3).[18]

Therefore, it is critical to the interpretation of findings in nutritional epidemiological studies that the contrast in dietary patterns between high and low saturated fat intake be well characterized. Simply comparing disease rates between people in a population who have low compared with high intake of saturated fat is fraught with potential for misinterpretation and misunderstanding.

Willett[44] developed a statistical framework for multivariable regression analysis that isolates effects of specific macronutrient exchanges. The method compares high saturated fat intake separately with high polyunsaturated fat, monounsaturated fat, *trans* unsaturated fat, and carbohydrates. The multivariable analysis equalizes other prognostic factors. In this way, the method simulates a randomized trial that compares 5 diets differing in type and amount of fat and carbohydrates. To determine the relationship of saturated fat with CVD outcomes in prospective observational studies, we used systematic reviews and meta-analyses published from 2009 to 2015,[12,17] the 2015 US Dietary Guidelines Advisory Committee Report,[13] and studies published after the report was released.[18,45] We considered studies that used multivariable regression analysis that isolates effects of specific nutrient exchanges.

The results showed that replacing 5% of energy intake from saturated fats with equivalent energy intake from polyunsaturated fats, monounsaturated fats, or carbohydrates from whole grains was associated highly significantly with a 25%, 15%, and 9% lower risk of CHD, respectively (Figure 3).[18] Replacing saturated fats with carbohydrates from refined starches/added sugars was not significantly associated with CHD risk (1% higher incidence). This pattern of results on dietary fats and CHD continued in analyses of total and cause-specific deaths; replacement of saturated fat by polyunsaturated fat (mainly linoleic acid) or monounsaturated fat was associated with lower rates of not only CVD death but also all deaths, deaths resulting from CVD, cancer, neurodegenerative disease, and lung disease (Figure 4).[45]

Key Points: Randomized Clinical Trials and Prospective Observational Studies on Replacement of Dietary Saturated Fat With Polyunsaturated or Monounsaturated Fat or Carbohydrates

- Four core randomized trials replacing saturated fat with polyunsaturated fat had at least 2 years'

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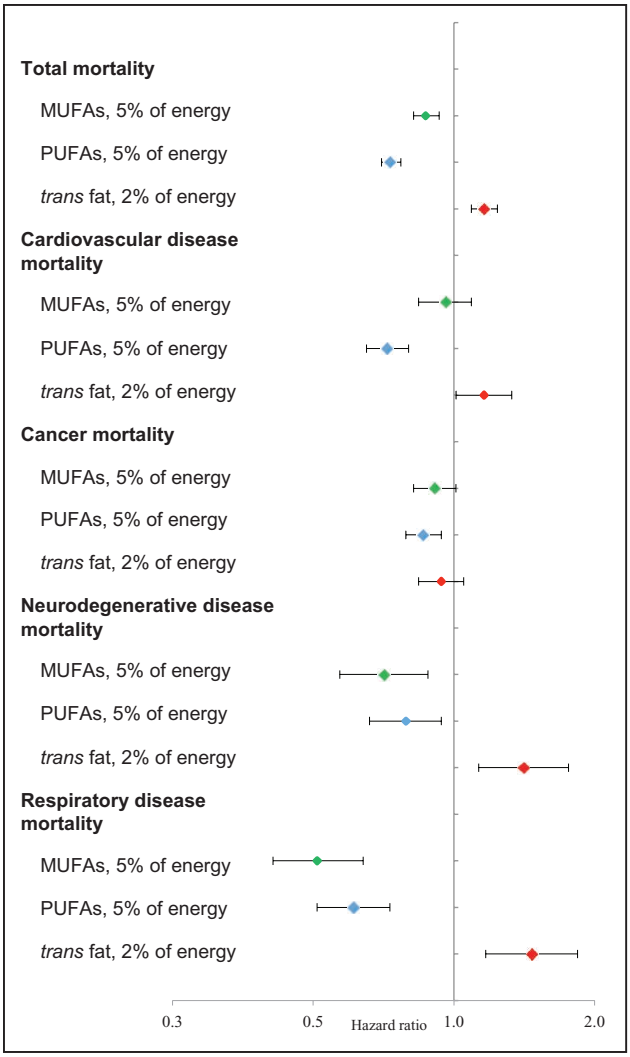

Figure 4. Replacement of saturated fat with other dietary fats.
Total and cause-specific mortality. Hazard ratio (95% confidence interval) for substituting energy from saturated fat by the same energy from specific types of fat. Nurses' Health Study and Health Professionals Follow-up Study. MUFA indicates monounsaturated fatty acids; and PUFA, polyunsaturated fatty acids. Modified with permission from Wang et al.[45] Copyright © 2016, American Medical Association. All rights reserved.

duration, good adherence proven by blood or tissue levels of cholesterol and/or polyunsaturated fat, and standard outcome ascertainment. Meta-analysis showed a 29% reduction in CHD events.

- Six additional trials were not considered core trials because of short duration, low adherence, or nonstandard outcome ascertainment. However, meta-analyses that included several of these trials along with some or all of the core trials also found a significant reduction in CHD events on the polyunsaturated fat diet.
- The Sydney Diet Heart Study showed that using a margarine rich in *trans* unsaturated fat to replace saturated fat increased CHD events, confirming similar adverse results in epidemiological studies.
- Several trials that replaced saturated fat with carbohydrates did not show reduced CHD. Adherence was much less than expected in these trials.
- Prospective observational studies consistently found the following:
  - Lower risk of CHD when saturated fat was replaced with polyunsaturated or monounsaturated fat, more so for polyunsaturated than monounsaturated.
  - No decrease in risk of CHD when saturated fat was replaced with carbohydrates, especially carbohydrates from refined grains and added sugars. However, replacement with whole grains was associated with reduced CHD.
  - Lower risk of death resulting from CVD and all causes with replacement of saturated with polyunsaturated or monounsaturated fat.

DIETARY PATHOGENESIS OF ATHEROSCLEROSIS IN NONHUMAN PRIMATES

Because of their evolutionary similarities to human beings, nonhuman primate species were studied to determine the effects of diet on atherosclerosis. In these experiments,[5,46] to induce hypercholesterolemia and atherosclerotic lesion formation, one group of monkeys typically was fed lard or palm oil at 35% of their daily energy intake and dietary cholesterol to raise serum cholesterol levels into the 300- to 400-mg/dL range to model hypercholesterolemia in human beings at high risk for CHD. A second group of monkeys was fed a monounsaturated fat, high-oleic safflower oil, and a third group was fed a polyunsaturated fat linoleic acid–rich diet using safflower oil. Saturated fatty acids promoted higher LDL cholesterol concentrations and more coronary artery atherosclerosis. Linoleic acid lowered LDL cholesterol concentrations and decreased the amount of coronary artery atherosclerosis. In the oleic acid group, LDL cholesterol concentrations were lowered to an extent similar to that in the linoleic acid group, but paradoxically, the amount of coronary artery atherosclerosis was more like that in the saturated fat group.[5,47] In the oleic acid–rich diet group, the LDL particles of the monkeys were enriched in cholesteryl oleate and bound to arterial proteoglycans more avidly compared with the polyunsaturated fat diet group, an action that may be viewed as promoting atherosclerosis.[47,48] In humans as well, intake of high-oleic canola oil enriches LDL with cholesteryl oleate, but opposite to the findings in monkeys, this LDL has reduced bind-

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ing to vascular proteoglycan, a potentially beneficial mechanism.[49] Atherosclerosis extent has consistently been positively correlated with high LDL proteoglycan binding affinity.[48,50]

Finally, a diet typical of the 1980s in the United States, high in saturated fat, fed to rhesus monkeys for 2 years increased serum cholesterol to 383 mg/dL and caused atherosclerosis that had complex pathological features similar to atherosclerosis in young human adults who died of trauma.[51] In contrast, a "prudent" diet recommended by the AHA to prevent CHD, low in saturated and high in polyunsaturated fat, produced lower serum cholesterol levels, 199 mg/dL, and less atherosclerosis.

In summary, in rhesus monkeys, African green monkeys, and cynomolgus monkeys, dietary saturated fat promoted coronary atherosclerosis during 1 to 5 years, whereas polyunsaturated fat reduced LDL cholesterol and coronary atherosclerosis.[5,6,46–51] The results strongly support the strong atherogenicity of saturated fatty acids through effects to raise LDL cholesterol concentrations compared with the effects of n-6 polyunsaturated fatty acids. Although monounsaturated fatty acids promoted atherosclerosis despite lowering LDL cholesterol, mechanisms related to LDL binding to proteoglycan may differ in humans. Generalization from these studies is limited by the high serum cholesterol levels produced by the atherogenic diets. Clearly, in >50 years of studies in nonhuman primates, saturated fat has proven to be atherogenic compared with polyunsaturated fat.

LDL CHOLESTEROL–MEDIATING DIETARY EFFECTS ON CVD

Dietary saturated and polyunsaturated fats are notable for their established opposing connections to LDL cholesterol levels. Reducing LDL cholesterol is a primary focus for preventive therapy. Replacing dietary saturated fat with unsaturated fat decreases LDL cholesterol levels, n-6 polyunsaturated fat more than monounsaturated fat.[4]

The LDL theory of atherosclerosis and CVD has support from the widest range of research studies[52]: studies that compare populations that vary in LDL cholesterol[52]; studies in single populations[52]; genetic studies of high LDL cholesterol caused by mutations impairing the action of LDL receptors to remove LDL from the blood circulation and lower LDL cholesterol levels[52]; studies of mutations in numerous other genes that affect LDL cholesterol by other mechanisms[53,54]; pharmacological studies that lower LDL cholesterol by decreasing cholesterol synthesis and increasing synthesis of LDL receptors by statins,[31] decreasing cholesterol absorption,[55] or inhibiting proprotein convertase subtilisin/kexin type 9 to increase LDL receptors[56]; studies of mutations in genes that interfere with assembly of LDL and its precursor very-low-density lipoprotein (VLDL) in the liver that decrease the amounts that are secreted into the circulation; correlations between LDL cholesterol and CVD reduction in meta-analyses of randomized clinical trials of statin and other LDL cholesterol–lowering treatments[31,55]; animal models that increase LDL cholesterol by diet or by genetic manipulation[6,57]; and studies of the processes by which atherosclerosis starts, progresses, and regresses in arterial vessels and cells.[57–59] Taking into consideration the totality of evidence, LDL cholesterol links saturated fat and its replacement macronutrients to CVD by very strong scientific evidence that satisfies rigorous criteria for causality.[60] Three independent guidelines committees rated this evidence as Level A, Strong.[3,13,61]

QUANTITATIVE EFFECTS OF DIETARY FATS AND CARBOHYDRATES ON LDL CHOLESTEROL

A systematic review and meta-regression analysis published last year identified and evaluated 84 randomized controlled trials including 2353 participants that studied the effect of dietary fats on LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol.[4] The results were expressed as the amount of change in these lipids caused by a decrease in saturated fats of 1% of total daily calories and a 1% increase in polyunsaturated fat, monounsaturated fat, or carbohydrates. Polyunsaturated fat lowered LDL cholesterol by 2.1 mg/dL, monounsaturated fat by 1.6 mg/dL, and carbohydrates by 1.3 mg/dL (Figure 5, left). Replacing saturated with polyunsaturated fat is the most effective of these exchanges because the change from saturated to polyunsaturated fat combines a reduction in a LDL cholesterol–raising fat, saturated fat, with an increase in a LDL cholesterol–lowering fat, polyunsaturated fat. The independent effect of polyunsaturated fat is demonstrated by comparing it with carbohydrates: Replacing carbohydrates with polyunsaturated fat, 1% of daily energy, lowers LDL cholesterol by 0.9 mg/dL. The reductions in total or LDL cholesterol after diet change correlate well with the extent of reductions in CVD.[10]

The lifestyle report of the AHA and American College of Cardiology summarized studies that assessed the effect of dietary patterns on LDL cholesterol.[3] The report, taking an efficacy-based biological approach, reviewed "feeding trials" that composed complete diets and gave them to the study participants. These trials were DASH (Dietary Approaches to Stop Hypertension),[62] DASH-Sodium,[63] and DELTA (Dietary Effects on Lipoproteins

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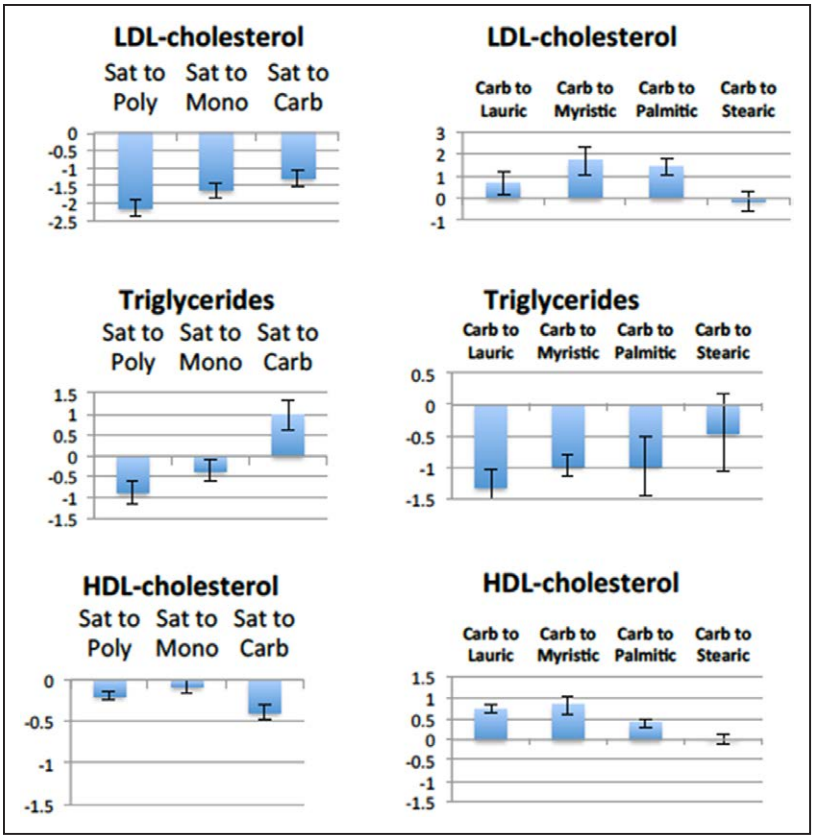

Figure 5. Effects of dietary fat and carbohydrates on blood low-density lipoprotein (LDL) cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol (mg/dL) in meta-regression analysis.
Left, Replacing saturated fat (Sat) with polyunsaturated fat (Poly) (n-6), monounsaturated fat (Mono), or carbohydrates (Carb). **Right**, Replacing carbohydrates with individual saturated fatty acids, lauric, myristic, palmitic, or stearic acid. Error bars show 95% confidence intervals. Data from Mensink.[4]

and Thrombogenic Activity).[64] Taken together, the trials found that a reduction in saturated fat in the context of dietary patterns intended to benefit lipid and other CVD risk factors lowered LDL cholesterol by amounts similar to those predicted by the meta-analysis.[4]

LDL Sizes

Some observational studies found that the concentration or proportion of large LDL predicts higher rates of CVD,[65–67] whereas other studies reported that small LDL predicts CVD[68,69] or both large and small LDLs predict CVD.[70,71] Still other studies found that LDL size, per se, does not predict CVD in a multivariable analysis that includes triglycerides or LDL concentration.[65,72–76] Dietary fat, in an equal combination of saturated and polyunsaturated replacing carbohydrates, increased the concentration of larger LDL and decreased smaller LDL sizes.[77] In another study, monounsaturated fat, replacing carbohydrates, reduced medium and small LDL, also shifting the distribution to the larger size.[78] Therefore, the effects of replacing carbohydrates with various kinds of fats qualitatively at least may be similar by increasing larger and decreasing smaller LDL sizes. Replacing saturated with monounsaturated fat lowered the concentrations of large, medium, and small LDL.[79] Replacing monounsaturated fat from olive oil with polyunsaturated fat from corn oil significantly lowered the concentrations of the total LDL cholesterol concentration, intermediate-density lipoprotein cholesterol, large LDL cholesterol, and nonsignificantly small LDL cholesterol.[80] Replacing *trans* unsaturated soybean oil with n-6 polyunsaturated corn oil lowered the concentration of small LDL.[81] In conclusion, this sparse set of findings suggests that replacement of saturated with monounsaturated or polyunsaturated fat reduces the concentration all sizes of LDL.

HDL CHOLESTEROL AND TRIGLYCERIDES: ADDITIONAL LIPID MEDIATORS

HDL Cholesterol

The aforementioned meta-analysis[4] also computed the effects of dietary fats and carbohydrates on 2 other blood lipid biomarkers of CVD risk, HDL cholesterol and triglycerides. A low HDL cholesterol level is associated with a high incidence of CVD in the context of a wide variety of concomitant conditions such as diabetes mellitus and obesity.[82] HDL can stimulate the removal of cholesterol from cells, including those involved in atherosclerosis, and can deliver the cholesterol to the liver where some of it may be secreted in bile and excreted, a process called reverse cholesterol transport.[83] However, unlike LDL cholesterol, genetic variation that affects HDL cholesterol is not associated with expected differences in

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CVD unless LDL cholesterol or triglyceride is also affected by the genetic variants[84] or reverse cholesterol transport is impaired.[85] Still, these genetic studies, often called mendelian randomization, may not be capturing important loci for the protective effect of HDL that may be reflective in HDL cholesterol raising by dietary fats compared with carbohydrates. Although increases in HDL cholesterol by some pharmacological treatments have not decreased CVD,[86,87] this does not directly pertain to the effects of dietary fat because the underlying mechanisms of effects of drugs such as a cholesterylester transfer protein inhibitor and nicotinic acid are probably not the same as those affected by dietary fats and carbohydrates. The HDL field is working toward a functional approach to CVD risk prediction and treatment. For example, a small experimental study showed that consumption of saturated fat reduces the anti-inflammatory potential of HDL and impairs arterial endothelial function. In contrast, the anti-inflammatory activity of HDL improves after consumption of polyunsaturated fat.[88]

Replacing saturated fat with polyunsaturated or monounsaturated fat (1% daily energy exchanged) lowers HDL cholesterol slightly by 0.2 and 0.1 mg/dL (Figure 5, left).[4] Using carbohydrates as a replacement lowers HDL cholesterol more by 0.4 mg/dL. Carbohydrates also lower HDL cholesterol when replacing monounsaturated or polyunsaturated fats. Both low- and high-glycemic-index carbohydrates lower HDL cholesterol.[89,90]

Triglycerides

The plasma level of triglyceride is a well-established independent biomarker of CVD risk,[91] and triglyceride-rich lipoproteins have atherogenic properties. Triglyceride predicts CVD in a wide range of circumstances. Its association with CVD risk is partly attenuated by adjustment for HDL cholesterol, with which it is moderately correlated.[92] Genetic variation associated with lifelong low triglyceride levels is associated with a lower incidence of CVD.[90] Triglyceride is carried primarily within large lipoproteins, chylomicrons, and VLDL, which are also rich in cholesterol and like LDL can enter the arterial wall and stimulate atherosclerosis. These triglyceride-rich lipoproteins carry various atherogenic proteins such as apolipoprotein C-III, itself associated with atherosclerosis and CVD.[93]

Replacing 1% of daily energy intake from saturated fat with polyunsaturated or monounsaturated fat lowers triglyceride by 0.9 or 0.4 mg/dL, respectively (Figure 5, left),[4] perhaps more in those with hypertriglyceridemia.[91] Replacing the 1% saturated fat with 1% carbohydrates raises serum triglycerides by ≈1 mg/dL. Dietary carbohydrates raise plasma triglyceride levels by increasing the production by the liver of triglycerides and subsequent incorporation into VLDL.[91] The magnitude that dietary carbohydrates increase plasma triglyceride is similar whether the carbohydrate has a high or low glycemic index.[89]

INDIVIDUAL SATURATED FATTY ACIDS

The Mensink[4] meta-regression analysis determined the effects on blood lipids of replacing carbohydrates with the individual saturated fatty acids that are in common foods, including lauric, myristic, palmitic, and stearic acids. Lauric, myristic, and palmitic acids all had similar effects in increasing LDL cholesterol and HDL cholesterol and decreasing triglycerides when replacing carbohydrates (Figure 5, right).

Stearic acid makes up ≈20% of the fat in beef, 30% of the fat in pure cocoa (chocolate), and 10% to 15% in lard (pork fat) and lamb fat (Table). In contrast to the other saturated fatty acids, stearic acid does not increase LDL cholesterol or HDL cholesterol or decrease triglycerides when replacing carbohydrates (Figure 5, right). However, replacing stearic acid with unsaturated fat lowers LDL cholesterol.[4]

In summary, the common individual saturated fats raise LDL cholesterol. Their replacement with monounsaturated or polyunsaturated fats lowers LDL cholesterol. Differences in the effects of the individual fatty acids are small and should not affect dietary recommendations to lower saturated fat intake.

COCONUT OIL

A recent survey reported that 72% of the American public rated coconut oil as a "healthy food" compared with 37% of nutritionists.[94] This disconnect between lay and expert opinion can be attributed to the marketing of coconut oil in the popular press. The fatty acid profile of coconut oil is 82% saturated, about half lauric acid, and the rest myristic, palmitic, stearic, and short-chain fatty acids (Table). Lauric acid replacing carbohydrates increases LDL cholesterol but by about half as much as myristic and palmitic acids (Figure 5, right). Lauric acid increases HDL cholesterol about as much as myristic but more than palmitic acid. The net effect of increasing lauric acid and decreasing carbohydrates is a slight reduction in the ratio of LDL cholesterol to HDL cholesterol. However, as discussed earlier in this report, changes in HDL cholesterol caused by diet or drug treatments can no longer be directly linked to changes in CVD, and therefore, the LDL cholesterol–raising effect should be considered on its own. Furthermore, with respect to CVD, the informative comparison is between coconut oil and vegetable oils high in monounsaturated and polyunsaturated fats. A carefully controlled experiment compared the effects of coconut oil, butter, and safflower oil supplying polyunsaturated linoleic acid.[95]

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Both butter and coconut oil raised LDL cholesterol compared with safflower oil, butter more than coconut oil, as predicted by the meta-regression analysis of individual dietary saturated fatty acids (Figure 5, right). Another carefully controlled experiment found that coconut oil significantly increased LDL cholesterol compared with olive oil.[96] A recent systematic review found 7 controlled trials, including the 2 just mentioned, that compared coconut oil with monounsaturated or polyunsaturated oils.[97] Coconut oil raised LDL cholesterol in all 7 of these trials, significantly in 6 of them. The authors also noted that the 7 trials did not find a difference in raising LDL cholesterol between coconut oil and other oils high in saturated fat such as butter, beef fat, or palm oil. Clinical trials that compared direct effects on CVD of coconut oil and other dietary oils have not been reported. However, because coconut oil increases LDL cholesterol, a cause of CVD, and has no known offsetting favorable effects, we advise against the use of coconut oil.

DAIRY PRODUCTS

Dairy fat is composed of 27% palmitic acid, 12% stearic acid, 9% myristic acid, and 3% lauric acid, for a total of 51% saturated fatty acids that raise LDL cholesterol compared with the unsaturated fatty acids (Table). Short-chain saturated fatty acids total 11%; monounsaturated, 26%; and polyunsaturated, 4%. Dairy fat also contains a very small amount of odd-chain fatty acids, 15:0 and 17:0, ≈0.5% to 1% of total fatty acids, and *trans* unsaturated fat, 4%, both made by bacteria in the ruminant gut. As we discuss subsequently, *trans* unsaturated fat made by ruminants has adverse effects on lipid risk factors similar to those of *trans* made industrially by partial hydrogenation.

Recent epidemiological studies measured blood levels of odd-chain fatty acids; one study found that they are associated with lower risk of CHD,[98] whereas another did not find such a relation.[99] It is not clear whether blood levels of odd-chain fatty acids represent intake of dairy fat or an effect of fat absorption and metabolism because the correlations between dairy fat intake and blood levels of odd-chain fatty acids (15:0, 17:0) are low (0.3).[99] Because of increasing consumption of low- and reduced-fat milk and other dairy products and decreasing consumption of full-fat dairy, especially whole milk, in the US population, the amount of dairy fat from low-fat compared with full-fat dairy is likely to have substantially increased. Therefore, dairy fat biomarkers may reflect both high- and low-fat dairy consumption patterns in the population. To the best of our knowledge, there are no biological mechanisms that link odd-chain fatty acids to protection against atherosclerosis and CVD.

For many years, there has been sporadic speculation that cheese is a unique food category, protective against CVD because it is manufactured by fermentation. To the best of our knowledge, no information from controlled studies supports the hypothesis that fermentation adds beneficial nutrients to cheese that counteract the harmful effects of its saturated fat. Recently, a clinical trial compared 3 diets, one with a high content of cheese, another with a high content of beef, and a third that was low in all types of fat, saturated, monounsaturated, and polyunsaturated.[100] The cheese and beef diets had higher amounts of saturated, monounsaturated, and polyunsaturated fatty acids. Neither the beef nor the cheese diet increased LDL cholesterol compared with the low-fat diet, as expected because of the counteracting effects of saturated and unsaturated fats on LDL cholesterol. Both the cheese and meat diets increased HDL cholesterol, consistent with the known effects of dietary fat to raise HDL cholesterol.[4] Therefore, the findings from this study do not support the hypothesis that cheese has special protective effects compared with beef on lipid risk factors for CVD.

Many controlled trials showed that dairy fat, often the major source of saturated fat in a study, increased LDL cholesterol compared with monounsaturated and polyunsaturated vegetable oils, reflecting the preponderance of saturated fatty acids, as reviewed previously in this report. Prospective observational studies found that the substitution of polyunsaturated fat for dairy fat, 5% of total daily calories, was associated with a 24% to 25% lower risk of CHD and stroke.[101] In contrast, substituting refined carbohydrates for dairy fat was not associated with reduced risk of CVD, whereas substituting carbohydrates from whole grains for dairy fat was associated with a 34% lower incidence of CHD and a 16% lower incidence of stroke. This analysis demonstrates again that it is essential to analyze the effects of unsaturated fats, refined carbohydrates, and whole grains separately to reach an informed and useful result for dietary advice.

In Finland, a successful nationwide health project to lower the very high rate of CHD mortality, started in 1972, had as a major goal the reduction in the high intake of saturated fat.[102] The project reduced intake of high-fat milk and butter, which lowered serum cholesterol by 13% in men and 18% in women. By 1992, CHD death rates decreased by 55% in men and 68% in women. Reduction in serum cholesterol accounted for ≈50% of the total reduction in CHD mortality.[103] Other dietary changes that may have contributed to the lower CHD mortality included increased fruits and vegetables, increased fish, decreased sugar, a shift from fatty to lean meats, and reduced sodium.

TRANS UNSATURATED FATS AND CVD

Trans unsaturated fatty acids are monounsaturated or polyunsaturated fatty acids containing at least 1 double bond in the *trans* configuration. There are 2 major types of *trans* fatty acids: naturally occurring found in meat and

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milk of ruminant animals (eg, cattle and sheep), called ruminant *trans* fatty acids, and produced by chemical and enzymatic action for use in partially hydrogenated vegetable oils, called industrial *trans* fatty acids.[40,41] Both sources of *trans* fatty acids contain a range of fatty acid isomers, and there is considerable overlap. Food manufacturers have taken advantage of the low cost, long shelf-life, and the ability of *trans* fatty acids to withstand repeated heating and use partially hydrogenated vegetable oil in a variety of processed foods, including margarines, baked foods, and commercial deep-fried foods.

Clinical trials have consistently documented the adverse effects of *trans* fatty acids on the lipid risk factors for CVD. Replacement of calories from other types of fats with *trans* fatty acids raises LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein(a), as well as lowering HDL cholesterol and apolipoprotein A1.[104] Such effects are particularly large when *trans* fatty acids replace monounsaturated or polyunsaturated fatty acids but also occur when substituted for saturated fatty acids. The effects of *trans* fatty acids on blood lipids are potentially mediated through mechanisms including a reduction in the catabolism of LDL apolipoprotein B-100 and an increase in the catabolism of HDL apolipoprotein A-I, as well as enhancement of cholesteryl ester transfer protein activity.[105–107] Although most human trials were conducted with partially hydrogenated vegetable oil, emerging evidence suggest the ruminant *trans* fatty acids have similar adverse effects on blood lipids.[108–110]

Prospective observational studies have consistently concluded that higher total *trans* fatty acid intake is associated with elevated risk of CHD. A recent systematic review and meta-analysis of observational studies reported that higher intake of total *trans* fatty acid intake was associated with a 21% higher risk in total CHD (95% CI, 10–33; n=6 studies) and a 28% higher risk in CHD mortality (95% CI, 9–50; n=5 studies).[111] Although industrial *trans* fatty acids were consistently associated with total CHD and CHD death in observational studies, ruminant *trans* fatty acids were generally not.[112] The exact reason for these discrepant relationships remains unknown but may relate to the very low levels of ruminant trans fatty acids in these studied populations (mean intake, ≈0.7% of total energy),[112] differences in *trans* fatty acid isomers between ruminant and industrial *trans* fatty acids that have diverse biological effects, or confounding by the high amount of saturated fat in the major source of ruminant *trans* fatty acids.

In summary, the concordance between the adverse effects of *trans* fatty acids on lipid risk factors for CVD and the robust association of higher *trans* fatty acid intake with elevated CHD risk in observational studies provides the impetus for current policy actions of many local and national jurisdictions to reduce industrial *trans* fatty acids in the food supply.[113] Recognizing the need to act, in addition to requiring the *trans* fatty acid content of packaged foods to be listed on the Nutrition Facts label, the US Food and Drug Administration has recently revoked the generally recognized as safe status of partially hydrogenated vegetable oil, which should ensure further reductions in the population-level industrial *trans* fatty acid intake.[43]

N-3 (OMEGA-3) FATTY ACIDS

Polyunsaturated fatty acids exist in the n-3 or n-6 isomeric configuration. Both isomers are essential nutrients and have different biological effects. N-3 and n-6 fatty acids are not interconverted. Dietary n-6 polyunsaturated fatty acids, primarily linoleic acid, are much more prevalent than n-3 polyunsaturated fatty acids in vegetable oils and the total diet. α-Linolenic acid, a dietary n-3 polyunsaturated fatty acid, is present in soybean and rapeseed (canola) oil, walnuts, some green vegetables in very small amounts, chickens fed high–α-linolenic acid feed and their eggs, and grass-fed beef. Fish oil contains the very-long-chain n-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid.

α-Linolenic Acid (Vegetable Omega-3)

A systematic review identified 4 randomized controlled trials that tested α-linolenic acid 2 to 6 g/d.[16] The Alpha-Omega trial tested the effect of α-linolenic acid 2 g/d compared with the same amount of oleic acid (both from 20 g margarine) in an older Dutch population with CHD.[114] There were ≈2400 participants in the α-linolenic acid and the oleic acid groups. After an average of 3.4 years of follow-up, the incidence of major cardiovascular events was 13.2% compared with 14.5% in the α-linolenic acid and control group, a 9% difference, not statistically significant. Two trials were conducted in Norway, one in 200 men who had CHD[115] and another in 13 400 men who were healthy and without CHD.[116] α-Linolenic acid 5 g/d supplied by flaxseed or linseed oil was tested and compared with sunflower oil, which has mainly n-6 linoleic acid. α-Linolenic acid did not significantly reduce CHD in either trial.

A meta-analysis of 7 prospective observational studies on dietary α-linolenic acid found an overall relative risk of 1.02 for CHD (nonsignificant).[16] However, there is consistent evidence that higher α-linolenic acid intake and higher blood levels of α-linolenic acid are associated with lower risk of fatal CHD.[117,118] α-Linolenic acid does not lower LDL cholesterol, but it has been shown to have antiarrhythmic properties in experimental studies.[119,120]

It has been proposed that α-linolenic acid affects CVD mainly in the low part of its range in the diet or when the background diet of the population under

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study is almost completely devoid of eicosapentaenoic acid and docosahexaenoic acid.[121,122] This interesting hypothesis requires evidence from clinical trials.

In summary, randomized controlled trials and observational studies do not provide clear evidence that α-linolenic acid reduces the overall incidence of CVD, although higher intake of α-linolenic acid may reduce fatal CHD.

Eicosapentaenoic Acid, Docosapentaenoic Acid, and Docosahexaenoic Acid

The n-3 marine fatty acids eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid are present in fish and dietary supplements having a >10-fold range of n-3 fatty acid contents. High-dose prescription forms are also available to treat hypertriglyceridemia. The n-3 fatty acids contribute little energy to the daily diet and do not pertain closely to the topic covered by the present advisory. We refer readers who have interest in this complex topic to the AHA's library of guidelines, statements, and advisories.

MEDITERRANEAN DIETS, LYON HEART STUDY, AND PREDIMED

The Seven Countries Study kindled interest in Mediterranean diets.[11] Total fat intake was highest in Crete, Greece, at 43%, mainly from olive oil, where prevalence of CVD was lowest worldwide. Traditionally, Mediterranean diets had an abundance of plant foods, including vegetables, legumes, nuts, fruits, and grains, and fish.[123] As dietary patterns trended away from a traditional Mediterranean diet in Greece, individuals who maintained traditional diets experienced lower rates of death resulting from CVD, cancer, and all causes.[124]

The Lyon Heart Study[125] was a randomized controlled trial that provided α-linolenic acid 2 g/d as part of a Mediterranean diet intervention in 605 men with acute myocardial infarction. The Mediterranean diet replaced animal fat with polyunsaturated vegetable oil rich in α-linolenic acid; meat, butter, and cream were reduced, and fish, legumes, bread, fruits and vegetables were increased. A control group was assigned a low-fat diet. Mean follow-up was 27 months. Cardiovascular death or nonfatal myocardial infarction totaled 8 in the Mediterranean group and 33 in the control group, a significant difference. Although the researchers emphasized the α-linolenic acid component of the diet as contributing to the benefit, many other dietary changes occurred as part of the Mediterranean diet, making it impossible to determine to what extent α-linolenic acid contributed to the reduction in recurrent CHD.

The PREDIMED trial (Prevencion con Dieta Mediterranea) was a parallel-group, multicenter randomized trial in Spain conducted among 7447 men (age, 55–80 years) and women (age, 60–80 years) free of CVD at baseline and having either type 2 diabetes mellitus or 3 other risk factors for CVD.[126] They were assigned at random to a Mediterranean diet supplemented with 50 g extra virgin olive oil, a Mediterranean diet supplemented with 30 g nuts (half walnuts, one fourth almonds, and one fourth hazelnuts), or a reduced-fat control diet. Follow-up was 4 to 5 years. The primary end point, a composite of myocardial infarction, stroke, and death resulting from CVD, was lower significantly by 30% in the olive oil group and 29% in the nut group. The olive oil group increased intake of olive oil, partly replacing their usual kind of olive oil low in polyphenols with extravirgin olive oil high in polyphenols. The nuts group increased intake of α-linolenic acid and linoleic acid. Saturated fat intake was low, 9% of daily energy in all 3 groups during the trial. Monounsaturated fat intake was 21% to 22% in the Mediterranean groups compared with 19% in the reduced-fat group. Total fat was 41% in the Mediterranean and 37% in the reduced fat group. As intended by the researchers, the dietary changes reflected the aim to test a Mediterranean dietary pattern, not a specific alteration in dietary fat intake. Intake of fruits, vegetables, legumes, nuts, wine, and fish increased in the Mediterranean diet groups compared with the control diet group.

In summary, observational studies and 2 randomized clinical trials together suggest that a Mediterranean dietary pattern in which unsaturated fats predominate lowers the incidence of CVD.

CHILDREN

In 2012, the National Heart, Lung, and Blood Institute published the "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents."[127] An expert panel reviewed the evidence building from the 2010 US Dietary Guidelines Advisory Committee Report.[128] Although evidence for dietary fat and cardiovascular risk in children was limited, key epidemiological studies provided the strongest data available. The Bogalusa Heart Study found that in children intake of animal fat, the major source of dietary saturated fat, was associated with higher body weight.[129]

The Cardiovascular Risk in Young Finns study (Young Finns) was a multicenter longitudinal cohort study of 3956 individuals 3 to 18 years of age in 1980 who had ongoing follow-up assessment of diet and blood lipids over 21 years.[130] Two major dietary patterns emerged, a "traditional" pattern including rye, potatoes, butter, sausages, milk, and coffee and a "health-conscious" pattern including vegetables, legumes and nuts, rye, cheese and other dairy products, and alcoholic beverages. In both men and women, at the end of follow-up, those following the traditional diet had higher levels of

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Circulation. 2017;136:e1–e23. DOI: 10.1161/CIR.0000000000000510

total serum cholesterol and LDL cholesterol. Higher levels of LDL cholesterol in childhood predicted increased common carotid artery intima-media thickness, an indicator of atherosclerosis.[131]

The National Heart, Lung, and Blood Institute National Growth and Health Study recruited 2379 black and white 9-year-old girls in 3 different US cities and followed up their diets, growth, and development for a decade.[132] Girls who consumed a dietary pattern higher in fruits and vegetables, dairy products, and fiber-rich grains and lower in sugar, fried foods, burgers, pizza, and total fat for >10 years had lower body mass index, percentage of body fat, and waist circumference; these differences were significant for white girls.[132] Body mass index and central adiposity were correlated with LDL cholesterol.[133]

The STRIP trial (Special Turku Coronary Risk Factor Intervention Project for Babies) with >20 years of follow-up is the only randomized study that examined and reported improved long-term health effects from a multifactorial program that included a reduction in saturated fat starting in infancy compared with usual dietary intake and lifestyle among normal children from infancy through adolescence.[134,135] LDL cholesterol levels were lower in the intervention compared with the control group through 14 years of age, significant in boys but not girls.[135]

Likewise, the Diet Intervention Study in Children[136,137] was a randomized controlled trial designed to assess the safety and efficacy of a reduced-fat dietary intervention among prepubertal children with elevated LDL cholesterol levels (between the 80th and 98th percentiles) at baseline. A behavior-based, nutritionist-tailored intervention advocated adherence to a diet with 28% of energy from fat, <8% from saturated fat, and <9% from polyunsaturated fat. Saturated fat intake decreased in the intervention group compared with the control group throughout 7 years of follow-up.[136,137] LDL cholesterol was lower in the intervention compared with the control group, significant at 1 and 3 years but not at 5 and 7 years.

The PDAY study (Pathobiological Determinants of Atherosclerosis in Youth) provided crucial evidence that risk factors for developing CHD in adults were associated with atherosclerosis in men and women 15 to 34 years of age who died of accidents, homicide, or suicide.[138,139] Atherosclerosis was measured directly in the right coronary artery and abdominal aorta. The concentration of VLDL and LDL cholesterol was significantly directly associated and HDL cholesterol was inversely associated with early and intermediate lesions in both arteries. These results suggest that dietary factors that raise VLDL and LDL cholesterol produce atherosclerosis in teenagers and young adults.

Overall, these results suggest that reduced saturated fat intake within a healthful dietary pattern is feasible and effective for sustaining lower LDL cholesterol, a preventive effort against CVD in growing children.

CONCLUSIONS AND RECOMMENDATIONS

The key evidence to reduce saturated fat and replace it with polyunsaturated and monounsaturated fat is summarized below:

- Randomized clinical trials showed that polyunsaturated fat from vegetable oils replacing saturated fats from dairy and meat lowers CVD.
- A dietary strategy of reducing intake of total dietary fat, including saturated fat, and replacing the fats mainly with unspecified carbohydrates does not prevent CHD.
- Prospective observational studies in many populations showed that lower intake of saturated fat coupled with higher intake of polyunsaturated and monounsaturated fat is associated with lower rates of CVD and all-cause mortality.
- Saturated fat increases LDL cholesterol, a major cause of atherosclerosis and CVD, and replacing it with polyunsaturated or monounsaturated fat decreases LDL cholesterol
- Replacing saturated with polyunsaturated or monounsaturated fat lowers blood triglyceride levels, an independent biomarker of risk for CVD.
- Replacing saturated with polyunsaturated fat prevents and regresses atherosclerosis in nonhuman primates.
- Overall, evidence supports the conclusion that polyunsaturated fat from vegetable oils (mainly n-6, linoleic acid) reduces CVD somewhat more than monounsaturated fat (mainly oleic acid) when replacing saturated fat.

Evidence has accumulated during the past several years that strengthens long-standing AHA recommendations to replace saturated fat with polyunsaturated and monounsaturated fat to lower the incidence of CVD. Reduction in total dietary fat or a goal for total fat intake is not recommended. This shift from saturated to unsaturated fats should occur simultaneously in an overall healthful dietary pattern such as the DASH or Mediterranean diet as emphasized by the 2013 AHA/American College of Cardiology lifestyle guidelines and the 2015 to 2020 Dietary Guidelines for Americans.

FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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The American Heart Association requests that this document be cited as follows: Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG, Stone NJ, Van Horn LV; on behalf of the American Heart Association. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation.* 2017;136:e1–e23. doi: 10.1161/CIR.0000000000000510.

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*Modest.

†Significant.

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REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JHY, Alger HM, Wong SS, Muntner P; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association [published correction appears in *Circulation*. 2017;135:e646]. *Circulation*. 2017;135:e146-e603. DOI: 10.1161/CIR.0000000000000485.
2. 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.
3. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ. 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 [published corrections appear in *Circulation*. 2014;129(suppl 2):S100–S101 and *Circulation*. 2015;131:e326]. *Circulation*. 2014;129(suppl 2):S76–S99. doi: 10.1161/01.cir.0000437740.48606.d1.
4. Mensink RP. *Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis*. Geneva, Switzerland: World Health Organization; 2016.
5. Rudel LL, Parks JS, Sawyer JK. Compared with dietary monounsaturated and saturated fat, polyunsaturated fat protects African green monkeys from coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1995;15:2101–2110.
6. Wolfe MS, Sawyer JK, Morgan TM, Bullock BC, Rudel LL. Dietary polyunsaturated fat decreases coronary artery atherosclerosis in a pediatric-aged population of African green monkeys. *Arterioscler Thromb*. 1994;14:587–597.
7. Watts GF, Lewis B, Brunt JN, Lewis ES, Coltart DJ, Smith LD, Mann JI, Swan AV. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet*. 1992;339:563–569.
8. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, McLanahan SM, Kirkeeide RL, Brand RJ, Gould KL. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. 1990;336:129–133.
9. 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. doi: 10.1371/journal.pmed.1000252.
10. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev*. 2015:CD011737. doi: 10.1002/14651858.CD011737.
11. Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA: Harvard University Press, 1980.
12. Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, Willett WC, Hu FB. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation*. 2014;130:1568–1578. doi: 10.1161/CIRCULATIONAHA.114.010236.
13. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. Washington, DC: US Department of Agriculture; 2015. https://health.gov/dietaryguidelines/2015-scientific-report/. Accessed January 4, 2017.
14. Rehm CD, Peñalvo JL, Afshin A, Mozaffarian D. Dietary intake among US adults, 1999-2012. *JAMA*. 2016;315:2542–2553. doi: 10.1001/jama.2016.7491.
15. 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. doi: 10.3945/ajcn.2009.27725.
16. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis [published correction appears in *Arch Intern Med*. 2014;160:658]. *Ann Intern Med*. 2014;160:398–406. doi: 10.7326/M13-1788.
17. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. 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. doi: 10.3945/ajcn.2008.27124.
18. Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, Sampson L, Rexrode KM, Rimm EB, Willett WC, Hu FB. 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. doi: 10.1016/j.jacc.2015.07.055.
19. US Department of Agriculture, Agricultural Research Service, National Nutrient Database for Standard Reference, release 28, 2016. https://ndb.nal.usda.gov/ndb/search/list. Accessed May 23, 2017.
20. 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(suppl II):II-1–II-63.
21. Leren P. The Oslo Diet-Heart Study: eleven-year report. *Circulation*. 1970;42:935–942.
22. Controlled trial of soya-bean oil in myocardial infarction. *Lancet*. 1968;2:693–699.
23. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet*. 1989;2:757–761.
24. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666. doi: 10.1001/jama.295.6.655.
25. Low-fat diet in myocardial infarction: a controlled trial. *Lancet*. 1965;2:501–504.

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26. Bronte-Stewart B, Antonis A, Eales L, Brock JF. Effects of feeding different fats on serum-cholesterol level. *Lancet*. 1956;270:521–526.
27. Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. *Lancet*. 1957;273:959–966.
28. Ahrens EH Jr, Insull W Jr, Blomstrand R, Hirsch J, Tsaltas TT, Peterson ML. The influence of dietary fats on serum-lipid levels in man. *Lancet*. 1957;272:943–953.
29. Malmros H, Wigand G. The effect on serum-cholesterol of diets containing different fats. *Lancet*. 1957;273:1–7.
30. 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.
31. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.
32. Houtsmuller AJ, van Hal-Ferwerda J, Zahn KJ, Henkes HE. Favorable influences of linoleic acid on the progression of diabetic micro- and macroangiopathy in adult onset diabetes mellitus. *Prog Lipid Res*. 1981;20:377–386.
33. Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart disease. *Br Med J*. 1965;1:1531–1533.
34. Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. *Arteriosclerosis*. 1989;9:129–135.
35. Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, Ringel A, Davis JM, Hibbeln JR. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis [published correction appears in *BMJ*. 2013;346:f903]. *BMJ*. 2013;346:e8707.
36. Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish Mental Hospital Study. *Int J Epidemiol*. 1983;12:17–25.
37. Miettinen M, Turpeinen O, Karvonen MJ, Elosuo R, Paavilainen E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes: a twelve-year clinical trial in men and women. *Lancet*. 1972;2:835–838.
38. Keys A. Serum cholesterol response to dietary cholesterol. *Am J Clin Nutr*. 1984;40:351–359.
39. Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, Davis JM, Ringel A, Suchindran CM, Hibbeln JR. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). *BMJ*. 2016;353:i1246.
40. Wang Q, Imamura F, Lemaitre RN, Rimm EB, Wang M, King IB, Song X, Siscovick D, Mozaffarian D. Plasma phospholipid trans-fatty acids levels, cardiovascular diseases, and total mortality: the Cardiovascular Health Study. *J Am Heart Assoc*. 2014;3:e000914 doi: 10.1161/JAHA.114.000914.
41. Lichtenstein AH. Dietary trans fatty acids and cardiovascular disease risk: past and present. *Curr Atheroscler Rep*. 2014;16:433. doi: 10.1007/s11883-014-0433-1.
42. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006;354:1601–1613. doi: 10.1056/NEJMra054035.
43. US Food and Drug Administration. FDA News Release: The FDA takes step to remove artificial trans fats in processed foods. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm451237.htm. Accessed January 14, 2016.
44. Willett W. *Nutritional Epidemiology*. 3rd ed. New York, NY: Oxford University Press; 2013:1–16, 317–319.
45. Wang DD, Li Y, Chiuve SE, Stampfer MJ, Manson JE, Rimm EB, Willett WC, Hu FB. Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern Med*. 2016;176:1134–1145. doi: 10.1001/jamainternmed.2016.2417.
46. Rudel LL, Parks JS, Hedrick CC, Thomas M, Williford K. Lipoprotein and cholesterol metabolism in diet-induced coronary artery atherosclerosis in primates: role of cholesterol and fatty acids. *Prog Lipid Res*. 1998;37:353–370.
47. Rudel LL, Haines J, Sawyer JK, Shah R, Wilson MS, Carr TP. Hepatic origin of cholesteryl oleate in coronary artery atherosclerosis in African green monkeys. Enrichment by dietary monounsaturated fat. *J Clin Invest*. 1997;100:74–83. doi: 10.1172/JCI119524.
48. Manning JM, Gebre AK, Edwards IJ, Wagner WD, Rudel LL, Parks JS. Dietary polyunsaturated fat decreases interaction between low density lipoproteins and arterial proteoglycans. *Lipids*. 1994;29:635–641.
49. Jones PJ, MacKay DS, Senanayake VK, Pu S, Jenkins DJ, Connelly PW, Lamarche B, Couture P, Kris-Etherton PM, West SG, Liu X, Fleming JA, Hantgan RR, Rudel LL. High-oleic canola oil consumption enriches LDL particle cholesteryl oleate content and reduces LDL proteoglycan binding in humans. *Atherosclerosis*. 2015;238:231–238. doi: 10.1016/j.atherosclerosis.2014.12.010.
50. Melchior JT, Sawyer JK, Kelley KL, Shah R, Wilson MD, Hantgan RR, Rudel LL. LDL particle core enrichment in cholesteryl oleate increases proteoglycan binding and promotes atherosclerosis. *J Lipid Res*. 2013;54:2495–2503. doi: 10.1194/jlr.M039644.
51. Wissler RW, Vesselinovitch D, Hughes R, Turner D, Frazier L. Arterial lesions and blood lipids in rhesus monkeys fed human diets. *Exp Mol Pathol*. 1983;38:117–136.
52. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of the Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2015;132:e397]. *Circulation*. 2015;132:2167–2192. doi: 10.1161/CIR.0000000000000297.
53. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707–713. doi: 10.1038/nature09270.
54. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, UCLEB Consortium, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F,

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Samani NJ, Keating BJ, Hingorani AD, Casas JP. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36:539–550. doi: 10.1093/eurheartj/eht571.
55. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489.
56. Chapman MJ, Stock JK, Ginsberg HN; PCSK9 Forum. PCSK9 inhibitors and cardiovascular disease: heralding a new therapeutic era. *Curr Opin Lipidol*. 2015;26:511–520. doi: 10.1097/MOL.0000000000000239.
57. Bartels ED, Christoffersen C, Lindholm MW, Nielsen LB. Altered metabolism of LDL in the arterial wall precedes atherosclerosis regression. *Circ Res*. 2015;117:933–942.
58. Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. *J Cell Biol*. 2015;209:13–22. doi: 10.1083/jcb.201412052.
59. Williams KJ, Tabas I, Fisher EA. How an artery heals. *Circ Res*. 2015;117:909–913. doi: 10.1161/CIRCRESAHA.115.307609.
60. Bradford Hill A. President's address: the environment and disease: association or causation? *Proc R Soc Med*. 1965;295–300.
61. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National lipid association recommendations for patient-centered management of dyslipidemia, part 1: full report. *J Clin Lipidol*. 2015;9:129–169. doi: 10.1016/j.jacl.2015.02.003.
62. Obarzanek E, Sacks FM, Vollmer WM, Bray GA, Miller ER 3rd, Lin PH, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA; DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr*. 2001;74:80–89.
63. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10. doi: 10.1056/NEJM200101043440101.
64. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states. *Am J Clin Nutr*. 2007;86:1611–1620.
65. Sacks FM, Campos H. Clinical Review 163: low density lipoprotein size and cardiovascular disease: a reappraisal. *J Clin Endocrinol Metab*. 2003;88:4525–4532.
66. Campos H, Moye LA, Glasser SP, Stampfer MJ, Sacks FM. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA*. 2001;286:1468–1474.
67. Campos H, Roederer GO, Lussier-Cacan S, Davignon J, Krauss RM. Predominance of large LDL and reduced HDL2 cholesterol in normolipidemic men with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 1995;15:1043–1048.
68. Austin MA, Rodriguez BL, McKnight B, McNeely MJ, Edwards KL, Curb JD, Sharp DS. Low-density lipoprotein particle size, triglycerides, and high-density lipoprotein cholesterol as risk factors for coronary heart disease in older Japanese-American men. *Am J Cardiol*. 2000;86:412–416.
69. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA*. 1996;276:875–881.
70. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939. doi: 10.1161/CIRCULATIONAHA.108.816181.
71. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211–217. doi: 10.1016/j.atherosclerosis.2006.05.007.
72. Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, Otvos JD, Armitage J, Collins R; on behalf of the Heart Protection Study Collaborative Group. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation*. 2012;125:2469–2478. doi: 10.1161/CIRCULATIONAHA.111.073684.
73. Jungner I, Sniderman AD, Furberg C, Aastveit AH, Holme I, Walldius G. Does low-density lipoprotein size add to atherogenic particle number in predicting the risk of fatal myocardial infarction? *Am J Cardiol*. 2006;97:943–946. doi: 10.1016/j.amjcard.2005.10.062.
74. Kamigaki AS, Siscovick DS, Schwartz SM, Psaty BM, Edwards KL, Raghunathan TE, Austin MA. Low density lipoprotein particle size and risk of early-onset myocardial infarction in women. *Am J Epidemiol*. 2001;153:939–945.
75. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, Hennekens CH. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276:882–888.
76. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002;106:1930–1937.
77. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res*. 2010;51:3324–3330. doi: 10.1194/jlr.M005769.
78. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia [published correction appears in *Am J Clin Nutr*. 2006;84:668]. *Am J Clin Nutr*. 2006;83:1025–1031; quiz 1205.
79. Mangravite LM, Chiu S, Wojnoonski K, Rawlings RS, Bergeron N, Krauss RM. Changes in atherogenic dyslipidemia induced by carbohydrate restriction in men are dependent on dietary protein source. *J Nutr*. 2011;141:2180–2185. doi: 10.3945/jn.111.139477.
80. Maki KC, Lawless AL, Kelley KM, Kaden VN, Geiger CJ, Palacios OM, Dicklin MR. Corn oil intake favorably impacts lipoprotein cholesterol, apolipoprotein and lipoprotein particle levels compared with extra-virgin olive oil. *Eur J Clin Nutr*. 2017;71:33–38. doi: 10.1038/ejcn.2016.169.
81. Vega-López S, Matthan NR, Ausman LM, Ai M, Otokozawa S, Schaefer EJ, Lichtenstein AH. Substitution of vegetable oil for a partially-hydrogenated fat favorably alters cardiovascular disease risk factors in moderately hypercholesterolemic postmenopausal women. *Atherosclerosis*. 2009;207:208–212. doi: 10.1016/j.atherosclerosis.2009.03.039.
82. Emerging Risk Factors Consortium. Major lipids, apolipoproteins and risk of vascular disease. *JAMA*. 2009;302:1993–2000
83. Rosenson RS, Brewer HB Jr, Davidson WS, Fayad ZA, Fuster V, Goldstein J, Hellerstein M, Jiang XC, Phillips MC, Rader DJ, Remaley AT, Rothblat GH, Tall AR, Yvan-Charvet L. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation*. 2012;125:1905–1919. doi: 10.1161/CIRCULATIONAHA.111.066589.
84. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580. doi: 10.1016/S0140-6736(12)60312-2.

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85. Zanoni P, Khetarpal SA, Larach DB, Hancock-Cerutti WF, Millar JS, Cuchel M, DerOhannessian S, Kontush A, Surendran P, Saleheen D, Trompet S, Jukema JW, De Craen A, Deloukas P, Sattar N, Ford I, Packard C, Majumder Aa, Alam DS, Di Angelantonio E, Abecasis G, Chowdhury R, Erdmann J, Nordestgaard BG, Nielsen SF, Tybjærg-Hansen A, Schmidt RF, Kuulasmaa K, Liu DJ, Perola M, Blankenberg S, Salomaa V, Männistö S, Amouyel P, Arveiler D, Ferrieres J, Müller-Nurasyid M, Ferrario M, Kee F, Willer CJ, Samani N, Schunkert H, Butterworth AS, Howson JM, Peloso GM, Stitziel NO, Danesh J, Kathiresan S, Rader DJ; CHD Exome+ Consortium; CARDIoGRAM Exome Consortium; Global Lipids Genetics Consortium. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science*. 2016;351:1166–1171. doi: 10.1126/science.aad3517.
86. AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy [published correction appears in *N Engl J Med*. 2012;367:189]. *N Engl J Med*. 2011;365:2255.
87. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099. doi: 10.1056/NEJMoa1206797.
88. Nicholls SJ, Lundman P, Harmer JA, Cutri B, Griffiths KA, Rye KA, Barter PJ, Celermajer DS. Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function. *J Am Coll Cardiol*. 2006;48:715–720. doi: 10.1016/j.jacc.2006.04.080.
89. Sacks FM, Carey VJ, Anderson CA, Miller ER 3rd, Copeland T, Charleston J, Harshfield BJ, Laranjo N, McCarron P, Swain J, White K, Yee K, Appel LJ. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *JAMA*. 2014;312:2531–2541. doi: 10.1001/jama.2014.16658.
90. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.
91. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S; on behalf of the American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2292–2333. doi: 10.1161/CIR.0b013e3182160726.
92. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450–458. doi: 10.1161/CIRCULATIONAHA.106.637793.
93. Wyler von Ballmoos MC, Haring B, Sacks FM. The risk of cardiovascular events with increased apolipoprotein CIII: a systematic review and meta-analysis. *J Clin Lipidol*. 2015;9:498–510. doi: 10.1016/j.jacl.2015.05.002.
94. Quealy K, Sanger-Katz M. Is sushi "healthy"? What about granola? Where Americans and nutritionists disagree. *New York Times*. July 5, 2016. https://www.nytimes.com/interactive/2016/07/05/upshot/is-sushi-healthy-what-about-granola-where-americans-and-nutritionists-disagree.html?_r=0 Y. Accessed July 5, 2016.
95. Cox C, Mann J, Sutherland W, Chisholm A, Skeaff M. Effects of coconut oil, butter, and safflower oil on lipids and lipoproteins in persons with moderately elevated cholesterol levels. *J Lipid Res*. 1995;36:1787–1795.
96. Voon PT, Ng TK, Lee VK, Nesaretnam K. Diets high in palmitic acid (16:0), lauric and myristic acids (12:0 + 14:0), or oleic acid (18:1) do not alter postprandial or fasting plasma homocysteine and inflammatory markers in healthy Malaysian adults [published correction appears in *Am J Clin Nutr*. 2012;95:780]. *Am J Clin Nutr*. 2011;94:1451–1457. doi: 10.3945/ajcn.111.020107.
97. Eyres L, Eyres MF, Chisholm A, Brown RC. Coconut oil consumption and cardiovascular risk factors in humans. *Nutr Rev*. 2016;74:267–280. doi: 10.1093/nutrit/nuw002.
98. de Oliveira Otto M, Nettleton JA, Lemaitre RN, Steffen LM, Kromhout D, Rich SS, Tsai MY, Jacobs DR, Mozaffarian D. Biomarkers of dairy fatty acids and risk of cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2013;2:3000092. doi: 10.1161/JAHA.113.000092.
99. 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;86:929–937.
100. Thorning TK, Raziani F, Bendsen NT, Astrup A, Tholstrup T, Raben A. Diets with high-fat cheese, high-fat meat, or carbohydrate on cardiovascular risk markers in overweight postmenopausal women: a randomized crossover trial. *Am J Clin Nutr*. 2015;102:573–581. doi: 10.3945/ajcn.115.109116.
101. Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, Willett WC, Rimm ER, Hu FB. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr*. 2016;104:1209–1217.
102. Pietinen P, Nissinen A, Vartiainen E, Tuomilehto A, Uusitalo U, Ketola A, Moisio S, Puska P. Dietary changes in the North Karelia Project (1972-1982). *Prev Med*. 1988;17:183–193.
103. Pietinen P, Vartiainen E, Seppänen R, Aro A, Puska P. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Prev Med*. 1996;25:243–250. doi: 10.1006/pmed.1996.0053.
104. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr*. 2009;63(suppl 2):S22–S33.
105. Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. Stearic acid, trans fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr*. 1997;65:1419–1426.
106. Gatto LM, Sullivan DR, Samman S. Postprandial effects of dietary trans fatty acids on apolipoprotein(a) and cholesteryl ester transfer. *Am J Clin Nutr*. 2003;77:1119–1124.
107. Matthan NR, Welty FK, Barrett PH, Harausz C, Dolnikowski GG, Parks JS, Eckel RH, Schaefer EJ, Lichtenstein AH. Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women. *Arterioscler Thromb Vasc Biol*. 2004;24:1092–1097. doi: 10.1161/01.ATV.0000128410.23161.be.
108. Brouwer IA, Wanders AJ, Katan MB. Trans fatty acids and cardiovascular health: research completed? *Eur J Clin Nutr*. 2013;67:541–547. doi: 10.1038/ejcn.2013.43.
109. Gebauer SK, Destaillats F, Dionisi F, Krauss RM, Baer DJ. Vaccenic acid and trans fatty acid isomers from partially hydrogenated oil both adversely affect LDL cholesterol: a double-blind, randomized controlled trial. *Am J Clin Nutr*. 2015;102:1339–1346. doi: 10.3945/ajcn.115.116129.
110. Stender S. In equal amounts, the major ruminant trans fatty acid is as bad for LDL cholesterol as industrially produced trans fatty acids, but the latter are easier to remove from foods. *Am J Clin Nutr*. 2015;102:1301–1302. doi: 10.3945/ajcn.115.123646.
111. de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, Uleryk E, Budylowski P, Schunemann H, Beyene J, Anand SS. 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. doi: 10.1136/bmj.h3978.
112. Bendsen NT, Christensen R, Bartels EM, Astrup A. Consumption of industrial and ruminant trans fatty acids and risk of coronary heart disease: a systematic review and meta-analysis of cohort studies. *Eur J Clin Nutr*. 2011;65:773–783. doi: 10.1038/ejcn.2011.34.
113. Downs SM, Thow AM, Leeder SR. The effectiveness of policies for reducing dietary trans fat: a systematic review of the evidence. *Bull World Health Organ*. 2013;91:262–269H. doi: 10.2471/BLT.12.111468.
114. Kromhout D, Giltay EJ, Geleifnse JM; Alpha Omega Trial Group. N-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363:2015–2026.
115. Borchgrevink CF, Skaga E, Berg KJ, Skjaeggestad O. Absence of prophylactic effect of linolenic acid in patients with coronary heart-disease. *Lancet*. 1966;2:187–189.
116. Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiotz EH, Westlund K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease: the Norwegian vegetable oil experiment of 1965-66. *Scand J Clin Lab Invest Suppl*. 1968;105:1–20.
117. Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, Mozaffarian D, Hu FB. α-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr*. 2012;96:1262–1273. doi: 10.3945/ajcn.112.044040.

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118. Del Gobbo LC, Imamura F, Aslibekyan S, Marklund M, Virtanen JK, Wennberg M, Yakoob MY, Chiuve SE, Dela Cruz L, Frazier-Wood AC, Fretts AM, Guallar E, Matsumoto C, Prem K, Tanaka T, Wu JH, Zhou X, Helmer C, Ingelsson E, Yuan JM, Barberger-Gateau P, Campos H, Chaves PH, Djoussé L, Giles GG, Gómez-Aracena J, Hodge AM, Hu FB, Jansson JH, Johansson I, Khaw KT, Koh WP, Lemaitre RN, Lind L, Luben RN, Rimm EB, Risérus U, Samieri C, Franks PW, Siscovick DS, Stampfer M, Steffen LM, Steffen BT, Tsai MY, van Dam RM,Voutilainen S, Willett WC, Woodward M, Mozaffarian D; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Fatty Acids and Outcomes Research Consortium (FORCe). ω-3 Polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. *JAMA Intern Med*. 2016;176:1155–1166. doi: 10.1001/jamainternmed.2016.2925.
119. McLennan PL, Dallimore JA. Dietary canola oil modifies myocardial fatty acids and inhibits cardiac arrhythmias in rats. *J Nutr*. 1995;125:1003–1009.
120. Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation*. 1999;99:2452–2457.
121. Rastogi T, Reddy KS, Vaz M, Spiegelman D, Prabhakaran D, Willett WC, Stampfer MJ, Ascherio A. Diet and risk of ischemic heart disease in India. *Am J Clin Nutr*. 2004;79:582–592.
122. Petrova S, Dimitrov P, Willett WC, Campos H. The global availability of n-3 fatty acids. *Public Health Nutr*. 2011;14:1157–1164. doi: 10.1017/S1368980010003678.
123. Willett WC, Sacks FM, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. *Am J Clin Nutr*. 1995;61(suppl):1402S–1406S.
124. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348:2599–2608. doi: 10.1056/NEJMoa025039.
125. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99:779–785.
126. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet [published correction appears in *N Engl J Med*. 2014;370:886]. *N Engl J Med*. 2013;368:1279–1290. doi: 10.1056/NEJMoa1200303.
127. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/index.htm. Accessed July 12, 2016.
128. US Department of Agriculture, US Department of Health and Human Services, and US Department of Agriculture. *Dietary Guidelines for Americans, 2010*. 7th ed. Washington, DC: US Government Printing Office; 2011.
129. Nicklas TA, Farris RP, Smoak CG, Frank GC, Srinivasan SR, Webber LS, Berenson GS. Dietary factors relate to cardiovascular risk factors in early life: Bogalusa Heart Study. *Arteriosclerosis*. 1988;8:193–199.
130. Mikkilä V, Räsänen L, Raitakari OT, Marniemi J, Pietinen P, Rönnemaa T, Viikari J. Major dietary patterns and cardiovascular risk factors from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *Br J Nutr*. 2007;98:218–225. doi: 10.1017/S0007114507691831.
131. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Akerblom HK, Viikari JS. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283. doi: 10.1001/jama.290.17.2277.
132. Ritchie LD, Spector P, Stevens MJ, Schmidt MM, Schreiber GB, Striegel-Moore RH, Wang MC, Crawford PB. Dietary patterns in adolescence are related to adiposity in young adulthood in black and white females. *J Nutr*. 2007;137:399–406.
133. Morrison JA, Sprecher DL, Barton BA, Waclawiw MA, Daniels SR. Overweight, fat patterning, and cardiovascular disease risk factors in black and white girls: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 1999;135:458–464.
134. Simell O, Niinikoski H, Rönnemaa T, Lapinleimu H, Routi T, Lagström H, Salo P, Jokinen E, Viikari J. Special Turku Coronary Risk Factor Intervention Project for Babies (STRIP). *Am J Clin Nutr*. 2000;72(suppl):1316S–1331S.
135. Niinikoski H, Lagström H, Jokinen E, Siltala M, Rönnemaa T, Viikari J, Raitakari OT, Jula A, Marniemi J, Näntö-Salonen K, Simell O. Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. *Circulation*. 2007;116:1032–1040. doi: 10.1161/CIRCULATIONAHA.107.699447.
136. Lauer RM, Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VW, Barton BA, Stevens VJ, Kwiterovich PO Jr, Franklin FA Jr, Kimm SY, Lasser NL, Simons-Morton DG. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. *Am J Clin Nutr*. 2000;72(suppl):1332S–1342S.
137. Obarzanek E, Kimm SY, Barton BA, Van Horn L, Kwiterovich PO Jr, Simons-Morton DG, Hunsberger SA, Lasser NL, Robson AM, Franklin FA Jr, Lauer RM, Stevens VJ, Friedman LA, Dorgan JF, Greenlick MR; DISC Collaborative Research Group. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). *Pediatrics*. 2001;107:256–264.
138. McGill HC Jr, McMahan CA, Malcom GT, Oalmann MC, Strong JP. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. *Arterioscler Thromb Vasc Biol*. 1997;17:95–106.
139. McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC, Strong JP. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth: the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol*. 2000;20:1998–2004.

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