Review

Types of Dietary Fat and Risk of Coronary Heart Disease: A Critical Review

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During the past several decades, reduction in fat intake has been the main focus of national dietary recommendations to decrease risk of coronary heart disease (CHD). Several lines of evidence, however, have indicated that types of fat have a more important role in determining risk of CHD than total amount of fat in the diet. Metabolic studies have long established that the type of fat, but not total amount of fat, predicts serum cholesterol levels. In addition, results from epidemiologic studies and controlled clinical trials have indicated that replacing saturated fat with unsaturated fat is more effective in lowering risk of CHD than simply reducing total fat consumption. Moreover, prospective cohort studies and secondary prevention trials have provided strong evidence that an increasing intake of n-3 fatty acids from fish or plant sources substantially lowers risk of cardiovascular mortality. In this article, we review evidence from epidemiologic studies and dietary intervention trials addressing the relationship between dietary fat intake and risk of CHD, with a particular emphasis on different major types of fat, n-3 fatty acids and the optimal balance between n-3 and n-6 fatty acids. We also discuss the implications of the available evidence in the context of current dietary recommendations.

Key teaching points:

- In the past several decades, reduction in fat intake has been the main focus of national dietary recommendations to lower risk of coronary heart disease (CHD).
- Metabolic studies have long established that the type of fat, but not total amount of fat, predicts serum cholesterol levels.
- Results from epidemiologic studies and controlled clinical trials have indicated that replacing saturated fat with unsaturated fat is more effective in lowering risk of CHD than simply reducing total fat consumption.
- Prospective cohort studies and secondary prevention trials have provided strong evidence that a higher intake of n-3 fatty acids from fish or plant sources lowers risk of CHD.
- Recent national dietary guidelines have shifted the emphasis from total fat reduction to distinguishing different types of fat.

INTRODUCTION

During the past several decades, reduction in fat intake has been the main focus of national dietary recommendations. In the public's mind, the word "dietary fat" has become synonymous with obesity and heart disease, whereas the words "low-fat" and "fat-free" have become synonymous with heart health. In response to the low-fat campaign, the food industry has produced numerous commercial products labeled as "low-fat" or "fat-free," but with high amounts of refined carbohydrates and sugar. Ironically, while dietary fat intake as percentage of energy intake has declined in the U.S. over the years, total caloric intake has not declined, and the prevalence of obesity and type 2 diabetes has grown dramatically [1,2].

It is now increasingly recognized that the low-fat campaign has been based on little scientific evidence and may have caused unintended health consequences. It is also increasingly appreciated that different types of fats have different health effects. In this article, we review epidemiologic evidence and dietary intervention studies regarding the relationship between dietary fat intake and risk of CHD, with particular emphasis on different major types of fat and n-3 fatty acids.

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MAJOR TYPES OF DIETARY FAT

A higher intake of total and saturated fat is widely believed to contribute to the development of CHD. This belief is largely based on ecological studies relating dietary intake of saturated fat and rates of CHD. In the Seven Countries Study [3], intake of saturated fat as a percentage of calories was strongly correlated with coronary death rates across 16 defined populations in seven countries ($r = 0.84$). Interestingly, the correlation between the percentage of energy from total fat and CHD incidence was much weaker ($r = 0.39$). Indeed, the regions with the highest CHD rate (Finland) and the lowest rate (Crete) had the same amount of total fat intake, at about 40% of energy, which was the highest among the 16 populations. In a more recent analysis of the Seven Countries Study [4], Kromhout and colleagues found a strong positive correlation of 25-year death rates from CHD with intakes of four major long-chain saturated fatty acids (all $r > 0.80$) and *trans* fatty acids ($r = 0.78$).

Data from international comparisons as well as migration studies, although providing evidence for the importance of diet and environmental factors in the cause of CHD, are inadequate in testing specific hypotheses regarding the role of individual dietary components due to confounding by other aspects of diet, physical activity, smoking, obesity and economic development. Prospective cohort studies of individuals, in which diet is assessed prior to the occurrence of disease, are typically considered as the strongest nonrandomized design. Despite the long-standing interest in the diet-heart hypothesis, the number of cohort studies that have directly addressed associations between dietary fat intake and risk of CHD is surprisingly small and the results are not consistent. A significant positive association between saturated fat intake and risk of CHD was found in two studies [5,6], but not in others [7–13]. A significant inverse association between polyunsaturated fat intake and CHD was found in only one study [11], but not in others [7–10,12,13]. The interpretation of these findings is complicated by small study size, inadequate dietary assessment, incomplete adjustment for intake of total energy, failure to account for *trans* isomers of unsaturated fats and lack of control for intakes of other types of fat and other components of diet.

More recently, using 14-year follow-up data from the Nurses' Health Study, Hu and colleagues [14] conducted detailed prospective analyses of dietary fat and CHD among 80,082 women aged 34 to 59. The study was particularly powerful because of large sample sizes and repeated assessments of diet. Hu *et al.* found a weak positive association between saturated fat intake and risk of CHD, but a significant and strong positive association with intake of *trans* fatty acids. Five percent of energy from saturated fat, compared with equivalent energy from carbohydrates, was associated with a 17 percent greater risk of CHD (relative risk = 1.17, 95 percent confidence interval 0.97–1.41, $p = 0.10$). Compared with equivalent energy from carbohydrates, the relative risk for two percent of energy from *trans* fat was 1.93 (1.43–2.61, $p < 0.001$); for five percent of energy from monounsaturated fat, 0.81 (0.65–1.00, $p = 0.05$); and for five percent energy from polyunsaturated fat, 0.62 (0.46–0.85, $p = 0.002$). Total fat was intake not significantly related to risk (for five percent energy 1.02, 0.97–1.07, $p = 0.55$). It was estimated that replacement of five percent of energy from saturated fat by unsaturated fats would reduce risk by 42 percent (23–56, $p < 0.001$), and replacement of two percent of energy from *trans* fat by unhydrogenated unsaturated fats would reduce risk 53 percent (34–67, $p < 0.001$) (Fig. 1). These findings challenge the widely recommended low-fat high-carbohydrate diets because they suggest that replacing saturated and *trans* fats with unhydrogenated unsaturated fats is more effective in preventing CHD than reducing overall fat intake.

Individual Saturated Fatty Acids

The association between saturated fat and CHD observed in the Nurses' Health Study was much weaker than that predicted by international comparisons [3], but is consistent with the possibility that the proportional increase in plasma HDL concentration produced by saturated fat somewhat compensates for its adverse effect on LDL level. In metabolic studies, different classes of saturated fatty acids have different effects on plasma lipid and lipoprotein levels [15] (Fig. 2). Specifically, saturated fatty acids with 12–16 carbon atoms tend to increase plasma total and LDL cholesterol levels, whereas stearic acid (18:0) does not have a cholesterol-raising effect in comparison with oleic acid (18:1). Among the cholesterol-raising saturated fatty acids, myristic acid (14:0) appears to be more potent than lauric

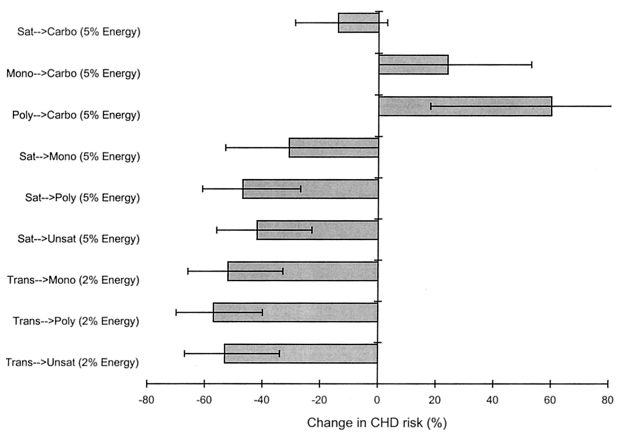

Fig. 1. Estimated changes (% with 95% confidence intervals) in risk of coronary heart disease (CHD) associated with isocaloric dietary substitutions. Adjusted for coronary risk factors and total energy intake. Sat = saturated fat, Carbo = carbohydrate, Mono = monounsaturated fat, Poly = polyunsaturated fat, Trans = *trans* fatty acids, Sat-Carbo = substitute carbohydrates for saturated fat. (Reproduced from [14] with permission of the Massachusetts Medical Society, Copyright © 1997 Massachusetts Medical Society.)

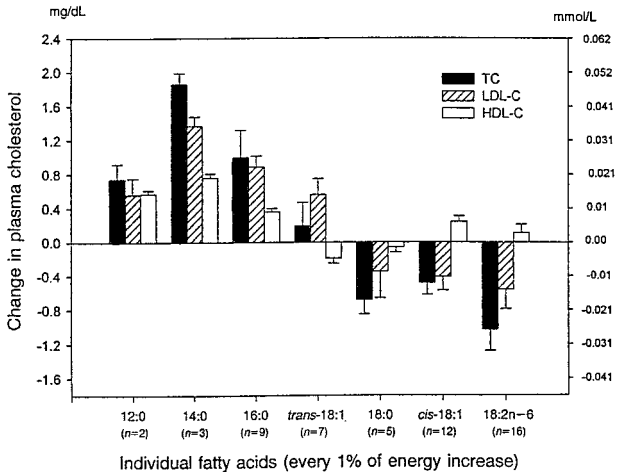

Fig. 2. Effects of lauric (12:0), myristic (14:0), palmitic (16:0), elaidic (*trans*-18:1), stearic (18:0), oleic (cis-18:1), and linoleic (18:2n-6) acids on total cholesterol (TC), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C). (Reproduced from [15] with permission of the American Society for Clinical Nutrition.)

acid (12:0) or palmitic acid (16:0) [15], but the data are not entirely consistent [16].

Because stearic acid does not raise plasma cholesterol levels, it has been suggested it not be included with saturated fat on food labels. However, until recently, there has been no study directly looking at the relationship between stearic acid intake and risk of CHD. In a recent analysis of the Nurses' Health Study [17], Hu and colleagues found that dietary intake of short to medium chain saturated fatty acids (4:0–10:0) was not significantly associated with risk of CHD (relative risk (RR) for a 1% increase in energy = 0.97, 95% confidence interval (CI), 0.90–1.05). In contrast, intakes of longer-chain saturated fatty acids (12:0–18:0) were each separately associated with a small increase in risk. After adjustment for coronary risk factors, the RR for a 1% energy increase from the stearic acid was 1.19 (1.02–1.37). Due to the high correlations among specific saturated fats, distinguishing among their relationships with CHD risk was difficult. Nevertheless, further adjustment for other long-chain saturates did not appreciably alter the RR for stearic acid.

Although stearic acid has little effect on total and LDL cholesterol concentrations compared to carbohydrate, it may lower HDL compared to monounsaturated or polyunsaturated fatty acids, and the HDL-lowering effect of stearic acid was particularly strong among women [18]. Aro *et al.* [19] recently reported that, compared with myristic and palmitic acids, stearic acid reduced LDL concentration, but also reduced HDL level. Thus, the ratios of LDL to HDL and apo B to apo A-I were not affected. Moreover, stearic acid increased Lp(a) concentration [19] and may activate Factor VII [20] and impair fibrinolysis [21]. These data, along with the findings from the Nurses' Health Study, suggest that distinguishing stearic acid from other saturated fats in dietary advice to reduce coronary risk does not appear to be justified. Moreover, these saturated fats are highly correlated in typical diets due to shared food sources (e.g., beef and dairy products).

N-6 Polyunsaturated Fat

Numerous metabolic studies have shown strong cholesterol-lowering effects for vegetable oils rich in linoleic acid when substituted for dietary saturated fat [22]. Also, dietary intervention trials using high-polyunsaturated-fat diets have been more effective than those using low-fat high-carbohydrate diets in lowering total serum cholesterol as well as rates of CHD (discussed below) [23]. In prospective cohort studies among men, a strong inverse association for polyunsaturated fat was found in the Western Electric Study [11], and borderline significant inverse associations were found in the Ireland-Boston Heart Study [6] and the usual care group of the Multiple Risk Factor Intervention Trial [24]. The inverse association between polyunsaturated fat and CHD observed in the Nurses' Health Study is consistent with previous findings, but stronger than predicted by the effects of polyunsaturated fat on blood lipids alone, based on the Keys [25] and Hegested equations [26] derived from metabolic studies. This suggests that n-6 polyunsaturated fat may have other beneficial effects on cardiovascular disease besides improving lipid profile. In animal and metabolic studies, an increased intake of n-6 polyunsaturated fatty acid improves insulin sensitivity [27,28]. In the Nurses' Health Study, a higher intake of n-6 polyunsaturated fat was associated with a significantly lower incidence of type 2 diabetes [29]. In addition, animal studies have suggested an anti-arrhythmic effect when sunflower oil (rich in linoleic acid) was fed [30], although the effect was less than that when fish oil was fed.

In the Nurses' Health Study [17], the ratio of polyunsaturated fat to long-chain saturated fatty acids (P:S ratio) was strongly associated with a lower risk of CHD. After adjustment for age, smoking, other nondietary variables and intakes of monounsaturated fat, *trans* fat, protein and total energy, the RR of CHD was 0.79 (95% CI 0.70–0.89) for each 0.2 unit increment in the ratio. In the categorical analysis, the multivariate RRs across deciles of the ratio (the median values ranged from 0.23 to 0.72 from the lowest to highest deciles) were 1.0 (reference), 0.92, 0.90, 0.87, 0.94, 0.81, 0.68, 0.72, 0.58, and 0.58(0.41–0.83) (p for trend < 0.0001) (Fig. 3). These data suggest that replacing long chain saturated fat with polyunsaturated fat is likely to substantially reduce the risk of CHD. In addition, when intakes of polyunsaturated and *trans* fat were considered together [14], the lowest risk of CHD was observed among those who were in the lowest quintile of *trans* fat and the highest quintile of polyunsaturated fat; the RR comparing women in this category with those with highest intake of *trans* fat and lowest intake of polyunsaturated fat was 0.31 (95% CI 0.11–0.88). These results indicate a substantial benefit to substituting polyunsaturated fat (such as unhydrogenated soybean

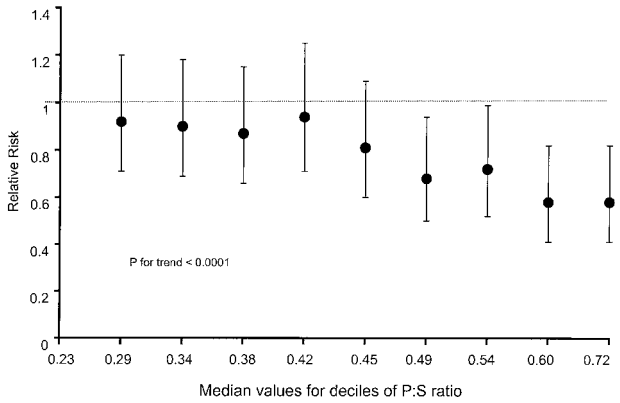

Fig. 3. Multivariate relative risks of coronary heart disease according to deciles of the ratio of polyunsaturated to long-chain saturated fatty acids (P:S ratio). Adjusted for coronary risk factors, other fatty acids and total energy intake. (Reproduced from [17] with permission of the American Society for Clinical Nutrition.)

or corn oil) for *trans* fat (such as hard margarine) in the diet or other foods high in *trans* fatty acids.

Monounsaturated Fat

Ecological studies have suggested an inverse association between monounsaturated fat intake and total mortality, as well as with CHD death [31]. In particular, the mortality rate from CHD is very low in the traditional Mediterranean populations that use olive oil (a major source of oleic acid) as the primary source of fat [22].

Prospective cohort studies that address the association between intake of monounsaturated fat and CHD risk are sparse. Two studies found an increased risk of CHD with a higher intake of monounsaturated fat in younger, but not older participants [32,33]. However, neither study adjusted for intake of other types of fat. A more recent study found an inverse association for monounsaturated fat after adjusting for intakes of other types of fat [12]. Because the main source of monounsaturated fat in the U.S. diet is beef and dairy fats and partially hydrogenated vegetable oils, intake of monounsaturated fat is strongly correlated with saturated and *trans* fats. Thus, the relative risks for monounsaturated fat intake not adjusted for saturated and *trans* fats are likely to be seriously confounded. In the Nurses' Health Study [14], after adjusting for other fats, monounsaturated fat intake was inversely associated with risk of CHD, although the association was weaker than that for polyunsaturated fat.

In metabolic studies, replacing carbohydrates with monounsaturated fat raises HDL without affecting LDL [34]. This replacement may also improve glucose tolerance and insulin sensitivity among patients with diabetes mellitus [35]. In addition, monounsaturated fat is resistant to oxidative modification [36].

The major non-animal sources of monounsaturated fat include olive and canola oils, nuts and avocados. Both canola oil and nuts are also important sources of polyunsaturated fat. In addition, liquid vegetable oils generally contain a higher amount of vitamin E, whereas animal fat contain little antioxidants.

Trans Fatty Acids

The positive relationship between *trans* fat intake and risk of CHD observed in the Nurses' Health Study is generally consistent with several prospective studies conducted in men, including the Health Professionals' Follow-up Study [13] and the Alpha-Tocopherol Beta-Carotene Study [12]. The concentration of *trans* fatty acids in adipose tissue was not significantly associated with risk of myocardial infarction in the EURAMIC study [37] or with sudden cardiac death in a small case-control study in the United Kingdom [38]. However, the 95% confidence intervals (CIs) for the relative risks in the highest categories of *trans*-fatty acids in both studies were very wide and included the estimate of relative risk in the Nurses' Health Study. Also, in the EURAMIC study, after exclusion of an uninformative area (Spain, where *trans* fat intake was uniformly very low due to high consumption of olive oil), the relative risk for the highest versus the lowest category (1.44, 95% CI 0.94–2.20) was close to that in the Nurses' Health Study (RR for extreme quintiles = 1.53, 95% CI 1.16–2.02).

A higher intake of *trans* fat can contribute to increased risk of CHD through multiple mechanisms. First, *trans* fatty acids raise LDL cholesterol levels [39–42] and lower HDL cholesterol [39,41,42] relative to *cis* unsaturated fatty acids. As such, the increase in the ratio of total to HDL cholesterol for *trans* fat is approximately double that for saturated fat [43]. Second, *trans* fat increases lipoprotein (a) levels [44,45], which are positively associated with risk of CHD [46]. Third, *trans* fat raises plasma triglyceride levels [47], and increased triglycerides are independently associated with increased risk of CHD [48,49]. Fourth, *trans* fatty acids can adversely affect essential fatty acid metabolism and prostaglandin balance by inhibiting the enzyme delta-6-desaturase and, as a result, may promote thrombogenesis [50–52]. Finally, recent data have suggested that high intake of *trans* fat may promote insulin resistance in humans [28].

The major sources of *trans* fatty acids in the U.S. are stick margarine, commercially baked products, and deep fried fast food. In Europe, virtually all margarines have become *trans* fat free due to rapid response by the manufactures to these health concerns. The change from stick margarine to *trans* fat free margarine, however, has been slow in the U.S. On the other hand, in the U.S., margarine now accounts for only 25 percent to 37 percent of *trans* fatty acids; the remainder is "hidden" in baked goods, fried fast foods, and other prepared foods [53]. For example, a medium-size French fries contains 5–6 grams, a doughnut contains 2 grams, and an ounce of crackers contains 2 grams of *trans* fatty acids [54]. Unfortunately, many of these products do not need to be labeled under the proposed regulations to label *trans* fatty acids which are now under consideration by the Food and Drug Administration.

NUT CONSUMPTION AND RISK OF CHD

Up to 80% of energy in nuts comes from fat. Because of their high fat content, nuts are traditionally included among foods to be avoided to lower blood cholesterol and risk of CHD. However, so far, five large prospective cohort studies (the Adventist Health Study, the Iowa Women Health Study, the Nurses' Health Study, the Physicians' Health Study and the Cholesterol and Recurrent Events Study (CARE)) have examined the relation between nut consumption and risk of CHD, and all have found an inverse association [55]. In particular, women in the Nurses' Health Study who consumed nuts five or more times a week had significantly lower risk of total CHD (RR = 0.65, 95% CI 0.47–0.89, p for trend = 0.0009), as compared to women who rarely ate nuts (never or less than once a month), after adjusting for age, smoking and other known CHD risk factors [56]. The magnitude of risk reduction was similar for fatal CHD (RR = 0.61, 0.35–1.05, p for trend = 0.007) and nonfatal MI (RR = 0.68, 0.47–1.00, p for trend = 0.04). A similar risk reduction was observed among the participants in the Adventist Health Study [57], whose nut consumption is substantially higher than the general U.S. population.

Several clinical studies have evaluated the effects of diets high in nuts (including walnuts, peanuts, almonds and other nuts) on blood lipids. In a randomized, controlled study, Sabate and coworkers [58] randomized 18 normocholesterolemic men to either a control or a high walnut diet and then switched after four weeks. Both diets conformed to the National Cholesterol Education Program Step I diet and were identical in foods and macronutrients, except that walnuts provided 20% of calories in the walnut diet (replacing meat, potato chips, oils, margarine and butter). When compared to the control diet, men in the walnut diet decreased total and LDL cholesterol levels by 12% and 16%, respectively. Although there was a slight decrease in HDL cholesterol level (4.9%) in the walnut diet, the ratio of LDL cholesterol to HDL cholesterol was significantly lowered by the walnut diet (12%). A cholesterol-lowering effect was also observed for diets supplemented with almonds [59,60]. In addition, a low-fat diet supplemented with peanuts significantly improved serum lipoprotein profiles compared to a regular low-fat diet among postmenopausal hypercholesterolemic women [61].

The beneficial effects of nut consumption observed in clinical and epidemiologic studies underscore the importance of distinguishing different types of fat. Although nuts are high in fat, the predominant types of fat in nuts are mono- and polyunsaturated (Table 1), which lower LDL cholesterol level. Other potentially protective constituents in nuts include vegetable protein, magnesium, vitamin E, fiber, and potassium.

Concern may exist that higher consumption of nuts would result in weight gain due to their relatively high energy density. Thus, nuts should not simply be added on the top of the diet. Instead, they should be used to replace other sources of calories such as red meats or refined carbohydrates.

INTERVENTION TRIALS OF DIETARY FAT

Clinical Endpoint Trials

Randomized clinical endpoint trials are the "gold standard" for establishing diet-disease relationships. However, in most circumstances, dietary trials are infeasible because of practical considerations, including ethical issues and potential lack of compliance in the long run. So far, only a handful of dietary trials with coronary disease endpoints have been conducted and most of these trials were conducted in men with existing myocardial infarction. These trials have been reviewed previously by several authors [62–64] (Table 2).

Earlier trials have tested two dietary approaches, one to lower total fat and the other to replace saturated fat with polyunsaturated fat leaving total fat unchanged. Three of the trials were primary prevention trials conducted among institutionalized patients to increase control over the diets [65–67]. Total fat intake was not reduced in these trials; rather, polyunsaturated fat was greatly increased to substitute for saturated

Table 1. Fat Composition of Nuts*

	Total fat, g	Saturated fat, g	Mono-unsaturated fat, g	Poly-unsaturated fat, g	Ratio of unsaturated to saturated fat, g
Almonds (~24 nuts)	14.5	1.5	10.0	3.0	8.7
Brazil nuts (8 medium nuts)	19.0	5.0	7.0	7.0	2.8
Cashews (~18 medium nuts)	13.0	2.5	8.0	2.5	4.2
Hazelnuts (~12 nuts)	18.0	1.0	15.0	2.0	17.0
Macadamia (~12 nuts)	20.0	2.5	16.5	1.0	7.0
Peanuts (~35 pieces)	13.5	2.0	7.0	4.5	5.8
Pecans (~15 halves)	19.0	2.0	12.0	5.0	8.5
Pistachios (~47 nuts)	14.0	2.0	8.0	4.0	6.0
Walnuts, English (~14 halves)	18.0	2.0	5.0	11.0	8.0
Average	16.6	2.3	9.8	4.4	6.2

* All values for dried or dry roasted nuts.

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Table 2. Dietary Intervention Trials on Coronary Events

Trial	Subjects in the intervention group	Dietary Intervention	Dietary fat (% energy) in the treatment group	P:S ratio in the treatment group	Duration (yrs)	Change in serum cholesterol[†]	Change in CHD[‡]
MRC low-fat [71]	123 MI patients, all males	Reduce total fat	22%	NR	3	−5%	+4%
DART [72]	1,015 MI patients, all males	Reduce total fat	32%	0.8	2	−3.5%	−9%
Finnish Mental Hospital [66]	676 males	Unsaturated fat- → saturated fat	35%	1.5	6	−15%	−43%
Los Angeles Veteran [65]	424 males, most had no evidence of existing heart disease	Unsaturated fat- → saturated fat	40%	NR	8	−13%	−31%
Oslo Diet Heart Study [68, 69]	206 MI patients, all males	Unsaturated fat- → saturated fat	39%	2.4	5	−14%	−25%
MRC soy oil [70]	199 MI patients, all males	Unsaturated fat- → saturated fat	46%	2.0	4	−16%	−12%
Minnesota Coronary Survey [67]	4,393 men and 4,664 women	Unsaturated fat- → saturated fat	38%	1.6	4.5	−14%	No change
Indian Experiment of Infarct Survival [75]	204 MI patients, primarily males	High fruits, vegetables, nuts, fish and pulses	24%	1.2	1	−9%	−40%
Lyon Diet Heart Study [73]	302 MI patients, primarily males	Mediterranean diet	31%	0.7	2.3	No change	−73%

[†] Change in cholesterol refers to the percentage change in serum cholesterol in the treatment group compared to the change io the control group.

[‡] Change in CHD refers to the percentage difference in coronary event rates in the treatment compared to the control group.

NR: not reported.

Adapted from [64].

fat. In all three trials, serum cholesterol was reduced substantially. In the Los Angeles Veteran Hospital Study [65], CHD rate was reduced by 31% during eight years of follow-up in the intervention group, while in the Finnish Mental Hospital study [66], the reduction of CHD rate was 43% over six years. In both trials, linoleic acid in adipose tissue (% of total fatty acids) increased substantially in the treatment group during the study period, indicating compliance with the prescribed high polyunsaturated-fat diet by the patients. In the Finnish trial, patients in the treatment group also substituted soft margarine for stick margarine. Thus, the reduction in serum cholesterol and CHD observed in this study was probably in part due to reduction in *trans* fat intake. In contrast, in the Minnesota study [67], cardiovascular events were not significantly reduced by the treatment diet, although serum cholesterol was reduced by 14% in the treatment group. However, this study was relatively short in duration (4.5 years), and the achieved P:S ratio (1.6) was far below the specified goal (2.5).

Two earlier secondary prevention trials also used high polyunsaturated-fat diets. The Oslo Diet-Heart Study, which included 21% energy from polyunsaturated fat, found a significant reduction in serum cholesterol and major coronary events (fatal and nonfatal MI) at five years of follow-up [68]. After 11 years, fatal MI was reduced by 44% ($p = 0.004$) and total cardiovascular mortality was reduced by 14% ($p = 0.13$) [69]. Another trial [70] using a high amount of soybean oil found a 16% reduction in serum cholesterol at six months and a 12% (nonsignificant) reduction in the rate of recurrent coronary events over four years. But deaths from cardiovascular disease were not affected by the treatment. In contrast to the favorable results observed in trials using high-polyunsaturated fat diets, two secondary prevention trials testing the approach of total fat reduction did not find a significant reduction in serum cholesterol or CHD events [71,72]. The low-fat intervention group in the Diet and Reinfarction Trial (DART) [72] was unable to achieve the goal set for total fat, raising questions about the compliance of the patients to a low-fat diet.

In the 1990s, two secondary prevention trials using the whole diet approach instead of modification of the amount of dietary fat reported favorable results. The Lyon Diet Heart Study tested the effects of a "Mediterranean" diet enriched with alpha-linolenic acid compared to a standard low fat diet [73]. The intervention diet included more bread, more fruits and vegetables, more fish and poultry and less red meat and butter. After a mean follow-up of 27 months, coronary events were reduced by 73% in the treatment group and total mortality was reduced by 70%. The benefit of the intervention diet was maintained up to four years after the first infarction [74]. Interestingly, blood lipids were not affected by the intervention, but blood levels of n-3 fatty acids, especially alpha-linolenic acid and anti-oxidant vitamins increased significantly in the treatment group.

The Indian Heart Study [75] tested a semi-vegetarian diet enriched with fruits, vegetables, whole grains and nuts among patients during hospitalization with acute myocardial infarction. After 12 weeks of treatment, coronary events were reduced by 36%, and at the end of trial (one year), coronary death was reduced by 41% and nonfatal MI by 38%. In the meantime,

serum cholesterol decreased by 8%, systolic blood pressure decreased by 8 mmHg, diastolic decreased by 6 mmHg and body weight decreased by 4 kg.

In both trials, total fat intake did not appreciably change. The success of these trials indicates that the right types of fatty acids and other components of diet are more important than total amount of fat in reducing coronary risk. These trials also support the clinical utility of the overall dietary pattern approach in the prevention of CHD. However, in these trials, it is not possible to determine which of the nutritional changes were responsible for the observed reduction in CHD. Also, both trials were conducted in myocardial infarction patients, and these diets have not yet been tested in the primary prevention of CHD.

Angiographic Trials

Several angiographic trials have examined the effects of dietary intervention on progression of coronary atherosclerosis. In an uncontrolled trial (The Leiden Intervention Trial), Arntzenius and coworkers [76] tested a vegetarian diet with a high ratio of polyunsaturated fat to saturated fat (P:S = 2) among 39 patients with stable angina pectoris. There was a significant retardation in coronary lesion growth after two years, which was primarily attributed to improved lipid profile. During the intervention, participants' linoleic acid content of cholesteryl esters significantly increased. The St. Thomas Atherosclerosis Regression Study (STARS) [77] tested the effects of a dietary intervention with a moderate amount of total fat (27% energy) but relatively high polyunsaturated fat (8% energy). The dietary intervention alone significantly reduced overall progression of coronary narrowing and increased overall regression of coronary artery disease. Adding a cholesterol-lowering medication, cholestyramine, to the dietary intervention further reduced the progression of coronary atherosclerosis.

The combined effects of diet and lifestyle modification on the progression of atherosclerosis have been investigated in several studies. In the Lifestyle Heart Study, Ornish and colleagues [78] assigned 28 MI patients to an intervention group with low-fat, strict vegetarian diet, exercise, stress management and yoga and 20 patients to a usual care group. After one year, blood cholesterol was lowered by 19% and the average percent diameter stenosis was reduced by 5.6% in the intervention group, as compared with the control group. At year five [79], coronary atherosclerosis continued to regress in the experimental group, but to progress in the control group, and significantly more "cardiac events" (MI, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, cardiac hospitalization, deaths) occurred in the control group. The number of "hard endpoints" (MI and deaths), however, was too small to allow for meaningful analyses. Interestingly, in the control group coronary stenosis worsened (28% relative worsening) despite substantial reduction in fat intake (from 31% of energy to 25% of energy) and LDL cholesterol (19% reduction). Thus, it is not clear whether the low-fat dietary component contributed to the regression of coronary atherosclerosis over and beyond exercise and other programs in the intervention. Indeed, in an angiographic trial conducted in Germany, increased exercise was the most important variable that predicted the reduction in coronary stenosis [80]. The low-fat regimen in the Lifestyle Heart Study has been criticized as being extreme and unnecessarily rigid. Even fatty fish and nuts, which have been documented to protect against CHD, are excluded. Poor adherence to such diet is another major concern in the application of such diet to the public.

Two other multifactorial intervention trials have yielded favorable results on progression of atherosclerosis among patients with existing coronary disease [80,81]. Both trials involved a low saturated fat and relatively high polyunsaturated diet (P:S ratio >1) and intensive physical exercise. In the trial conducted in Germany [80], the treatment also comprised intensive physical exercise in group training sessions (minimum, 2 hr/wk) and daily home exercise periods (20 min/day). After 12 months, 32% patients in the intervention group experienced regression of coronary lesions as compared with 17% in the control group. In contrast, 48% patients in the control group experienced progression of coronary lesions as compared with 23% in the treatment group. Besides dietary intervention, the Stanford Coronary Risk Intervention Project (SCRIP) [81] involved exercise, smoking cessation, weight loss and cholesterol-lowering medications. After four years, the rate of narrowing of diseased coronary artery segments in the intervention group was 47% less than that for subjects in the control group. The success of these secondary prevention trials using angiographic endpoints is in direct contrast to the disappointing results from several primary prevention trials of multifactorial approach [82,83]. However, because multiple dietary, lifestyle and even medication changes were made simultaneously in these trials, the interpretation of any observed difference in outcome is complicated. In addition, whether coronary stenosis detected by angiography is a valuable endpoint is not yet settled [84].

In summary, dietary intervention trials in general support the benefit of replacing saturated fat with polyunsaturated fat. Evidence regarding the replacement of total or saturated fat by carbohydrate is more limited, but is generally unsupportive of benefit. These results are consistent with prospective cohort studies and metabolic studies indicating the importance of types of fat. Although the ideal randomized trial of dietary fat and primary prevention of CHD in free-living populations has not been and may never be conducted due to feasibility concerns, the existing evidence powerfully supports the strategy of replacing saturated and *trans* fats with unhydrogenated unsaturated fats.

FISH AND MARINE N-3 FATTY ACIDS

A low rate of cardiovascular disease in populations with very high intake of fish, such as Alaskan Native Americans [85,86], Greenland Eskimos [87,88] and Japanese living fishing

villages [89,90], suggests that fish oil may be protective against atherosclerosis. Subsequent prospective cohort studies have found an inverse association between fish consumption and risk of cardiovascular mortality in diverse populations. Krombout *et al.* [91] demonstrated in the Dutch component of the Seven Countries Study, with 20 years of follow-up, that men who consumed 30g of fish per day had a 50% lower CHD mortality than men who rarely ate fish. In the Western Electric Study, Daviglus *et al.* [92] have found that men who consumed 35g or more of fish per day had a 40% lower risk of fatal CHD. In the US Physicians' Health Study, Albert *et al.* [93] found that weekly fish consumption led to a RR of 0.48 (95% CI 0.24–0.96) for sudden cardiac death, although in the same cohort, no significant association was observed between fish consumption and overall cardiovascular endpoints [94]. In the Health Professionals' Follow-up Study, Ascherio *et al.* [95] found no overall association between dietary intake of n-3 fatty acids or fish intake and the risk of coronary disease, but there was a non-significant trend for a reduction in risk for fatal CHD with increasing fish consumption. These studies suggest that fish is probably more protective against fatal CHD than nonfatal myocardial infarction.

Two interventional studies, the Diet and Reinfarction Trial (DART) [96] and the GISSI-Prevenzione trial [97], have evaluated whether fish consumption or fish oil supplementation reduces coronary mortality among MI patients. The diet and reinfarction trial (DART), which included 2033 men allocated to three dietary interventions, showed that subjects who received fish advice had a significant reduction in total mortality of 29% after two years. While not statistically significant, there was also a trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption. The more recent GISSI-Prevenzione trial randomly assigned 11,324 myocardial infarction patients to four different groups: n-3 fatty acids (850–882 mg EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) (1:2)), vitamin E (330 mg alpha-tocopherol), a combination of n-3 and vitamin E and control. Daily supplementation with n-3 fatty acids resulted in a 10% to 15% reduction in the main endpoints (death, non-fatal MI and stroke). Most of the reduction was attributable to the decrease in cardiovascular death, especially sudden cardiac death. These two trials provide support for a therapeutic role of fish oil in the treatment of MI patients.

The protective effects of marine n-3 fatty acids are probably due to multiple mechanisms, including reducing triglyceride levels [98], reducing platelet aggregation [99] and anti-arrhythmic effects [100]. There is growing evidence to suggest that fish oil may improve endothelial dysfunction, an early marker of atherosclerosis [101,102]. *In vitro* studies have consistently shown that n-3 fatty acids decrease expression of adhesion molecules on the endothelium and also decrease leukocyte/endothelium interactions [101]. Additionally, clinical experimental studies have shown that n-3 fatty acid supplementation improves endothelial-dependent vasomotor function [102,103].

ALPHA-LINOLENIC ACID (ALA)

ALA is an essential n-3 fatty acid for humans [104,105]; adequate intake of ALA and long-chain n-3 fatty acids is especially important for infants, young children [106] and patients requiring parenteral and enteral nutrition [106–108]. In animals and humans, ALA can be metabolized to long-chain polyunsaturated n-3 fatty acids, including eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids through the desaturation-chain elongation pathway [109]. Increased dietary consumption of ALA may decrease platelet aggregation and reduce formation of pro-aggregatory thromboxane A_2 by inhibiting the conversion of linoleic acid (18:2, n-6) to arachidonic acid (20:4, n-6) [110]. In a dietary intervention study of French farmers, Renaud and colleagues [111] changed the type of fats by replacing butter by oil and margarine rich in ALA (rapeseed oil). After two years, the EPA content of plasma lipids and platelet phospolipids increased significantly and platelet aggregation was significantly diminished.

Experimental studies have suggested an antiarrhythmic effect of ALA. In cell culture studies, the addition of ALA slows the beating rate of isolated neonatal rat cardiac myocytes [112]. In animal experiments in which arrhythmias were induced by coronary occlusion and reperfusion, significant reductions in the incidence of ventricular fibrillation and cardiac mortality were observed in rats fed with ALA-rich diets. In one of the experiments [113], similar significant reductions in cardiac arrhythmia were observed in animals fed red meat supplemented with fish oil and in those fed red meat supplemented with canola oil (8% ALA), when compared to the control group (fed only red meat). Interestingly, mortality was even lower in the canola oil group than in fish oil group (7% vs. 10%). In another experiment [114], mortality due to ventricular fibrillation was significantly lower in rats fed a diet containing canola oil, compared to those fed olive oil. The antiarrhythmic effect of ALA may be attributable to an increased electrical threshold for induction of ventricular fibrillation [114]. In a secondary prevention trial conducted among patients with existing myocardial infarction (Lyon Diet Heart Trial) [73], no sudden death occurred in patients randomized to a Mediterranean diet enriched with ALA, compared with eight deaths in the control group. This study supports an antiarrhythmic effect of ALA in humans although other dietary changes were made simultaneously in this trial.

Several epidemiologic studies have examined the association between ALA intake and risk of CHD. In the usual care group of the Multiple Risk Factor Intervention Trial [24], men in the highest quintile of ALA intake (expressed as percent of energy) had a 40% lower CHD mortality compared to men in the lowest quintile. In the Health Professionals Follow-up Study [13], a 1% increase in linolenic intake (expressed as percent of energy) was associated with a 40% lower risk of fatal CHD. In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [12], men in the highest quintile of

energy-adjusted ALA intake had 25% lower CHD mortality. In these three studies, however, the association between ALA intake and CHD was not the main focus, and none were adequately adjusted for other dietary factors, including intakes of other fats, dietary vitamins, folate and vegetables.

Recently, Hu and colleagues examined the relation of ALA intake to incidence of fatal CHD during 10 years of follow-up in the Nurses' Health Study [115]. After adjusting for coronary risk factors, the RRs of fatal CHD from the lowest to highest quintiles of ALA intake were 1.0, 0.89, 0.90, 0.66, and 0.52 [95% CI 0.30–0.90], p for trend = 0.01. The major contributors of ALA in the Nurses' Health Study were oil and vinegar (e.g., Italian salad dressing) and mayonnaise salad dressings; these products are typically made with soybean oil, which contains approximately 7% ALA if it is not hydrogenated. Hu *et al.* [115] found an approximately 50% lower risk of fatal CHD among women who consumed oil and vinegar salad dressing frequently (five to six times or more a week) compared to those who consumed this salad dressing less than once a month, after adjusting for vegetable consumption.

Given the strong evidence to support beneficial effects of ALA on cardiovascular disease, flaxseed as well as other important dietary sources of ALA (e.g., unhydrogenated canola and soybean oils and walnuts) (Table 3) can be incorporated into a healthy and balanced diet for the prevention of cardiovascular disease [116]. This is especially important for those choosing not to consume fish. The above findings also raise concern that the widespread promotion of fat-free salad dressings and mayonnaise, a primary source of ALA in the U.S. diet, may have an adverse effect on CHD rates.

Table 3. α-Linolenic Acid Content of Various Oils and Foods

Product	α-Linolenic acid
	% by wt
Flaxseed oil	50.8
Soy oil	7.0
Canola oil	9.3
Olive oil	0.6
Chocolate	0.1
Corn oil	1.0
Coconut oil	Trace
Safflower oil	0.4
English walnuts, dry roasted	6.8
Hazelnuts, dry roasted	0.2
Almonds, dry roasted	0.4
Peanuts, dry roasted	Trace
Cashews, dry roasted	0.2
Green leafy vegetables, raw edible portion	
Spinach	0.12
Brussels sprouts	0.20
Kale	0.13

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THE BALANCE BETWEEN N-3 AND N-6 POLYUNSATURATED FATTY ACIDS

Due to the competition between ALA and linoleic acid for the desaturation and chain elongation pathway [117], ALA's incorporation into plasma and tissue lipids and its conversion to long-chain n-3 fatty acids are influenced by linoleic acid levels. Thus, the optimal balance between dietary ALA and linoleic acid may be important to prevent thrombosis and atherosclerosis [114,118]. In the Nurses' Health Study [115], the ratio of ALA to linoleic acid was less strongly related to risk of fatal CHD than was ALA alone. The multivariate RRs of fatal CHD across quintiles of the ratio (median values 0.07, 0.09, 0.10, 0.11, and 0.14) were 1.0, 1.02, 0.84, 0.87, and 0.84 (0.53–1.33) [p for trend = 0.40]. These results suggest a modest reduction in CHD risk with a ratio of ALA to linoleic acid greater than 0.10.

Because ALA and its metabolite, EPA, can decrease generation of thromboxane A2, a pro-aggregatory vasoconstrictor, through their inhibitory action on the conversion from linoleic acid to arachidonic acid and the activity of enzyme cyclooxygenase [112,119–121], it is expected that a greater ratio of ALA to linoleic acid will lower risk of CHD, through decreasing thrombotic tendency. However, the prostanoid pathway is only one mechanism through which dietary fatty acids influence the development of CHD. The primary mechanism by which n-6 polyunsaturated fat lowers risk of CHD is through lowering LDL cholesterol, although n-6 fatty acids may also have other beneficial effects, such as improving insulin sensitivity [28] and lowering the threshold for ventricular fibrillation [121]. Because both n-6 and n-3 fatty acids are associated with a lower risk of CHD, although through different biological pathways, the ratio is only weakly related to CHD risk. Nevertheless, it is generally agreed that the ratio of n-3 to n-6 fatty acids in the U.S. diet is less than optimal and should be improved. The point of controversy lies in how to improve the ratio. Although most researchers have proposed to increase the consumption of n-3 fatty acids from both fish and plant sources, others have suggested a reduction in consumption of n-6 fatty acids [122]. Considering the strong protective effect of n-6 polyunsaturated fat against CHD observed in epidemiologic studies and clinical trials, the latter strategy does not seem justifiable. On the contrary, available data strongly support the strategy of replacing animal and hydrogenated fats with natural liquid vegetables oils, which contain both monounsaturated and polyunsaturated fats, in reducing risk of CHD. Such replacement can also increase the intake of n-3 fatty acids because several vegetable oils including canola and soybean oils contain a substantial amount of ALA. Meanwhile, an increase in fish consumption to at least two servings per week has been recommended for the prevention of CHD [123]. These strategies will substantially increase the absolute amount of n-3 fatty acids in the diet and help to achieve a more desirable ratio of

n-3 to n-6 fatty acids, without sacrificing the benefit of n-6 polyunsaturated fat.

DIETARY CHOLESTERAL AND EGGS

Dietary cholesterol raises LDL cholesterol levels and very high intakes cause atherosclerosis in numerous animal models [124]. In controlled metabolic studies conducted in humans, dietary cholesterol raises levels of total and LDL cholesterol in blood [25,125], but the effects are relatively small compared with saturated and *trans* fatty acids [126,127], and individuals vary widely in their responses [128,129]. A significant positive association between dietary cholesterol and CHD was found in some epidemiologic studies [5,11], but not in others [12,13,32,33]. In a pooled analysis of four studies [5–7,11], the relative risk of CHD was 1.30 (1.10–1.50) for a difference of 200 mg/1000 kcal in dietary cholesterol [124]. But this analysis included only those studies with positive findings. The Nurses' Health Study found a weak and nonsignificant positive association between dietary cholesterol and risk of CHD (relative risk for each increase of 200 mg/1000 kcal = 1.12, 95% confidence interval 0.91–1.40) [130].

To avoid elevations in blood cholesterol and reduce CHD risk, the public has been advised to consume no more than 300 mg cholesterol daily and limit consumption of eggs, which contain about 213 mg cholesterol per egg [131,132]. In controlled metabolic studies, ingestion of cholesterol by feeding egg yolks or whole eggs raises blood total and LDL cholesterol levels [126–128,133]. In most egg feeding studies, intakes of other nutrients such as fatty acids, carbohydrates and protein were balanced between egg and no-egg groups so that only dietary cholesterol varied. Therefore, these studies did not really examine the impact of ingestion of eggs *per se* on blood lipids.

Surprisingly, there is little direct evidence linking higher egg consumption and increased risk of CHD. In the Framingham study, Dawber and colleagues [134] found no significant association between egg consumption and incidence of CHD despite a wide range of egg intake. In an earlier analysis of the Seventh-Day Adventists study [135], higher egg consumption appeared to be associated with increased risk of fatal CHD, but this association was not present in a more recent analysis with a longer follow-up [136]. In a case-control study conducted in Italy [137], the frequency of egg consumption was not significantly associated with risk of CHD in women. In a detailed analysis of egg consumption and incidence of CHD among 117,933 apparently healthy subjects in the Nurses' Health Study and Health Professionals' Follow-up Study, Hu and colleagues [138] found no evidence of an overall positive association between egg consumption and risk of CHD in either men or women. The relative risks (RRs) of CHD across categories of intake (<1/week, 1/wk, 2–4/week, 5–6/week, >=1/day) were 1.0, 1.06, 1.12, 0.90, and 1.08 (p for trend = 0.75) in men and 1.0, 0.82, 0.99, 0.95, and 0.82 (p for trend = 0.95) in women.

The null association between egg consumption and risk of CHD observed in these studies may be somewhat surprising, considering the widespread belief that eggs are a major cause of heart disease. One egg contains about 200 mg cholesterol, but also appreciable amounts of protein, unsaturated fats, folate, B vitamins and minerals. It is conceivable that the small adverse effect caused by cholesterol is counterbalanced by potential beneficial effects of other nutrients.

One potential alternative explanation for the null finding is that background dietary cholesterol may be so high in the usual Western diet that adding somewhat more has little further effect on blood cholesterol. In a randomized trial, Sacks *et al.* [139] found that adding one egg per day to the usual diet of 17 lactovegetarians whose habitual cholesterol intake was very low (97 mg/day) significantly increased LDL cholesterol level by 12%. In a meta-analysis of controlled metabolic studies, Hopkins [140] found that serum cholesterol's response to added dietary cholesterol is modulated by baseline cholesterol intake. The higher the baseline cholesterol intake, the less the response induced by adding cholesterol to the diet. In the analyses conducted by Hu *et al.* [138], differences in non-egg cholesterol intake did not appear to be an explanation for the null association between egg consumption and risk of CHD. However, the possibility that egg consumption may modestly increase the risk among participants with very low background cholesterol intake cannot be excluded.

These findings do not suggest that one should go back to the traditional high cholesterol Western diet. Instead, they suggest that among healthy men and women, moderate egg consumption can be part of a nutritious and balanced diet. Because eggs are excellent and relatively inexpensive sources of essential amino acids and certain vitamins, they can substitute for other animal products such as red meat. These results also illustrate the danger of judging health effects of a food by single nutrients or components contained in the food.

CONCLUSIONS

Compelling evidence indicates the greater importance of types of fat than total amount of fat with respect to risk of CHD, although the optimal mixture of different fatty acids remains unsettled. The seminal metabolic studies conducted by Keys [25] and Hegested [26] have long established that the type of fat but not total amount of fat predicts serum cholesterol levels. Consistent with the metabolic studies, epidemiologic studies strongly support the idea that types of fat are more important than total amount of fat in determining the risk of CHD. Controlled clinical trials have also shown that replacing saturated fat with polyunsaturated fat is more effective in lowering serum cholesterol and reducing risk of CHD than simply reducing total fat consumption. Moreover, secondary prevention

trials have demonstrated that adding n-3 fatty acids from fish or plant sources to the diet without altering total amount of fat substantially reduces coronary and total mortality among post-MI patients.

A major purported benefit of a low-fat diet is weight loss. But long-term clinical trials have not provided convincing evidence that reducing dietary fat can lead to substantial weight loss [141]. On the contrary, there is some evidence that a diet containing a high amount of refined carbohydrates may increase hunger and promote overeating, which can lead to weight gain and obesity [142]. It is now generally agreed that total energy intake, whether from fat or carbohydrate, relative to energy expenditure, is a more important determinant of body weight than dietary fat *per se*.

It has been increasingly recognized that the widely promoted low-fat concept is too simplistic and not compatible with available scientific data. In this context, the recently revised national dietary guidelines [123,143] have de-emphasized the role of total fat in the prevention of CHD and other chronic diseases. In particular, the 2000 Dietary Guidelines for Americans recommend the public to "choose a diet that is low in saturated fat and cholesterol and moderate in total fat", which is modified from the recommendation to "choose a diet low in fat, saturated fat and cholesterol" stated in the 1995 edition of the guidelines. But the revised guidelines have inherited the recommendation of no more than 30% of calories from fat from previous editions of the guidelines. Also, in the food guide pyramid, all fats and oils are still lumped together on the top with no distinguishing of different types of fat. The revised 2000 American Heart Association (AHA) dietary guidelines have gone a step further to eliminate the upper limit of 30% of calories from fat as a major dietary recommendation to prevent cardiovascular disease. Moreover, the AHA major guidelines recommend the public to substitute unsaturated fatty acids from vegetable oils, fish, nuts and legumes for saturated and *trans* fatty acids. These guidelines, if followed, can have substantial potential in further reducing rates of CHD in the U.S. However, due to the campaign against total fat over the years, the belief that "fat is bad" has been strong and widespread. Thus, great educational efforts are needed to communicate nutritional messages about the health effects of different types of fat to the public and to translate current dietary recommendations into dietary practice as well.

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