

# Dietary fats and coronary heart disease

■ W. C. Willett

From the Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

**Abstract.** Willett WC (Harvard School of Public Health, Boston, MA, USA). Dietary fats and coronary heart disease (Review). *J Intern Med* 2012; **272**: 13–24.

The relation of dietary fat to risk of coronary heart disease (CHD) has been studied extensively using many approaches, including controlled feeding studies with surrogate end-points such as plasma lipids, limited randomized trials and large cohort studies. All lines of evidence indicate that specific dietary fatty acids play important roles in the cause and the prevention of CHD, but total fat as a percent of energy is unimportant. *Trans* fatty acids from partially hydrogenated vegetable oils have clear adverse effects and should be eliminated. Modest reductions in CHD rates by further decreases in saturated fat are possible if saturated fat is replaced by a combination of poly- and mono-

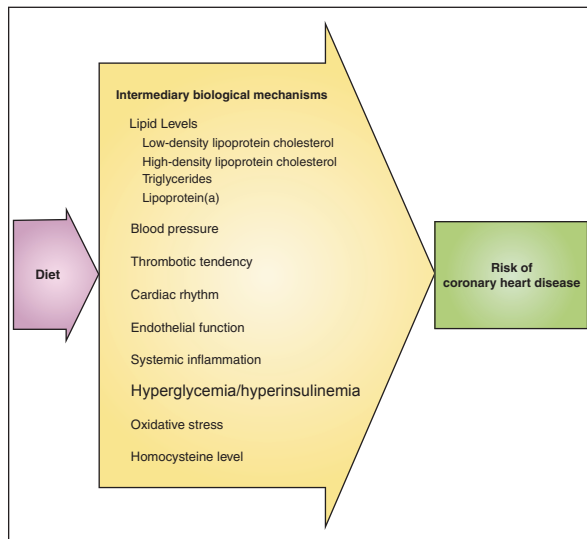
unsaturated fat, and the benefits of polyunsaturated fat appear strongest. However, little or no benefit is likely if saturated fat is replaced by carbohydrate, but this will in part depend on the form of carbohydrate. Because both N-6 and N-3 polyunsaturated fatty acids are essential and reduce risk of heart disease, the ratio of N-6 to N-3 is not useful and can be misleading. In practice, reducing red meat and dairy products in a food supply and increasing intakes of nuts, fish, soy products and nonhydrogenated vegetable oils will improve the mix of fatty acids and have a markedly beneficial effect on rates of CHD.

**Keywords:** coronary heart disease, trans fat, saturated fat, polyunsaturated fat, monounsaturated fat, blood cholesterol.

Early interest in the relation between dietary fats and cardiovascular disease emerged from animal studies conducted during the 1930s, showing that dietary cholesterol causes arterial lesions and that this is mediated largely through elevation in blood cholesterol levels [1–5]. Subsequent studies of heart disease rates in different populations, controlled feeding studies on the effects of dietary fats on serum cholesterol and epidemiologic studies relating serum cholesterol to risk of coronary heart disease (CHD) risk led to the conclusion that high intake of saturated fat is a major cause of heart disease. This concept has been widely incorporated in dietary recommendations and policies to reduce intake of saturated fats. In the 1970s, these recommendations emphasized replacement of saturated fat with polyunsaturated fat, but in the 1980s and 1990s, the emphasis shifted to replacement of all fats by carbohydrates. Recently, studies have cast doubt on the relation of saturated fat to risk of CHD and encouraged the promotion of low-carbohydrate diets that are often high in red meat and dairy products, and thus high in saturated fat. This review will examine the development of the classical diet-heart hypothesis, an expanded mechanistic perspective, and the implications of current evidence for dietary recommendations.

## The classical diet-heart hypothesis and beyond

According to the classic ‘diet-heart’ hypothesis, high intake of saturated fats and cholesterol and low intake of polyunsaturated fats increase the level of serum cholesterol, which leads to the development of atheromatous plaques. Accumulation of these plaques narrows the coronary arteries, reduces blood flow to the heart muscle and finally leads to myocardial infarction. However, the common clinical presentation of sudden, catastrophic chest pain is not adequately accounted for by a slowly progressive process that develops over decades, and in the last several decades, many additional mechanistic pathways potentially leading from diet to CHD have been identified (see Fig. 1). These include important mediating roles of thrombosis, hypertension, insulin resistance, inflammation, endothelial function and arrhythmia. Thus, we cannot assume that an effect of a dietary fat can be predicted by its effect on one pathway, such as blood total cholesterol level. For this reason, evidence directly relating a dietary factor to risk of CHD, which incorporates all competing and synergistic effects, is essential, and this review will focus on this evidence. Understanding the potential pathways by which an effect of diet is mediated can still be valuable; the vast literature on this topic will



**Fig. 1** Potential pathways mediating the effects of diet on risk of coronary heart disease (from the reference [93]).

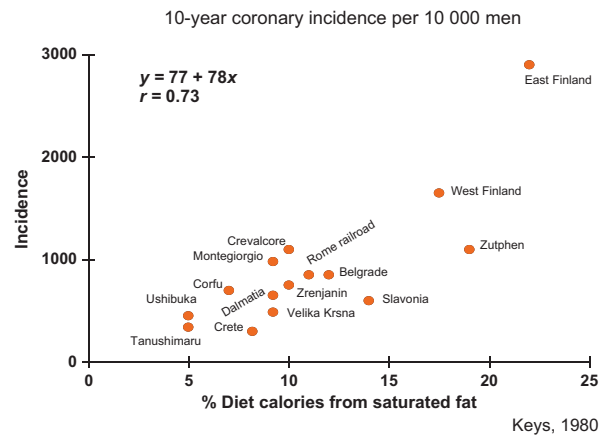
be mentioned only briefly but is discussed in detail elsewhere [6].

#### Descriptive studies of diet and CHD

Studies comparing rates of CHD across different geographical areas have documented that age-adjusted incidence and mortality rates vary by 10-fold or more. Coupled with studies showing that migrants from low- to high-risk areas adopt the rates of the new area [7, 8], this evidence indicated powerfully that the large differences in rates are not owing to genetic factors and are thus potentially modifiable. As shown in Fig. 2, intake of saturated fat as a percentage of calories was strongly correlated with coronary death rates ( $r = 0.84$ ) [9]. However, the countries with low saturated fat intake and low incidence of CHD were less industrialized and differed in many other ways from the wealthier countries, particularly in physical activity, obesity and, at that time, smoking habits.

#### Studies of blood cholesterol as an intermediary factor

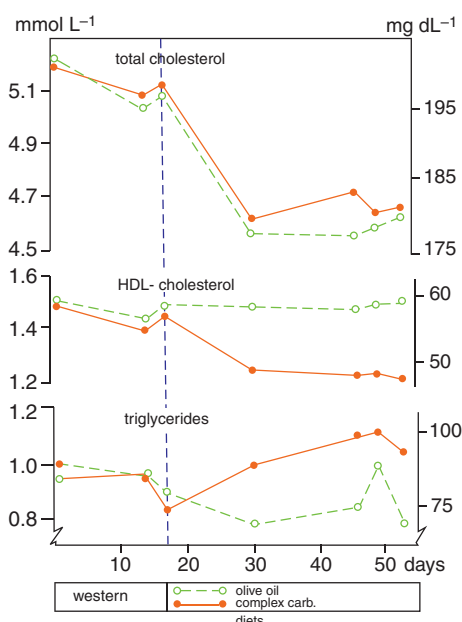
Studies of dietary fats and blood cholesterol level, and those relating cholesterol levels to risk of CHD, have played a central role in the classical diet-heart hypothesis. Studies of dietary factors and blood lipid levels have mainly been randomized controlled feeding trials in 10–50 humans, and hundreds of such studies have been conducted. Although details of the shape of the dose–response relationships have been



**Fig. 2** Ten-year coronary death rates of the cohorts plotted against the percentage of dietary calories supplied by saturated fatty acids (modified from the reference [9]).

debated by Keys and Hegsted [10, 11], compared isocalorically with carbohydrate, higher intakes of dietary cholesterol and saturated fats and lower intake of polyunsaturated fats clearly increase blood total cholesterol levels. Monounsaturated fat does not influence total serum cholesterol.

A frequent underlying assumption has been that serum cholesterol represents a surrogate end-point and that a dietary factor that changes serum cholesterol will also change risk of CHD in a similar manner. This logic, however, has been weakened by recognition that total serum cholesterol represents multiple sub-components, including the deleterious LDL and VLDL fractions, and the beneficial HDL component. Thus, the effect of a specific dietary change on total serum cholesterol might increase, decrease or not influence risk of CHD, depending on which cholesterol components were changed. More recent metabolic feeding studies have measured a variety of lipid fractions and have consistently observed the effects demonstrated in Fig. 3. As expected, substitution of carbohydrate for saturated fat reduces total cholesterol levels (and LDL cholesterol), but also reduces HDL cholesterol and increases fasting triglyceride levels. Substitution of monounsaturated fat (or polyunsaturated fat) for saturated fat similarly reduces LDL cholesterol but does not reduce HDL or increase triglycerides [12]. Thus, the ratio of total cholesterol to HDL cholesterol, which appears to summarize well the relation between serum lipids and CHD, is not appreciably influenced by saturated fat intake. However, when unsaturated fat replaces carbohydrate,



**Fig. 3** Mean serum total and HDL cholesterol and serum triglyceride concentrations throughout the experiment. All 48 subjects first received a Western-type diet high in saturated fat for 17 days. For the next 36 days, half of the subjects received an olive-oil-rich diet (symbol) and the other half a diet low in fat and high in complex carbohydrates and fibre (symbol) (from the reference [95]; reproduced with permission).

HDL increases and LDL changes little, suggesting benefit.

A monotonic relation between blood total cholesterol level and risk of CHD is firmly established by many studies in many countries. However, the ratio of LDL to HDL cholesterol (or total cholesterol to HDL cholesterol) provides a stronger prediction of risk because these fractions of cholesterol are related to risk in opposite directions. Ongoing work attempts to strengthen the prediction of CHD by further fractionating both the LDL and HDL components, but the value of this simple ratio remains [13].

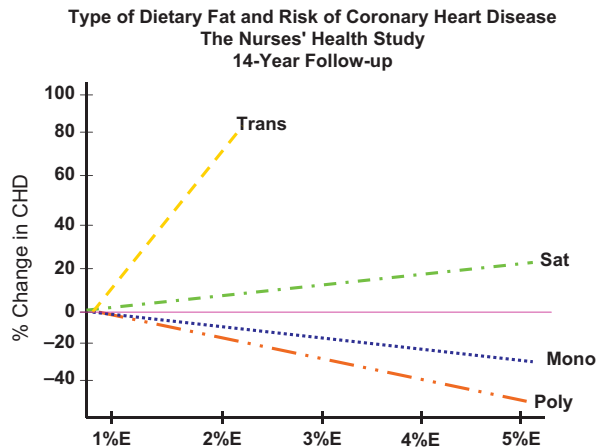
The causal relation between LDL cholesterol and risk of CHD was firmly established by randomized trial of LDL-lowering drugs that reduced CHD incidence [14–16]. Some have argued that the reductions in HDL resulting from a high carbohydrate diet do not have the same adverse effect as similar reductions caused by other factors. However, other factors that influence HDL levels including alcohol, estrogens, obesity, smoking, exercise and medications affect

CHD risk in the predicted direction [17, 18]. Nevertheless, uncertainties regarding the relevance of dietary effects on various lipid fractions should be resolved by evaluating the effects of diet on risk of myocardial infarction itself, either in carefully conducted cohort studies or in randomized trials.

#### Prospective cohort studies of diet and CHD

Biases related to the selection of control subjects and the recall of past diet in case-control studies are difficult to avoid or detect; thus, these studies are not discussed here. Because these biases are eliminated in prospective cohort studies, they should provide more consistent findings on diet and CHD. Many of the early studies, however, were not primarily designed as investigations into diet and heart disease and thus had numerous limitations. In these studies, the findings for specific dietary lipids were weak and inconsistent, and no relation between saturated fat intake and risk of CHD was seen in the most detailed investigation [19].

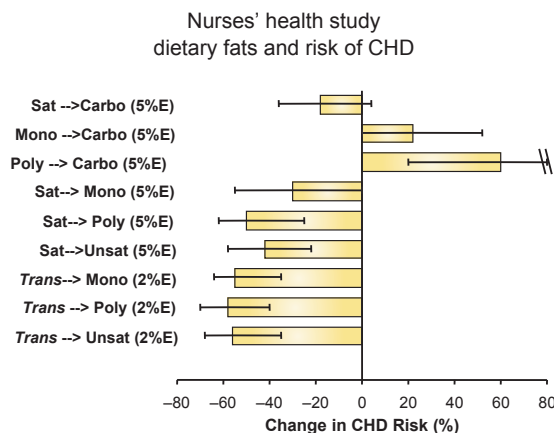
Although the early prospective studies did not provide consistent findings for any specific dietary lipid, they should not be interpreted as providing strong negative evidence. Serious limitations of most studies included small size, use of a single 24-h recall for dietary assessment, lack of updated dietary data during follow-up and no adjustment for total energy intake or other dietary factors. Many of these limitations have been addressed in more recent cohort studies of diet and CHD. For example, in the Nurses' Health Study, diet was assessed first in 1980 with a 61-item semi-quantitative food frequency questionnaire, and repeated assessments have collected since then at 4-year intervals using an expanded questionnaire. A detailed analysis was conducted amongst 80 082 women free of diagnosed CHD in 1980 [20], and during 14 years of follow-up, 939 incident cases of acute myocardial infarction or CHD death were documented. The percentage of energy from different fats, mutually adjusted for each other, was compared to the same percentage of energy from carbohydrate (see Fig. 4). By far, the strongest association was with intake of *trans* fatty acids; saturated fat was only weakly and nonsignificantly associated with risk of CHD, which is consistent with its lack of effect on the total cholesterol to HDL ratio. In contrast, monounsaturated fat was associated with a modestly lower risk of CHD, and polyunsaturated fat (specifically linoleic acid) was associated with a substantially lower risk. The stronger inverse relation of polyunsaturated fat than with monounsaturated fat may be due to



**Fig. 4** Multivariate relative risks of coronary heart disease with increasing intakes of specific types of fat, compared with the same energy intake from carbohydrate. Data are based on 14 years of follow-up in the Nurses' Health Study (from the reference [20]; used with permission).

beneficial effects on multiple pathways in addition to effects on blood lipids. The percentage of energy from total fat was not associated with risk of CHD. Comparing one type of fat with another isocalorically, the greatest reduction in risk would be expected from replacing *trans* or saturated fat with polyunsaturated fat (see Fig. 5).

Cohort studies of dietary fats and CHD have been summarized in a pooled analysis of original data [21].



**Fig. 5** Estimated changes in risk of CHD for isocaloric substitution one type of fat for another. Data are based on 14 years of follow-up of 80 082 women in the Nurse's Health Study (from the reference [20]).

As in the Nurses' Health Study, intake of saturated fat was not associated with higher risk of CHD when compared to the same percentage of energy from carbohydrates (for a 5% increase in saturated fat, RR = 0.97, 95% CI 0.81–1.16), but saturated fat was associated with higher risk if compared to polyunsaturated fat (for 5% of energy replacement, RR = 1.25, 95% CI 1.01–1.56). Total fat intake was not associated with risk of CHD. A limitation of this and most other pooled analyses is that it used only the baseline data because in most studies, only this information was available; as a result, the association with polyunsaturated fat intake is almost certainly a major underestimate of the true relationship. In a recent meta-analysis of cohort studies using only published data [22], saturated fat was also not associated with risk of CHD. In this analysis, the unstated comparison was with other calories in the diet because most studies did not specifically compare saturated fat with another source of energy; in most countries, these other calories would be predominately derived from refined grains and sugar.

#### Studies using biomarkers of fatty acid intake

One alternative to measuring dietary intake is to use biochemical analyses of fatty acids in plasma lipid fractions, platelet or red cell membranes, or subcutaneous adipose as biomarkers of fatty acid intake. These analyses can provide information about diet that may be difficult to obtain from questionnaires, such as the type of fat used in prepared foods and the degree to which it has been modified by processing. Although attractive in principle, fatty acid concentrations in blood or tissue need to be interpreted cautiously because saturated and monounsaturated fats can be synthesized endogenously; thus, these measurements may not reflect intake. Also, the levels of essential fatty acids in membranes or lipoproteins are often strongly regulated so their relation to diet may be weak and nonlinear. In case-control studies, the validity of plasma and platelet fatty acid measurements will usually be questionable because the levels may be affected by the acute infarction itself, or be influenced by changes in diet after the diagnosis of the disease.

The use of blood specimens collected before the occurrence of CHD, most frequently as a nested case-control analysis in which samples are stored and later only incident cases and selected controls are analysed, avoids the possible effects of disease or changes in diet after diagnosis on fatty acid levels. Surprisingly, few such studies have been conducted to



examine the relation of fatty acids in stored biological samples to risk of CHD. As described later in this chapter, whole blood omega-3 fatty acids in relation to risk of sudden cardiac death were studied amongst men participating in the Physicians' Health Study [23], and red cell *trans* fatty acids were examined in relation to risk of CHD in the Nurses' Health Study [24].

#### **Trials of dietary fat modification for prevention of CHD**

The most direct test of a diet-heart hypothesis is to conduct a randomized trial amongst healthy persons to determine whether changes in diet can reduce the risk of CHD. Two general strategies have been used to test the classical diet-heart hypothesis: replacement of saturated fat by polyunsaturated fat or replacement of saturated fat by carbohydrate. Most of the relevant trials were conducted several decades ago, but these remain important despite major limitations, including the small size of most.

Two early trials were conducted amongst institutionalized men, specifically residents of the Los Angeles Veterans Administration Hospital [25] and two Finnish mental hospitals [26]. In both studies, patients passively received modified diets; cholesterol intake was reduced largely by decreasing egg consumption, and polyunsaturated fats were increased to approximately 20% of calories by substitution for saturated fats in many foods. In the Veterans study, 846 men were randomized to either of the control or special diet and followed for up to 8 years. Seventy-one control men and 54 men on the special diets developed definite myocardial infarction or sudden death; this difference was not statistically significant. When cerebral infarction and other secondary end-points were included, however, the difference was significant ( $P = 0.02$ ). In the Finnish study, approximately 250 men in one hospital received the modified diet and a similar number in the other served as a control; after 6 years, the diets were reversed. CHD rates were reduced on the modified diet: 51% lower for CHD deaths alone ( $P = 0.10$ ) and 67% lower for CHD deaths or major electrocardiogram change ( $P = 0.001$ ). In a later US study of similar design, little evidence was seen for a reduction in CHD amongst the group with modified fat intake [27]; however, the mean follow-up of 1 year was likely too short to observe an effect.

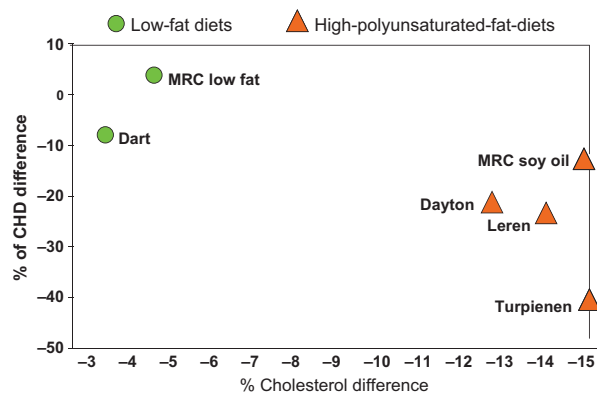
Because the sample size required for a randomized trial of CHD prevention in noninstitutionalized persons involving only change in dietary fats was estimated to be very large, two major trials were initiated

to evaluate the effect on CHD rates of dietary modification with simultaneous reduction in other risk factors including smoking. Such a study design can provide useful information, but may be difficult to interpret because the interventions are completely confounded, and any effect could be due to any combination of the interventions. In the Multiple Risk Factor Intervention Trial (MRFIT), over 12 000 US men at high risk of CHD were randomly assigned either to an intensive programme of dietary modification, smoking cessation and blood pressure control or to a control group involving an annual check-up [28]. The dietary intervention was relatively unsuccessful, in part because the control group also changed its diet (serum cholesterol was reduced by only 5–7% in both groups). No significant reduction in CHD mortality was found between the groups during the 10-year follow-up period. In the 16-year follow-up of the MRFIT cohort, long after intervention has stopped, a marginally significant reduction in deaths owing to acute MI, but not all CHD deaths, was seen [29], but no inference regarding diet is possible for reasons noted [29].

The Oslo Heart Study [30, 31] provided more convincing support for the diet-heart hypothesis. In this trial, 1232 normotensive men with high serum cholesterol levels, 80% of whom also smoked, were randomly assigned either to a programme of dietary intervention and smoking cessation or to a control group. Men who were already following a lipid-lowering diet, based on responses to a simple eight-item questionnaire, were excluded before randomization. Dietary intervention involved primarily a reduction in saturated fat and cholesterol; polyunsaturated fat intake increased only slightly. During the intervention period, serum cholesterol fell by 17% compared with the control group after 1 year, and after 5 years, it was 13% lower in the intervention group. The smoking intervention was less successful; only 25% of the smokers in the intervention group stopped compared with 17% in the control group. After 5 years, the incidence of nonfatal myocardial infarction and fatal CHD was 47% lower in the intervention group compared with controls ( $P = 0.03$ ). In a series of multivariate analyses to assess the relative effects of dietary intervention, most of the reduction in CHD incidence could be attributable to reduction in serum cholesterol. Although active intervention stopped in this population after 5 years, a similar reduction (approximately 45%) was observed after 102 months, and the difference in total mortality had become marginally significant (19 deaths in the intervention group compared with 31 in the control group).

The most recent and largest randomized trial of diet and heart disease was the Women's Health Initiative, in which over 48 000 women were randomized to a diet low in total fat or their usual diet [32]. The major types of fatty acids decreased proportionally, so the type of fat in the diet, as a percentage of total fat, was not appreciably changed. Although the main focus was reduction in breast cancer, CHD and total cardiovascular disease were also primary end-points. After a mean follow-up of 8.1 years, the intervention diet had no effect on risk of CHD (RR = 0.97; 95% CI 0.90–1.06) or total cardiovascular disease. However, this study is largely uninformative because the dietary intervention had no effect on plasma HDL cholesterol or triglycerides, which should have changed if there were truly differences in fat intake between groups [33].

In addition to primary prevention trials, several studies have examined the influence of dietary change amongst those with existing CHD [34–44]. These are described elsewhere [45] and discussed by Sacks and Katan [46, 47], who noted that the trials emphasizing overall fat reduction, or replacement of saturated fat by carbohydrate, had minimal effect on serum total cholesterol levels or CHD incidence. However, in trials focusing on the substitution of unsaturated for saturated fats, both serum cholesterol and CHD incidence were reduced (see Fig. 6). In a summary of the largest primary and secondary dietary prevention studies, Law *et al.* [48] estimated that for a 10% reduction in serum cholesterol ( $0.6 \text{ mmol L}^{-1}$ ), the risk of nonfatal myocardial infarction was reduced by 9% in the first 2 years of follow-up, 14% from years 2 to 5 and by 37% with more than 5 years of follow-up.



**Fig. 6.** Controlled trials of diet therapy and coronary heart disease (adapted from the reference [46]; reproduced with permission).

However, the results for 5 or more years of experience include a total of only 30 events and are based almost entirely on the Los Angeles Veterans Study that used a higher fat diet with 20% of energy from polyunsaturated fat.

Using a different dietary approach, in the Lyon Heart Study trial, patients with CHD were randomized to a typical low-fat diet or to a 'Mediterranean-type diet' that included high intake of alpha-linolenic acid (ALA), an N-3 fatty acid primarily from rapeseed oil, abundant consumption of fruits and vegetables and low intakes of red meat and dairy fat. Although the special diet had minimal effects on blood lipids and other risk factors, a large (70%) reduction in recurrence of CHD was seen amongst patients assigned to the 'Mediterranean-type diet' compared with those on the control diet [43]. As the special diet was multifaceted, attribution of the findings to a single dietary component is not possible. Several other dietary intervention studies, not reviewed here, have used changes in coronary occlusion assessed by angiography as the end-point. One such study has been used to promote an extremely low-fat diet, <10% of energy [49]. However, the intervention included a complete modification of lifestyle, including exercise, weight and stress reduction, and increased intake of vegetables and fruits; thus, attributing any benefit to a single aspect of this package is impossible.

#### Further aspects of dietary fats and CHD

**Saturated fatty acid chain length.** Not all saturated fats have similar effects on serum LDL cholesterol fractions or lipid fractions [50]. Butter and other dairy fats (high in 14 : 0, myristic acid) most strongly increase LDL, beef fat (containing palmitic acid, 16 : 0; stearic acid, 18 : 00) raised LDL to a lesser degree and cocoa butter (containing largely stearic acid) raises LDL only slightly [12, 51]. Medium-chain saturated fats, such as those found in coconut fat, appear to be more atherogenic in animals than predicted solely on the basis of their relationship with serum cholesterol [4], but they potently increase HDL cholesterol [52]. In one of the few attempts to investigate specific saturated fatty acids in prospective observational studies, Hu *et al.* [53] found that they were strongly correlated with each other and thus their effects were difficult to separate; however, stearic acid was most strongly associated with risk of CHD. At this time, clear conclusions cannot be made regarding the effects of different chain lengths of saturated fatty acids on risk of CHD in humans.

*N-6 polyunsaturated fatty acids.* As noted earlier, linoleic acid (the large majority of N-6 polyunsaturated fat) reduces total and LDL cholesterol, and this evidence formed the basis for policies that approximately doubled intake in the United States during the 1960s and 1970s, which corresponded to a large reduction in CHD mortality. More recently, a strong benefit has been supported by prospective cohort studies. Interestingly, the strength of the inverse association has been stronger than anticipated only on the basis of cholesterol lowering, suggesting that other pathways might be involved, such as reduction in insulin resistance and inflammation that is supported by considerable mechanistic evidence [54, 55]. Further, some evidence suggests that higher intake of N-6 polyunsaturated fat may reduce sudden death by raising the threshold for ventricular arrhythmias [56]. Based simply on the relationship with total serum cholesterol, one could conclude that maximizing the intake of polyunsaturated fat would be desirable, and some guidelines suggest that intake be increased to 10% of energy (compared with US averages of about 3% in the 1950s and 6 or 7% at present) with a P/S ratio of 1.0 [57]. Using platelet aggregability rather than serum cholesterol to evaluate the effect of diet, Renaud and colleagues [58] have suggested that a dietary P/S ratio of 0.6 to 0.8 may be superior to a ratio of 1.0. Within the Nurses' Health Study, intakes up to about 8% of energy could be studied and the dose-response relation appeared to be linearly inverse with no evidence of a plateau [59]. Much higher intakes are feasible; for example, in Taiwan, the average intake is about 12% of energy [60]. Also, as noted previously, the early intervention trials that showed marked reductions in cardiovascular disease used very high intakes of polyunsaturated fatty acids, primarily linoleic acid, up to about 20% of energy.

Others have suggested that high intakes of linoleic acid, even at current levels, are harmful and should be reduced [61]. This theoretical argument is based on the possibility that N-6 and N-3 polyunsaturated fatty acids in the diet compete with each other in elongation and desaturation pathways and that longer-chain N-6 polyunsaturated fatty acids are precursors to pro-inflammatory eicosanoids. This ignores that the elongation of linoleic acid to longer-chain fatty acids is highly regulated and that linoleic acid can influence CHD risk favourably through many other pathways. There is no actual evidence that linoleic acid is pro-inflammatory in the range of current diets, and the opposite may be true [54].

*N-3 fatty polyunsaturated fatty acids.* Low rates of CHD in Japan and Greenland led to speculation that the high consumption of fish in these areas might be protective [62, 63]. The initial hypothesized mechanism was that the high concentrations of N-3 fatty acids in fish reduce thrombus formation in coronary arteries by inhibiting platelet function. A benefit was supported by the finding that Dutch men consuming more than 30 g of fish per day had only about half the risk of fatal CHD compared with men who consumed none [64]. Lower rates of CHD mortality amongst persons who consumed higher amounts of fish were also observed in other early prospective studies [65–68], but not in large prospective studies of CHD incidence that included nonfatal end-points [69–71]. More recently, omega-3 fatty acids have been hypothesized to act primarily by increasing the threshold for ventricular fibrillation [72]; if so, there may be little relation with nonfatal CHD and the benefit may be only for fatal CHD and sudden cardiac death. In a meta-analysis of prospective studies and randomized trials, Mozaffarian [73] estimated that consuming 250 mg day<sup>-1</sup> of EPA + DHA (equivalent to approximately 1–2 servings per week of oily fish), compared to no intake, was associated with a 36% lower risk of CHD death, but little additional benefit was gained with higher intakes. Even stronger inverse associations were seen in nested case-control studies using fatty acid levels in blood; for example, in the Physicians' Health Study, the adjusted relative risk of sudden cardiac death for men in the highest versus lowest quintile was 0.19 (95% CI 0.05–0.71) [23].

In a recent, large randomized trial in the Netherlands [74], neither supplementation with long-chain fish oils nor ALA, the major plant N-3 fatty acid, reduced overall incidence of CHD. Nonsignificant effects were also seen for ventricular arrhythmias, but the number of events was modest and the confidence intervals included important reductions in risk (for fish oils RR = 0.90, 95% CI 0.65–1.26), and for ALA RR = 0.79, 95% CI 0.57–1.10). The observational data based on fatty acid analyses should show stronger associations than would be seen in randomized trials with fish oil supplements because in the observational data, levels representing intakes above the threshold for maximal benefit are compared to very low levels. In a randomized trial, the control group has the distribution of levels in a population; many persons may be above the threshold for benefit and not experience any benefit from supplementation. Because fish consumption differs greatly amongst various populations, this means that the results of supplementation trials are likely to vary; if the

population intake of fish is relatively high, the findings could be null but in a population with low fish intake, an important benefit might be seen. Notably, N-3 fatty acid intake from both fish and plant forms is high in the Netherlands, where the recent lack of benefit was seen [75].

Although benefits of long-chain omega-3 fatty acids in reducing cardiac death are well supported, and this has been translated into advice to consume at least two servings of fish per week [76], additional issues remain unresolved. Most important is whether ALA has similar benefits in reducing cardiovascular disease [77]. This is a major issue globally because fish consumption is very low in vast regions of the world [75], and the catch of wild fish cannot be increased further.

**Trans fatty acids.** *Trans* fatty acids are produced when liquid vegetable oils, which normally have all double-bonds in the *cis* position, are heated in the presence of metal catalysts to form vegetable shortening and margarine. This process, called partial hydrogenation, was developed around 1900 and production increased steadily until about the 1960s as processed vegetable fats displaced animal fats in many diets, first because of costs and then because of purported health benefits. This increase has occurred worldwide; for example, in parts of India, a partially hydrogenated fat containing approximately 60% of fat as *trans* isomers is widely used as a replacement for ghee (butter fat) [78]. Fat from cattle and other ruminants (for example, in red meat and butter) also has small amounts (typically 4 or 5%) of *trans* fatty acids due biohydrogenation in the rumen of these animals.

Concern that *trans* fatty acids might have adverse effects on CHD risk was greatly heightened by a controlled feeding study by Mensink and Katan [79] in which 10% of energy as *trans* fatty acids raised LDL cholesterol to a similar degree as did saturated fat and also reduced HDL when both were compared to monounsaturated fat. Thus, the increase in the ratio of total cholesterol to HDL cholesterol owing to *trans* isomers was about twice that seen with saturated fat. These findings have been reproduced consistently, and *trans* fatty acids have also been shown to reduce the particle size of LDL cholesterol, increase blood levels of Lp(a), increase inflammatory factors and adversely affect endothelial function [80].

Positive associations between intake of *trans* fatty acids and risk of CHD were observed in the Nurses'

Health Study cohort [81] and confirmed in other large prospective studies [80]. In a meta-analysis, the summary relative risk for an increment of 2% of energy from *trans* fat was 1.23 (95% CI 1.11–1.37;  $P < 0.001$ ). More recently, the relation between *trans* fatty acids in red cell membranes and risk of CHD was examined in the Nurses' Health Study using a nested case-control design [24]; the relative risk for the highest versus lowest quartile was 3.3 (1.5–7.2,  $P$  for trend  $< 0.01$ ).

The combination of many metabolic studies demonstrating adverse effects of *trans* fatty acids on blood lipid fractions and prospective epidemiologic studies has provided strong support for an adverse effect on CHD risk. Thus, actions to reduce intake have included banning the use of partially hydrogenated fats in Denmark, Brazil and Chile and in many cities in the United States. Although much progress has been made in reducing the intake of some countries, intake remains high in other parts of the world. Also, even if the average intake has been greatly reduced in a country, a modest percent of the population may still consume large amounts of *trans* fats.

The number of different *trans* isomers in partially hydrogenated vegetable oils is very large because the *trans* double-bonds can vary in number (usually 0, 1 or 2) and position in the carbon chain, and the number of carbons atoms can differ. In two studies using analyses of red cells or adipose tissue [24, 82], 18 : 2 *trans* isomers were substantially more strongly associated with risk of CHD than were 18 : 1 *trans* isomers. This can have practical implications because if the degree of partial hydrogenation is reduced but not eliminated, the amounts of 18 : 2 *trans* isomers can be increased. This light degree of hydrogenation has often been used when the goal was to destroy ALA (which is susceptible to oxidation, thus producing rancidity and shortened shelf life) rather than to create a hard fat. Although our understanding of the effects of different *trans* isomers is incomplete, the goal should be to eliminate partial hydrogenation, not just reduce it.

*Trans* isomers from ruminant fats will usually not exceed one percent of fatty acids, even with high intakes of red meat and butter fat, but this has become of greater interest as other sources of *trans* fatty acids have been reduced. The relation between the intake of *trans* fatty acids from ruminants and the risk of CHD has been examined in four prospective studies; none identified a significant positive association and in three a nonsignificant inverse trend was observed [81, 83–85].



Although major progress has been made in understanding the consequences of partial hydrogenation of vegetable oils, not all issues regarding cooking fats are resolved. The sustained heating of fats, as used in the deep frying processes of the fast food industry, can lead to the oxidation of polyunsaturated fatty acids [86], but intake is usually low because oxidation creates undesirable flavours. Virtually, no epidemiologic data exist on the consequences of oxidized cooking fats.

*Fatty acids, dietary fats and dietary patterns.* Most studies have focused on specific fatty acids rather than on dietary fats, even though fats are what we select and eat, and these contain a combination of different fatty acids in the triglyceride molecule. Further, plant oils contain many other components besides fatty acids, usually a variety of antioxidants such as vitamin E and polyphenols, which protect the embryonic plant in the seeds from which the oils are extracted. Also, fatty acids from animal sources are not consumed in isolation; other components include cholesterol and other sterols. Many of these fats are consumed as part of foods with many other constituents such as in cheese and red meat, which contains proteins, abundant heme iron and many other nutrient and non-nutrient components [87].

Amongst the few studies to specifically compare types of dietary fats in relation to risk of CHD was a large Costa Rican case-control study of CHD designed to compare soybean oil with palm oil, which was hypothesized to be less adverse than predicted owing to its high content of tocotrienols [88]. In this comparison, consumption of soybean oil was associated with the lowest risk, consistent with its fatty acid composition that includes both N-6 and N-3 polyunsaturated fatty acids. In an example explicitly comparing food sources, red meat, a major source of saturated fat, was associated with higher risk of CHD when compared with other major protein sources [89]. Whether the substantial differences were due only to the differences in fatty acid composition is not clear, but components of these foods may contribute. Such comparisons can provide more direct evidence for dietary guidance than data based solely on fatty acid intakes.

#### *Dietary fatty acids and other diseases*

Decisions about diet should be made considering all important outcomes. Although dietary total fat and saturated fat have been hypothesized to increase risks of many cancers, no clear relationships have been documented despite intense investigation.

Some evidence suggests that risks of prostate cancer [90] and macular degeneration [91] might be increased by high intakes of ALA, the main plant N-3 fatty acid, but these relationships need further investigation. In the most detailed dietary study of type 2 diabetes, the ratio of polyunsaturated to saturated fat was associated with reduced risk and *trans* fat intake was associated with elevated risk [92]. Thus, at present, the relation between fatty acids and risk of CHD can serve as the basis for dietary guidance about types of fat.

#### *Additional diet-heart hypotheses*

Although substantial evidence supports a major role of dietary fatty acids and fats in the aetiology of CHD, many other aspects of diet are also likely to influence risk of this disease, possibly mediated by changes in lipid fractions, platelet aggregability, fibrinogen levels, arrhythmia, blood pressure, glucose levels, insulin resistance, endothelial damage, obesity and other mechanisms that have yet to be discovered. These are discussed elsewhere [93, 94] and include alcoholic beverages, sugar-sweetened beverages, glycaemic load, dietary fibre, fruit and vegetables, and sodium intake.

#### **Summary**

Excess body fat, the result of the imbalance between energy intake and expenditure, is a powerful risk factor for CHD but in many randomized trials has not been related to the percentage of energy from dietary fat. Abundant evidence from controlled feeding studies of blood lipids, prospective observational studies and limited randomized trials have shown that specific dietary fatty acids play important roles in the cause and prevention of CHD. *Trans* fatty acids from partially hydrogenated vegetable oils have clear adverse effects and should be eliminated. Modest reductions in CHD rates by further decreases in saturated fat are possible if saturated fat is replaced by a combination of poly- and mono-unsaturated fat, and the benefits of polyunsaturated fat appear strongest. However, little or no benefit is likely if saturated fat is replaced by carbohydrate, but this will in part depend on the form of carbohydrate. Because both N-6 and N-3 polyunsaturated fatty acids are essential and reduce risk of heart disease, the ratio of N-6 to N-3 is not useful and can be misleading. The optimal amounts of both need to be better defined.

Also, much evidence indicates that replacement of red meat with alternative protein sources including fish and nuts will reduce risk of CHD. Additional

reduction in risk will be achieved by a diet generous in fruits, vegetables and whole grains and low in refined starches, sugar-sweetened beverages, potatoes and salt.

#### Conflict of interest

No conflict of interest to declare.

#### References

- Gordon T. The diet-heart idea. Outline of a history. *Am J Epidemiol* 1988; **127**: 220–5.
- Anitschkow N. A history of experimentation on arterio atherosclerosis in animals. In: Blumenthal HT, ed. *Cowdry's Arteriosclerosis*, 2nd edn. Springfield, IL, USA: Macmillan, 1967; 21–44.
- Katz LN, Stamler JS. *Experimental Atherosclerosis*. Springfield: Charles C. Thomas Publishing, 1953.
- Wissler RW, Vesselinovitch D. The effects of feeding various dietary fats on the development and regression of hypercholesterolemia and atherosclerosis. *Adv Exp Med Biol* 1975; **60**: 65–76.
- Grundey SM, Bilheimer D, Blackburn H *et al*. Rationale of the diet-heart statement of the American Heart Association. Report of Nutrition Committee. *Circulation* 1982; **65**: 839A–54A.
- Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). *A Report of the Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes*. <http://www.nap.edu/catalog/10490.html>. Washington, DC, USA: National Academy of Sciences, 2002.
- Kato H, Tillotson J, Nichaman MZ, Rhoads GG, Hamilton HB. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. *Am J Epidemiol* 1973; **97**: 372–85.
- Robertson TL, Kato H, Rhoads GG *et al*. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol* 1977; **39**: 239–43.
- Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA: Harvard University Press, 1980.
- Keys A. Serum-cholesterol response to dietary cholesterol. *Am J Clin Nutr* 1984; **40**: 351–9.
- Hegsted DM. Serum-cholesterol response to dietary cholesterol: a re-evaluation. *Am J Clin Nutr* 1986; **44**: 299–305.
- Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. *Arterioscler Thromb* 1992; **12**: 911–9.
- Sacks FM. Lipid and lipoprotein metabolism, and risk for cardiovascular disease. In: Eckel RH, ed. *Metabolic Risk for Cardiovascular Disease: The AHA Clinical Series*. West Sussex, UK: Wiley-Blackwell, 2011; 18–40.
- Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; **251**: 351–64.
- Shepherd J, Cobbe SM, Ford I *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia – West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**: 1301–7.
- Sacks FM, Pfeffer MA, Moye LA *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels – cholesterol and recurrent events trial investigators. *N Engl J Med* 1996; **335**: 1001–9.
- Sacks FM, Willett WC. More on chewing the fat – the good fat and the good cholesterol. *N Engl J Med* 1991; **325**: 1740–2.
- Katan MB, Grundey SM, Willett WC. Should a low-fat, high-carbohydrate diet be recommended for everyone? Beyond low-fat diets. *N Engl J Med* 1997; **337**: 563–7.
- Shekelle RB, Shryock AM, Paul O *et al*. Diet, serum cholesterol, and death from coronary heart disease: the Western Electric Study. *N Engl J Med* 1981; **304**: 65–70.
- Hu F, Stampfer MJ, Manson JE *et al*. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 1997; **337**: 1491–9.
- Jakobsen MU, O'Reilly EJ, Heitmann BL *et al*. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009; **89**: 1425–32.
- Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010; **91**: 535–46.
- Albert CM, Campos H, Stampfer MJ *et al*. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; **346**: 1113–8.
- Sun Q, Ma J, Campos H *et al*. A prospective study of trans fatty acids in erythrocytes and risk of coronary heart disease. *Circulation* 2007; **115**: 1858–65.
- 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): 1–63.
- Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paaivilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol* 1979; **8**: 99–118.
- Frantz IDJ, Dawson EA, Ashman PL *et al*. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. *Arteriosclerosis* 1989; **9**: 129–35.
- Multiple Risk Factor Intervention Trial Research Group. Multiple risk factor intervention trial: risk factor changes and mortality results. *JAMA* 1982; **248**: 1465–77.
- Multiple RFIITRG. Mortality after 16 years for participants randomized to the multiple risk factor intervention trial. *Circulation* 1996; **94**: 946–51.
- Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of a randomised trial in healthy men. *Lancet* 1981; **2**: 1303–10.
- Hjermann I, Holme I, Leren P. Oslo study diet and antismoking trial; results after 102 months. *Am J Med* 1986; **80**: 7–11.
- Howard BV, Van Horn L, Hsia J *et al*. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006; **295**: 655–66.
- Willett WC. The WHI joins MRFIT: a revealing look beneath the covers. *Am J Clin Nutr* 2010; **91**: 829–30.
- Morrison LM. Diet in coronary atherosclerosis. *JAMA* 1960; **173**: 884–8.

- 35 Koranyi A. Prophylaxis and treatment of the coronary syndrome. *Ther Hung* 1963; **12**: 17–20.
- 36 Rose GA, Thomson WB, Williams RT. Corn oil in treatment of ischaemic heart disease. *Br Med J* 1965; **1**: 1531–3.
- 37 Morris JN, Ball KP, Antonis A *et al*. Controlled trial of soya-bean oil in myocardial infarction. *Lancet* 1968; **2**: 693–9.
- 38 Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation* 1970; **42**: 935–42.
- 39 Woodhill JM, Palmer AJ, Leelarthaeapin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol* 1978; **109**: 317–30.
- 40 Burr ML, Fehily AM, Gilbert JF *et al*. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989; **2**: 757–61.
- 41 Watts GF, Lewis B, Brunt JNH *et al*. Effects of coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas' Atherosclerosis Regression Study (STARS). *Lancet* 1992; **339**: 563–9.
- 42 Singh RB, Rastogi SS, Verman R *et al*. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up. *Br Med J* 1992; **304**: 1015–9.
- 43 de Lorgeril M, Renaud S, Mamelle N *et al*. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease [Erratum in: *Lancet* 1995; 345: 738]. *Lancet* 1994; **343**: 1454–9.
- 44 Ball KP, Hanington E, McAllen PM *et al*. Low-fat diet in myocardial infarction – a controlled trial. *Lancet* 1965; **2**: 501–4.
- 45 Willett WC, Lenart EB. Dietary factors. In: Manson JE, Ridker PM, Gaziano JM, Hennekens CH, eds. *Prevention of Myocardial Infarction*. New York, NY, USA: Oxford University Press, 1996; 351–83.
- 46 Sacks F. Dietary fats and coronary heart disease. Overview. *J Cardiovasc Risk* 1994; **1**: 3–8.
- 47 Sacks FM, Katan MB. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am J Med* 2002; **113**(Suppl 9B): 13S–24S.
- 48 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *Br Med J* 1994; **308**: 367–72.
- 49 Ornish D. *Dr. Dean Ornish's Program for Reversing Heart Disease*. New York: Balantine Books, 1990.
- 50 Hunter JE, Zhang J, Kris-Etherton PM. Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review. *Am J Clin Nutr* 2010; **91**: 46–63.
- 51 Denke MA, Grundy SM. Effects of fats high in stearic acid on lipid and lipoprotein concentrations in men. *Am J Clin Nutr* 1991; **54**: 1036–40.
- 52 Katan MB, Zock PL, Mensink RP. Effects of fats and fatty acids on blood lipids in humans: an overview. *Am J Clin Nutr* 1994; **60**(Suppl 6): 1017S–22S.
- 53 Hu FB, Stampfer MJ, Manson JE *et al*. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr* 1999; **70**: 1001–8.
- 54 Willett WC. The role of dietary n-6 fatty acids in the prevention of cardiovascular disease. *J Cardiovasc Med (Hagerstown)* 2007; **8**(Suppl 1): S42–5.
- 55 Riserus U, Willett WC, Hu FB. Dietary fats and prevention of type 2 diabetes. *Prog Lipid Res* 2009; **48**: 44–51.
- 56 Charnock JS, McLennan PL, Abeywardena MY. Dietary modulation of lipid metabolism and mechanical performance of the heart. *Mol Cell Biochem* 1992; **116**: 19–25.
- 57 Anonymous. Consensus Conference. Lowering blood cholesterol to prevent heart disease. *JAMA* 1985; **253**: 2080–6.
- 58 Renaud S, Godsey F, Dumont E, Thevenon C, Ortchanian E, Martin JL. Influence of long-term diet modification on platelet function and composition in Moselle farmers. *Am J Clin Nutr* 1986; **43**: 136–50.
- 59 Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol* 2005; **161**: 672–9.
- 60 Lyu LC, Yeh CY, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ. Association of sex, adiposity, and diet with HDL subclasses in middle-aged Chinese. *Am J Clin Nutr* 2001; **74**: 64–71.
- 61 Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med (Maywood)* 2008; **233**: 674–88.
- 62 Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in North Western Greenland. *Am J Clin Nutr* 1980; **33**: 2657–61.
- 63 Kagawa Y, Nishizawa M, Suzuki M *et al*. Eicosapolyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. *J Nutr Sci Vitaminol* 1982; **28**: 441–53.
- 64 Kromhout D, Bosscheiter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985; **312**: 1205–9.
- 65 Shekelle RB, Missell L, Paul O, Shryock AM, Stamler J. Fish consumption and mortality from coronary heart disease (letter). *N Engl J Med* 1985; **313**: 820–4.
- 66 Norell SE, Ahlbom A, Feychting M, Pedersen NL. Fish consumption and mortality from coronary heart disease. *Br Med J* 1986; **293**: 426.
- 67 Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. *Proc Soc Exp Biol Med* 1992; **200**: 177–82.
- 68 Kromhout D, Feskens EJM, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol* 1995; **24**: 340–5.
- 69 Curb JD, Reed DM. Fish consumption and mortality from coronary heart disease (letter). *N Engl J Med* 1985; **313**: 820–4.
- 70 Ascherio A, Rimm EB, Stampfer MJ, Giovannucci E, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake and the risk of coronary disease among men. *N Engl J Med* 1995; **332**: 977–82.
- 71 Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH. Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study. *Am J Epidemiol* 1995; **142**: 166–75.
- 72 Leaf A. Omega-3 fatty acids and prevention of ventricular fibrillation. *Prostaglandins Leukot Essent Fatty Acids* 1995; **52**: 197–8.
- 73 Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. *Am J Clin Nutr* 2008; **87**: 1991S–6S.
- 74 Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010; **363**: 2015–26.
- 75 Petrova S, Dimitrov P, Willett WC, Campos H. The global availability of n-3 fatty acids. *Public Health Nutr* 2011; **14**: 1–8.

- 76 U.S. Department of Agriculture. *Dietary Guidelines for Americans*. Washington, DC, USA: U.S. Gov't Printing Offices, 2010.
- 77 Campos H, Baylin A, Willett WC. Alpha-linolenic acid and risk of nonfatal acute myocardial infarction. *Circulation* 2008; **118**: 339–45.
- 78 Achaya KT. Fat status of Indians – a review. *J Sci Ind Res* 1987; **46**: 112–26.
- 79 Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary cis and trans fatty acids on serum lipoprotein [a] levels in humans. *J Lipid Res* 1992; **33**: 1493–501.
- 80 Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med* 2006; **354**: 1601–13.
- 81 Willett WC, Stampfer MJ, Manson JE *et al*. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* 1993; **341**: 581–5.
- 82 Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H. High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in costarican adults. *J Nutr* 2003; **133**: 1186–91.
- 83 Pietinen P, Ascherio A, Korhonen P *et al*. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the ATBC Study. *Am J Epidemiol* 1997; **145**: 876–87.
- 84 Oomen C, Ocke M, Feskens E, van Erp-Baart M, Kok F, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet* 2001; **357**: 746–51.
- 85 Jakobsen MU, Overvad K, Dyerberg J, Heitmann BL. Intake of ruminant trans fatty acids and risk of coronary heart disease. *Int J Epidemiol* 2008; **37**: 173–82.
- 86 Kranner J. Dietary advanced lipid oxidation endproducts are risk factors to human health. *Mol Nutr Food Res* 2007; **51**: 1094–101.
- 87 Astrup A, Dyerberg J, Elwood P *et al*. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr* 2011; **93**: 684–8.
- 88 Kabagambe EK, Baylin A, Ascherio A, Campos H. The type of oil used for cooking is associated with the risk of nonfatal acute myocardial infarction in costa rica. *J Nutr* 2005; **135**: 2674–9.
- 89 Bernstein AM, Sun Q, Hu FB, Stampfer MJ, Manson JE, Willett WC. Major dietary protein sources and risk of coronary heart disease in women. *Circulation* 2010; **122**: 876–83.
- 90 Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer* 2007; **121**: 1571–8.
- 91 Cho E, Hung S, Willett WC *et al*. Prospective study of dietary fat and the risk of age-related macular degeneration. *Am J Clin Nutr* 2001; **73**: 209–18.
- 92 Hu FB, Manson JE, Stampfer MJ *et al*. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; **345**: 790–7.
- 93 Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002; **288**: 2569–78.
- 94 Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009; **169**: 659–69.
- 95 Mensink RP, Katan MB. Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoprotein in healthy men and women. *Lancet* 1987; **1**: 122–5.

*Correspondence:* Walter C. Willett MD, DrPH, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA.  
(fax: (617) 432 0464; e-mail: walter.willett@channing.harvard.edu) ■