Optimal Diets for Prevention of Coronary Heart Disease

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Context Coronary heart disease (CHD) remains the leading cause of mortality in industrialized countries and is rapidly becoming a primary cause of death worldwide. Thus, identification of the dietary changes that most effectively prevent CHD is critical.

Objective To review metabolic, epidemiologic, and clinical trial evidence regarding diet and CHD prevention.

Data Sources and Study Selection We searched MEDLINE through May 2002 for epidemiologic and clinical investigations of major dietary factors (fat, cholesterol, omega-3 fatty acids, *trans*-fatty acids, carbohydrates, glycemic index, fiber, folate, specific foods, and dietary patterns) and CHD. We selected 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials of diet and CHD.

Data Extraction Data were examined for relevance and quality and extracted by 1 of the authors.

Data Synthesis Compelling evidence from metabolic studies, prospective cohort studies, and clinical trials in the past several decades indicates that at least 3 dietary strategies are effective in preventing CHD: substitute nonhydrogenated unsaturated fats for saturated and *trans*-fats; increase consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources; and consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grain products. However, simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence. Many issues remain unsettled, including the optimal amounts of monounsaturated and polyunsaturated fats, the optimal balance between omega-3 and omega-6 polyunsaturated fats, the amount and sources of protein, and the effects of individual phytochemicals, antioxidant vitamins, and minerals.

Conclusions Substantial evidence indicates that diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight, may prevent the majority of cardiovascular disease in Western populations.

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THE RELATIONSHIP BETWEEN DIET and coronary heart disease (CHD) has been studied intensively for nearly a century. In 1908, Ignatowski produced atherosclerosis in rabbits with a diet high in cholesterol and saturated fat[1]; feeding the rabbits cholesterol alone produced identical lesions. In the early 1950s, controlled feeding studies demonstrated that saturated fatty acids and, to a lesser extent, cholesterol increased serum cholesterol concentration in humans.[2] Meanwhile, epidemiologic studies found that increased serum cholesterol predicted risk of CHD in human populations. These discoveries led to the classic diet-heart hypothesis, which postulated a primary role of dietary saturated fat and cholesterol in the cause of atherosclerosis and CHD in humans.[3] The diet-heart hypothesis gained further support from ecological correlations relating saturated fat intake to rates of CHD in cohorts from different countries[4] and from studies of migrants from low- to high-risk countries.[5]

Until recently, most epidemiologic and clinical investigations of diet and CHD have been dominated by the diet-heart hypothesis. However, the original hypothesis was overly simplistic because the effects of diet on CHD can be mediated through multiple biological pathways other than serum total cholesterol or low-density lipoprotein cholesterol (LDL-C) (FIGURE 1).[6] The existence of these multiple pathways heightens the need to study clinical outcomes because the use of a single intermediate end point as a surrogate of CHD risk could be misleading. In the past 2 decades, understanding of the nutrients and foods likely to promote cardiac health has grown substantially owing to studies of the molecular mechanisms of atherosclerosis and the metabolic effects of various nutrients and foods, large and carefully conducted prospective cohort investigations, and dietary intervention trials. Although the search for the optimal diet for prevention of CHD is far from over, more specific and firmer evidence on diet and CHD is now available.

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Figure 1. Mechanisms by Which Diet Potentially Influences Risk of Coronary Heart Disease

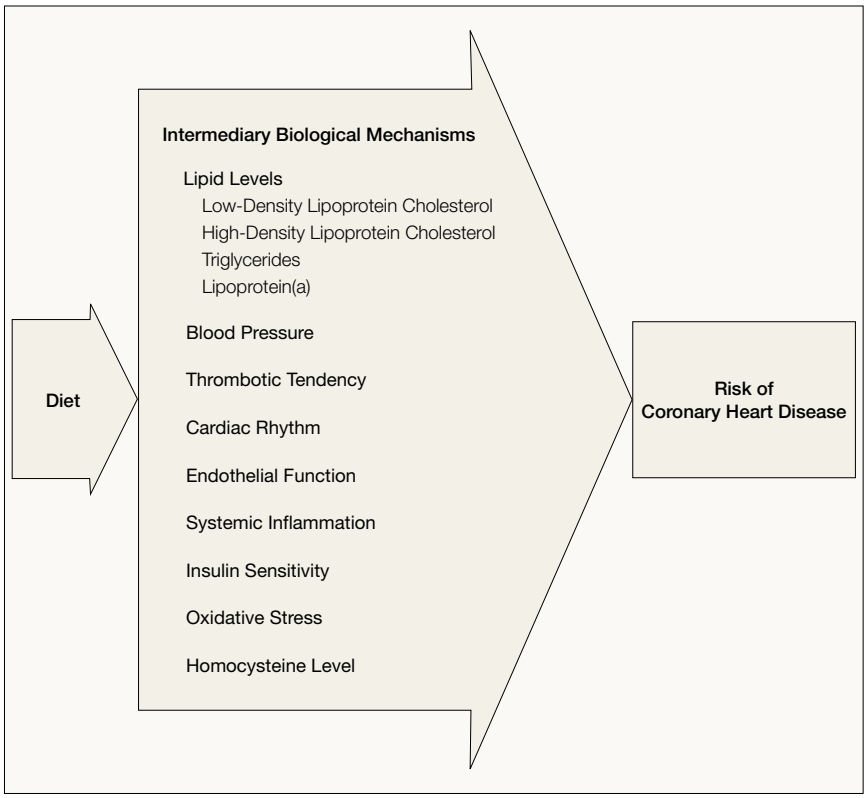
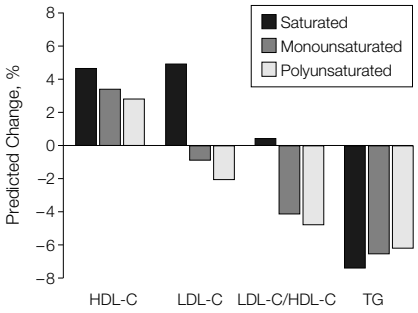


Figure 2. Predicted Changes in Serum Lipids and Lipoproteins



Predicted changes are based on replacement of 5% of energy as carbohydrates with specific fatty acids under isocaloric conditions, assuming baseline high-density lipoprotein cholesterol (HDL-C) levels of 50 mg/dL (1.30 mmol/L), low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL (3.37 mmol/L), and triglyceride (TG) levels of 150 mg/dL (1.70 mmol/L).[10]

METHODS

For this review, we searched MEDLINE through May 2002 for epidemiologic and clinical investigations of various dietary factors (fat, cholesterol, omega-3 fatty acids, *trans*-fatty acids, carbohydrates, glycemic index, fiber, folate, specific foods, and dietary patterns) and CHD. We selected 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials relating to diet and CHD. Data were examined for relevance and quality and extracted by 1 of the authors. Although we emphasized controlled trials with clinical end points, few such trials exist. Thus, we gave substantial weight to large prospective cohort studies that reported disease outcomes and metabolic studies with established intermediate end points. The evidence is considered strongest when results from different types of studies are consistent.

DIETARY FAT

Metabolic Effects of Dietary Fatty Acids

Numerous controlled feeding studies of the effects of different dietary fatty acids on serum cholesterol levels have been summarized in several meta-analyses from which predictive equations have been developed.[7-11] All such analyses confirm early reports by Keys[7] and Hegsted[8] that saturated fatty acids increase and polyunsaturated fatty acids decrease total and LDL cholesterol. All 3 classes of fatty acids (saturated, monounsaturated, and polyunsaturated) elevate high-density lipoprotein cholesterol (HDL-C) when they replace carbohydrates in the diet, and this effect is slightly greater with saturated fatty acids (FIGURE 2). Also, triglyceride levels increase when dietary fatty acids are replaced by carbohydrates. Because replacement of saturated fat with carbohydrates proportionally reduces both LDL-C and HDL-C, and, thus, has little effect on the LDL-HDL ratio and increases triglycerides, this change in diet would be expected to have minimal benefit on CHD risk. However, when monounsaturated or polyunsaturated fats replace saturated fat, LDL-C decreases and HDL-C changes only slightly. Moreover, substituting polyunsaturated fat for saturated fat may have beneficial effects on insulin sensitivity[12,13] and type 2 diabetes.[14,15]

In numerous controlled metabolic studies, *trans*-fatty acids (found in stick margarine, vegetable shortenings, and commercial bakery and deep-fried foods) have been shown to raise LDL-C levels and lower HDL-C relative to *cis*-unsaturated fatty acids,[16-24] and the increase in the ratio of total to HDL cholesterol for *trans*-fat is approximately twice that for saturated fat (FIGURE 3).[25] *Trans*-fat increases plasma levels of lipoprotein a[18,23] and triglycerides[26] and may reduce endothelial function by impairing flow-mediated dilation.[27] In addition, *trans*-fatty acids adversely affect essential fatty acid metabolism and prostaglandin balance by inhibiting the enzyme delta-6 desaturase.[28,29] Finally, high intake of *trans*-fat may promote insulin resistance[30] and increase risk of type 2 diabetes.[15]

Epidemiologic Studies

Geographic and migration studies showed strong positive correlations be-

tween saturated fat intake and rates of CHD.[4,5,31] Although these data provide evidence for the importance of environmental factors in the cause of CHD, they are seriously confounded by other aspects of diet, other lifestyle factors, and economic development. Prospective cohort studies of individuals can better control for potential confounding factors. Despite long-standing interest in the diet-heart hypothesis, prospective studies of diet and CHD are surprisingly few[32-40]; only 2 found a significant positive association between saturated fat intake and risk of CHD.[35,36] However, most earlier studies were limited by small study size, inadequate dietary assessment, or incomplete adjustment for confounding.[41]

The largest and most detailed analysis included 4 repeated measures of diet over 14 years among 80 082 women in the Nurses' Health Study cohort.[40] Higher intakes of *trans*-fat and, to a smaller extent, saturated fat were associated with increased risk, whereas higher intakes of nonhydrogenated polyunsaturated and monounsaturated fats were associated with decreased risk. Because of opposing effects of different types of fat, total fat as percentage of energy was not appreciably associated with CHD risk. Dietary cholesterol and modest egg consumption (1 egg per day) were not significantly associated with either CHD or stroke.[42]

In addition to the Nurses' Health Study, 3 other large prospective studies have consistently found elevated risk of CHD with higher *trans*-fat intake.[38,39,43] Combining the results of the 4 prospective studies, the pooled relative risk of CHD associated with a difference of 2% energy in *trans*-fatty acid intake (assessed at baseline) was 1.25 (95% confidence interval, 1.11-1.40).[43] Results from case-control studies using biochemical markers of *trans*-fat intake have been less consistent.[25] In a recent population-based case-control study of 179 cardiac arrest patients and 285 community controls, higher red-cell membrane levels of *trans*-fatty acids, especially *trans*-isomers frompartially hydrogenated vegetable oils, were associated with significantly increased risk of primary cardiac arrest.[44] No association was seen in a small UK study of sudden death.[45]

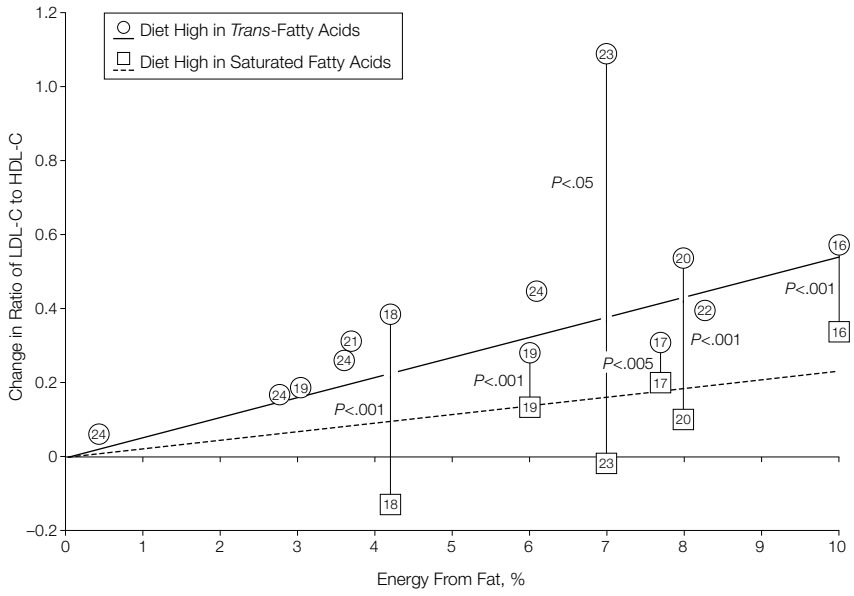
Trials of Change in Dietary Fat

Only a handful of dietary trials with CHD end points have been conducted and most were among patients with CHD (TABLE). Two dietary approaches were tested in earlier trials; one replaced saturated fat with polyunsaturated fat, leaving total fat unchanged; the other lowered total fat. In all the high-polyunsaturated-fat trials,[46-51] serum cholesterol was significantly reduced. In the Finnish Mental Hospital Study,[47] soft margarine replaced stick margarine, so the reduction in CHD was probably in part due to reduction in *trans*-fat intake. In the Minnesota Coronary Survey,[51] cardiovascular events were not significantly reduced by a high-polyunsaturated-fat diet despite a decrease in serum cholesterol, but the mean duration of dietary intervention was only about 1 year. Two secondary prevention trials testing the approach of total fat reduction did not find a significant reduction in serum cholesterol or CHD events.[52,53]

Omega-3 Fatty Acids

Omega-3 fatty acids may reduce risk of CHD by preventing cardiac arrhythmia, lowering serum triglyceride levels, decreasing thrombotic tendency, and improving endothelial dysfunction.[54,55] An inverse association between fish intake and coronary mortality was first reported in a Dutch population,[56] and more than 15 prospective studies have followed. A systematic review of the 11 studies published before 2000 concluded that the inverse association was stronger for fatal CHD than for nonfatal myocardial infarction (MI), and the benefit was most evident in populations with higher-than-average risk of CHD.[57] Since that review, 4 additional prospective cohort studies[58-61] and 1 case-control study[62] have provided further support for the protective effects of marine omega-3 fatty

Figure 3. Results of Metabolic Studies of the Effects of a Diet High in *Trans* or Saturated Fatty Acids on the Ratio of LDL-C to HDL-C



LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. A diet with isocaloric amounts of *cis*-fatty acids was used as the comparison group. References are indicated by numbers inside data markers. The solid line indicates the best-fit regression for *trans*-fatty acids. The dashed line indicates the best-fit regression for saturated fatty acids. Reprinted with permission.[25]

acids against CHD in diverse populations. Notably, 2 recent studies have shown that consuming 2 or more servings of fish per week was associated with 30% lower risk of CHD in women[60] and that blood levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were strongly associated with decreased risk of sudden cardiac death in men.[61]

α-Linolenic acid (ALA), an omega-3 fatty acid high in flaxseed, canola, and soybean oils, can be converted to EPA and DHA in humans and, thus, may have a role in prevention of CHD. An inverse association between intake of ALA and risk of fatal CHD was observed in most prospective cohort studies,[38,39,63,64] but not in 1 smaller study.[65] In a cohort of women, frequent consumption of oil-and-vinegar salad dressing (a major source of ALA in US diets) was associated with a significantly lower risk of fatal CHD.[63]

Three clinical trials have examined the effects of omega-3 fatty acids in secondary prevention of CHD (Table). In the Diet and Reinfarction Trial,[53] patients advised to eat fish twice weekly or to take fish oil (1.5 g/d) had a 29% lower mortality after 2 years. In the GISSI-Prevenzione trial,[66] daily supplementation with EPA plus DHA (1 g/d) reduced the main end point (composite of death, nonfatal MI, and stroke) by 15%, primarily because of a 45% reduction in sudden death after 3 months of treatment.[67] A trial from India suggested benefits of both fish oil and mus-

Table. Trials of Dietary Interventions and Coronary Events*

Trial	Patients in Intervention Group	Dietary Intervention	Dietary Fat (Energy) in Treatment Group, %	Energy From P and S Fat in Treatment Group, %	Overall Trial Duration, y	Change in Serum Cholesterol Level, %†	Change in CHD, %‡
Low-Fat Approach							
MRC (low fat)[52]	123 male MI patients	Reduce total fat	22	NR	3	−5	+4
DART[53]	1015 male MI patients	Reduce total fat	32	NR	2	−4	−9
High-Polyunsaturated-Fat Approach							
Finnish Mental Hospital Study[47]	676 men without CHD	Reduce saturated fat, increase polyunsaturated fat	35	P = 13; S = 9	6	−15	−44§
Los Angeles Veteran Study[46]	424 men; most had no evidence of existing CHD	Reduce saturated fat, increase polyunsaturated fat	40	P = 16; S = 9	8	−13§	−20 in CHD, −31§ in cardiovascular events
Oslo Diet-Heart Study[48,49]	206 male MI patients	Reduce saturated fat, increase polyunsaturated fat	39	P = 21; S = 9	5	−14§	−25§
MRC (soy oil)[50]	199 male MI patients	Reduce saturated fat, increase polyunsaturated fat	46	P:S ratio = 2	4	−15§	−12
Minnesota Coronary Survey[51]	4393 men and 4664 women	Reduce saturated fat, increase polyunsaturated fat	38	P = 15; S = 9	1‖	−14§	0
Increase Omega-3 Fatty Acid							
DART[53]	1015 male MI patients	Fish twice per week or fish oil (1.5 g/d)	NR	NR	2	NR	−16 in CHD events, −29§ in total mortality
GISSI-Prevenzione[66,67]	5666 MI patients, primarily men	Fish oil (EPA + DHA, 1 g/d)	NR	NR	3.5	0	−30§ in cardiovascular death, −45§ in sudden death
Indian Experiment of Infarct Survival 4[68]	242 MI patients, primarily men	Fish oil (EPA, 1.08 g/d) or mustard oil (ALA, 2.9 g/d)	NR	NR	1	0	−30§ in fish oil group, −19 in mustard oil group
Whole-Diet Approach							
Lyon Diet Heart Study[69,70]	302 MI patients, primarily men	High ALA intake and Mediterranean diet	31	P:S ratio = 0.7	3.8	0	−72§
Indian Experiment of Infarct Survival[117]	204 MI patients, primarily men	High intake of fruits, vegetables, nuts, fish, and pulses	24	P:S ratio = 1.2	1	−9§	−40§

*Adapted from Hu et al.[128] P indicates polyunsaturated fat; S, saturated fat; CHD, coronary heart disease; MRC, Medical Research Council; MI, myocardial infarction; NR, not reported; DART, Diet and Reinfarction Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and ALA, α-linolenic acid.
†Change in cholesterol level refers to the percentage change in serum cholesterol level in the treatment group compared with the change in the control group.
‡Change in CHD refers to the percentage difference in coronary event rates in the treatment group compared with the control group.
§$P<.05$.
‖The total duration of the study was 4.5 years, but the mean duration of the intervention was only 1 year.

tard oil in the treatment of MI patients.[68] In the Lyon Diet Heart Study, higher ALA consumption in the context of a Mediterranean diet dramatically reduced total and cardiovascular mortality as well as nonfatal MI.[69,70] These trials strongly support the protective effects of omega-3 fatty acids, including both ALA and fish oil, in secondary prevention of CHD. The role of fish oil supplements in primary prevention of CHD has not been tested.

CARBOHYDRATES

Prevailing dietary recommendations have emphasized high intake of complex carbohydrates, mainly starch, and avoidance of simple sugars.[71,72] However, many starchy foods, such as baked potatoes and white bread, are rapidly digested to glucose and produce even higher glycemic and insulinemic responses than sucrose (half glucose and half fructose). The glycemic index (GI) ranks foods based on rise in blood glucose (the incremental area under the curve for blood glucose levels) after ingestion compared with glucose or white bread, standardizing the carbohydrate content to 50 g.[73,74] Foods with a low degree of starch gelatinization (more compact granules), such as spaghetti and oatmeal, and a high level of viscose soluble fiber, such as barley, oats, and rye, tend to have a slower rate of digestion and, thus, lower GI values. In several controlled clinical studies,[75] feeding low-GI meals to diabetic patients led to significant improvement in glycemic control and lipid profile, but larger studies are needed.

Glycemic load (GL; the product of the GI value of a food and its carbohydrate content) has been used to represent both the quality and quantity of the carbohydrates consumed.[76,77] Dietary GL is more strongly associated with higher fasting triglycerides and lower HDL-C levels compared with GI.[78] A strong positive association between GL and risk of CHD was observed among 75 521 women during 10 years of follow-up.[79] The increased risk was more pronounced among overweight and obese women, consistent with metabolic studies that the adverse effects of a high GL diet are exacerbated by underlying insulin resistance.[80] Thus, carbohydrate-containing foods should not be judged simply by their GI values; the amount of carbohydrates, fiber, and other nutrients are also important.

Another way to classify dietary carbohydrates is to subdivide cereal grains—staple foods in most societies—into whole and refined grains. Most cereal grains are highly processed before they are consumed. Refined grain products contain more starch but substantially lower amounts of dietary fiber, essential fatty acids, and phytochemicals, although these products are typically enriched with some vitamins and minerals. In several epidemiologic studies, higher consumption of whole grains was associated with lower risk of CHD. Also, prospective cohort studies have consistently found an inverse association between fiber intake and risk of CHD.[81] Several studies have found a stronger association for cereal fiber than for fruit or vegetable fiber.[82-84] The inverse association for fiber observed in epidemiologic studies cannot be fully explained by its cholesterol-lowering effects; the low GI of foods with a high level of fiber and numerous micronutrients in whole grains may also contribute to the benefits.[85]

FOLATE

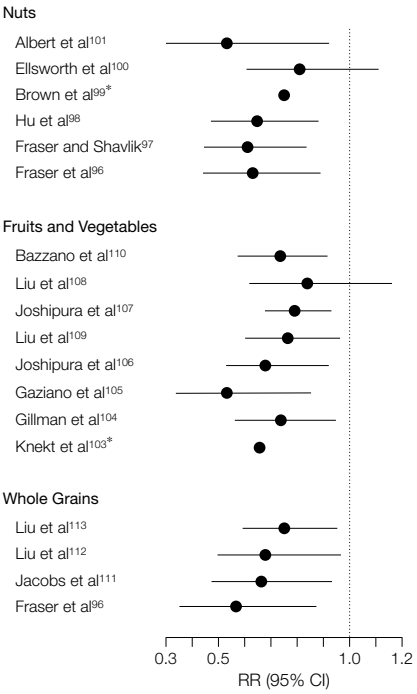
Much evidence suggests that adequate folate consumption is important for the prevention of CHD. Epidemiologic studies have found an inverse association between folate intake measured by dietary questionnaire or serum folate level and risk of CHD,[86-90] which is likely to be mediated through homocysteine-lowering effects of folic acid. Two randomized placebo-controlled trials evaluated effects of folic acid supplementation on the development and progression of atherosclerosis. Vermeulen et al[91] found that supplementation with folic acid and vitamin B_6 for 2 years significantly decreased subclinical atherosclerosis indicated by abnormal exercise electrocardiography tests among siblings of patients with existing cardiovascular disease. In the Swiss Heart Study, treatment with a combination of folic acid and vitamins B_6 and B_{12} significantly decreased restenosis and revascularization after coronary angioplasty at 6 months[92] and a combined cardiovascular end point at 11 months.[93] Ongoing clinical trials should provide more definitive data on the role of folic acid supplementation in CHD prevention, but the interpretation of the findings from trials conducted in the United States could be complicated by the fortification of flour with folic acid.[94]

SPECIFIC FOODS AND DIETARY PATTERNS

The relationship between consumption of specific foods or overall dietary patterns and risk of CHD has been examined in recent studies. Such analyses are valuable in evaluating additional diet-heart hypotheses and in making practical dietary recommendations. For example, replacement of red meat with chicken and fish has been associated with reduced risk of CHD.[95] An inverse association between nut consumption and risk of CHD has been seen consistently in prospective studies.[96-101] (FIGURE 4), which further underscores the importance of distinguishing different types of fat. Although nuts are high in fat and, thus, routinely proscribed in dietary recommendations, the predominant types of fat in nuts are monounsaturated and polyunsaturated, which lower LDL-C level.[102]

Although beneficial effects of fruits and vegetables are widely assumed, only in recent years has solid epidemiologic evidence begun to emerge[103-110] (Figure 4). In the largest study, including 84 251 women and 42 148 men,[107] Joshipura et al reported a significant inverse association between consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C–rich fruits and vegetables, and risk of CHD. Increased consumption of potatoes, however, was not associated with benefits. In several prospective studies, a higher consumption of whole grains as opposed to refined grains was

Figure 4. Prospective Cohort Studies of Cardiovascular Disease and Consumption of Nuts, Fruits and Vegetables, or Whole Grains



Relative risks (RRs) and 95% confidence intervals (CIs) were derived from the comparison of the incidence rates between the highest- and lowest-consumption groups (quintiles, quartiles, or specific intake categories) and were adjusted for nondietary and/or dietary covariates. In each category, studies are shown in the order of most recent to least recent publication. Asterisk indicates confidence intervals were not published in the original article.

associated with a lower risk of cardiovascular disease (Figure 4).[96,111-113]

Recently, several studies have reported the role of overall dietary patterns in predicting long-term risk of CHD.[114] In these analyses, a "prudent" pattern characterized by higher intakes of fruits, vegetables, legumes, whole grains, poultry, and fish was associated with lower risk of CHD, whereas a "Western" pattern characterized by higher intakes of red and processed meats, sweets and desserts, potatoes, french fries, and refined grains was associated with a higher risk, independent of lifestyle factors.[115,116]

Two randomized trials tested the whole-diet approach in secondary prevention of CHD (Table). In the Indian Heart Study,[117] a semivegetarian diet enriched with fruits, vegetables, whole grains, and nuts reduced coronary death by 41% and nonfatal MI by 38%. In the Lyon Diet Heart Study,[69,70] a Mediterranean diet enriched with ALA reduced CHD death by more than 70%. These findings, together with the results from prospective cohort studies and the Dietary Approaches to Stop Hypertension trials,[118,119] support the clinical utility of a whole-diet approach in the prevention of cardiovascular disease.

COMBINED EFFECTS OF DIET AND LIFESTYLE

The combination of multiple dietary factors is more powerful than a single factor alone. In the Nurses' Health Study cohort, a diet high in cereal fiber, marine omega-3 fatty acids, and folate and low in *trans*-fat and GL, with a high ratio of polyunsaturated fat to saturated fat, strongly predicted decreased risk of CHD (relative risk comparing highest with lowest quintiles of the composite score=0.40; 95% confidence interval, 0.31-0.53).[120] Also, improvement in these dietary factors explained much of the decline in the incidence of CHD during 14 years of follow-up of the cohort.[121]

Besides diet, several other behavioral factors strongly influence CHD risk. Analyses from the Nurses' Health Study estimated that 82% of CHD events in the study cohort could be potentially prevented by moderate diet and lifestyle modifications.[120] Among nonsmokers, 74% of coronary events might have been prevented by eating a healthy diet, maintaining a healthy body weight, exercising regularly for half an hour or more daily, and consuming a moderate amount of alcohol (≥5 g/d).

Results from several multifactorial primary prevention trials using diet and lifestyle intervention have been largely unimpressive, probably because of poor compliance and inadequate power.[122] The Oslo Heart Study, however, demonstrated that stopping smoking and increasing the ratio of polyunsaturated to saturated fats in the diet reduced CHD incidence by 47% among men with higher-than-average serum cholesterol levels.[123] In the Lifestyle Heart Study,[124] a combination of an extremely low-fat diet, exercise, stress management, and yoga significantly reduced progression of atherosclerosis, but the low-fat regimen is unnecessarily rigid and difficult for most people to follow.

AREAS OF UNCERTAINTY

The optimal amounts of monounsaturated and polyunsaturated fats in the diet are still unclear. Intake of linoleic acid is usually recommended not to exceed 10% of energy, in part because of little long-term human experience with such diets, although benefits from higher intake exist for blood lipids. There has been some concern that a high-polyunsaturated-fat diet may increase cancer risk, but this has not been substantiated in large epidemiologic studies.[125]

The optimal balance between omega-3 and omega-6 polyunsaturated fatty acids also remains unsettled. Some have proposed reducing the consumption of linoleic acid to achieve a greater ratio of omega-3 to omega-6 fatty acids in the diet.[126,127] However, there is little evidence that a higher ratio predicts a lower risk of CHD.[128] Both omega-3 and omega-6 fatty acids have important roles in reducing CHD risk, probably through different mechanisms. Thus, a good strategy is to substantially increase intake of omega-3 fatty acids from fish and plant sources (because intake for many people is clearly suboptimal) without decreasing intake of linoleic acid. This will improve the ratio and maximize the cardioprotective benefits of both omega-3 and omega-6 fatty acids.

The amount and type of protein in the diet is a matter of debate. Substitution of soy for animal protein reduces LDL-C,[129] and substituting animal protein for carbohydrates raises HDL-C and lowers triglyceride levels.[130] Consistent with the metabolic studies, a prospective cohort study found that a moderately high protein intake (24% vs 15% of energy from protein) was associated with a sig-

nificantly lower risk of CHD after adjustment for cardiovascular risk factors and dietary fat intake.[131] To avoid an increase in saturated fat intake, the major source of protein in the diet should come from nuts, soybeans, legumes, poultry, and fish.

The role of phytochemicals and antioxidants in the prevention of CHD is promising but unsettled. The cholesterol-lowering effects of plant sterol or stanol (saturated sterols) have been well documented in clinical trials[132] and commercial products made of these compounds are widely available, but their long-term effects remain to be seen. Six prospective cohort studies have evaluated the association between flavonoid intake and risk of CHD. A significant inverse association was observed in some studies[133-136] but not others.[137,138] Although a body of experimental evidence has demonstrated the role of antioxidant vitamins in reducing oxidative stress and substantial epidemiologic evidence has linked intake of vitamin E with a lower CHD risk, results from published clinical trials of vitamin E supplements, primarily among patients with clinical CHD, have been largely disappointing.[139,140] Ongoing primary prevention trials should provide more insights.

Finally, a large and inconclusive literature has examined the relationship between dietary minerals such as calcium, magnesium, zinc, and selenium and risk of CHD.[41] Most studies have been based on ecological correlations or case-control analyses. Additional large prospective studies or randomized trials with clinical end points are required to resolve the role of individual minerals from diet or supplements.

CONCLUSIONS

Compelling evidence from metabolic studies, epidemiologic investigations, and clinical trials in the past several decades converges to indicate that at least 3 dietary strategies are effective in preventing CHD: substitute unsaturated fats (especially polyunsaturated fat) for saturated and *trans*-fats; increase consumption of omega-3 fatty acids from fish oil or plant sources; and consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. A combination of these approaches can confer greater benefits than a single approach. However, simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence.

Obesity is an important avenue by which diet can influence risk of CHD. However, the relationship between diet, especially dietary fat, and obesity remains controversial. Although reduction in percentage of calories from dietary fat intake is commonly recommended for weight loss, long-term clinical trials have provided no good evidence that reducing dietary fat per se can lead to weight loss.[141,142] There is a growing consensus that excess calories, whether from carbohydrates or fat, will induce weight gain. A mildly hypocaloric moderate-fat diet, which allows for a great variety in choosing foods, can have better long-term compliance than a typical low-fat diet.[143] Small short-term studies have suggested roles of several diets in weight control, including a low-GI diet,[144] a high-protein diet,[145,146] and a diet high in dairy products,[147] but larger and long-term studies are needed.

Although prevailing dietary guidelines emphasize target intake of specific macronutrients (eg, not exceeding 30% of energy from fat),[71] such numerical criteria are not based on solid scientific evidence, and the public finds it difficult to make dietary changes based on such criteria. A variety of options exist for designing attractive and heart-healthy diets, with varying amounts of fat and carbohydrates, as long as the diet embraces healthy types of fat and carbohydrates and provides an appropriate balance in energy intake and expenditure. Evidence is now clear that diets including nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrate, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together with regular physical activity, avoidance of smoking, and maintaining a healthy weight, may prevent the majority of cardiovascular disease in Western populations.

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Drafting of the manuscript: Hu.
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To spend too much time in studies is sloth; to use them too much for ornament, is affectation; to make judgment wholly by their rules, is the humour of a scholar. . . . Read not to contradict and confute; nor to believe and take for granted; nor to find talk and discourse; but to weigh and consider. Some books are to be tasted, others to be swallowed, and some few to be chewed and digested. . . . Reading maketh a full man; conference a ready man; and writing an exact man. . . . Histories make men wise; poets witty; the mathematics subtile; natural philosophy deep; moral grave; logic and rhetoric able to contend.
—Francis Bacon (1561-1626)