CHAPTER 29

The Role of Diet in the Prevention and Treatment of Cardiovascular Disease

MICHAEL ROUSSELL, JESSICA GRIEGER, AND PENNY M. KRIS-ETHERTON
Pennsylvania State University, University Park, Pennsylvania

Contents

I. Introduction 515
II. Dietary Fat 516
III. Dietary Carbohydrate 526
IV. Dietary Protein 529
V. Alcohol 531
VI. Dietary Cholesterol 532
VII. Plant Sterols/Stanols 533
VIII. Supplements 534
IX. Food-Based Guidance 535
X. Summary/Conclusion 539
References 539

I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for more deaths per year than all other causes. In the past 25 years, there has been progress in reducing the number of deaths from CVD. For example, CVD mortality rate has declined by 41% since the early 1980s [1]. Despite this, medical treatments for cardiac conditions have increased. In addition, hospital discharges related to CVD are at an all-time high (>6,000,000 per year). The American College of Cardiology recently predicted that by 2050 the number of Americans diagnosed with CVD will double to 25 million [2]. Thus, despite the progress that has been made in reducing death rates from CVD, much remains to be achieved to decrease CVD risk, which in turn will reduce onset and progression of CVD on a population basis.

Prevention of CVD is a major public health goal. Accordingly, intensive efforts are ongoing to decrease CVD risk through the reduction of CVD risk factors in all population groups. Risk factors are classified as nonmodifiable or modifiable [3]. Nonmodifiable risk factors include age and family history. Major modifiable CVD risk factors include elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels, reduced high-density lipoprotein cholesterol (HDL-C) levels, hypertension, diabetes mellitus, and overweight and obesity. This chapter focuses primarily on lipids and lipoproteins, a major modifiable CVD risk factor, and the role that diet can play in reducing CVD risk via modifications in lipids and lipoproteins. Other major CVD risk factors are mentioned in this chapter; however, they are discussed in greater detail elsewhere in this book. Other increasingly important emerging CVD risk factors that can be modified by diet include elevated levels of lipoprotein (a); insulin; altered hemostatic factors; C-reactive protein; cytokines and inflammatory mediators (e.g., interleukin [IL]-6, IL-7, IL-8, IL-18); and small, dense LDL particles, among others. Thus, there is great potential for further decreasing CVD by favorably modifying multiple risk factors.

The importance of reducing major risk factors is illustrated by results from three large prospective studies (Chicago Heart Association Detection Project in Industry, Multiple Risk Factor Intervention Trial, and the Framingham Heart Study), which reported that 87–100% of men and women (ages 18–59 years) with at least one major risk factor died from coronary heart disease (CHD) [4]. In addition, another analysis of 112,458 patients with CHD reported that 80–90% of the participants had one or more major CVD factors [5]. It is important to note, however, that other risk factors also contribute to the development of CHD. This is best illustrated by the evidence that about 35% of CHD occurs in individuals with a total cholesterol (TC) less than 200 mg/dl [6]. Thus, modifying as many CVD risk factors as possible will have the greatest impact on decreasing CVD risk.

The impact of lowering major coronary heart disease risk factors has been reported in a recent analysis demonstrating that approximately one-half of the decrease in CHD in the United States between 1980 and 2000 can be attributed to reductions in total cholesterol, blood pressure, and body mass index (BMI) [1]. The reduction in these major risk factors is due to lifestyle and behavioral interventions, as well as pharmacotherapy. Thus, diet can have a significant impact on CVD risk factors, and, consequently, healthy diet and lifestyle practices can markedly decrease the risk for CHD.

Diet has been a cornerstone in the management of heart disease risk factors for more than 50 years. The American Heart Association (AHA) published their first dietary recommendations for CVD risk reduction in 1957 [7]. The AHA updates dietary recommendations routinely as new science emerges. Other groups such as the U.S. Department of Agriculture (USDA), Health and Human Services (HHS), National Cholesterol Education Program (NCEP), American Dietetic Association (ADA), and the American Diabetes Association continually update and publish diet and lifestyle recommendations to reduce risk of chronic diseases, including (or specifically focusing on) CVD. Traditionally these organizations have made dietary recommendations based on targeted nutrient levels (e.g., <7 to <10% of energy from saturated fatty acids [SFA]). Recently a more consumer-friendly approach has evolved and food-based dietary recommendations have been made (e.g., "Consume 3 cups per day of fat-free or low fat milk or equivalent products" [8]). This change is most notable in development of the MyPyramid.gov, the new graphic for communicating the 2005 U.S. Dietary Guidelines [9, 10]. These food-based recommendations are based on macronutrient and micronutrient recommendations made by the National Academies (Dietary Reference Intakes), as well as other organizations (e.g., NCEP). The American Dietetic Association Evidence Analysis Library on Disorders of Lipid Metabolism is an excellent summary of the literature about the role of diet on lipid and lipoprotein risk factors, including dietary recommendations for the management of CVD risk factors [11]. A food-based approach that integrates all nutrient recommendations is encouraged because it targets multiple CVD risk factors, as well as many other chronic diseases. It is important to note that this approach encompasses all dietary recommendations and translates to a greater health benefit for the population.

Historically dietary recommendations have focused on modifying the type and amount of fat. However, modifying the type and amount of carbohydrate and protein to lower CVD risk factors has attracted recent attention. The reduction and replacement of SFA and *trans* fatty acids (TFA) with unsaturated fat or carbohydrates is currently a widely accepted approach for decreasing major CVD risk factors. In addition, dietary protein is being considered as a substitute for SFA and TFA. The effects of protein on CVD is becoming a more well-defined area as an increasing number of studies are being performed that examine both type and amount of protein. In the past decade, dietary recommendations have been made for other nutrients based on the emerging evidence. For example, the cardioprotective benefits of a diet rich in omega-3 fatty acids, both marine- and plant-based, have been intensively studied, leading to specific dietary recommendations that have been made by certain organizations. With respect to dietary carbohydrates, studies are being conducted to evaluate dietary fiber, the glycemic index of carbohydrate-rich foods, and how the glycemic load of the diet affects CVD risk factors. Likewise, studies are ongoing to evaluate the physiological effects of amount and type of animal protein and plant protein on CVD risk.

This is an exciting era for gaining a better understanding of how macronutrients, micronutrients, and other dietary factors affect CVD risk, and thus it is not unreasonable to speculate that more effective dietary approaches for reducing CVD risk will be identified in the future. This chapter reviews the present understanding of how diet affects CVD risk status via changes in plasma lipid and lipoproteins, emerging physiological risk factors, and overall CVD-related morbidity and mortality.

II. DIETARY FAT

A. Total Fat

A diet low in SFA (<7% of energy from SFA) continues to be a major focus in the prevention and treatment of CVD. Typically, reducing total fat has been a major strategy recommended for decreasing SFA. Efforts are ongoing to determine the optimal quantity of total dietary fat. Currently the Dietary Reference Intakes (DRI) for Macronutrients from the National Academies recommend 20–35% of energy from fat for adults (>19 years old) [12]. The NCEP recommends 25–35% of energy from fat, an amount intended for the management of dyslipidemia (specifically high TG and low HDL-C levels) [13].

The upper and lower ranges for total fat intake were defined on the basis of achieving nutrient adequacy, as well as the range considered optimal for health. The upper range for total fat was set because SFA and energy intakes have been shown to increase beyond recommended levels when total fat exceeds 35% of energy [14–19]. Within the context of the amount of total fat in the diet that meets current recommendations, SFA, TFA, and cholesterol should be reduced as much as possible and nutrient adequacy should be met.

The lower range of the total fat recommendation was set to achieve nutrient adequacy and meet essential fatty acid requirements as well as promote compliance with the total fat recommendation. Adherence to very low-fat diets (<20% of energy) is problematic [20]. The decrease in compliance commonly seen with reduced-fat diets was most recently observed in the Women's Health Initiative Dietary Modification Trial (WHI) [21]. In this study, which enrolled almost 49,000 women, the total fat intake goal of 20% of energy was not achieved. However, the low-fat intervention group was able to decrease their total fat intake by at least 9 percentage points (37.8% down to 28.8% of energy), an average that was achieved after 6 years. Some women were able to reduce total fat further. The WHI trial

demonstrates that the total fat recommendations set by the National Academies and NCEP are achievable.

B. Saturated Fatty Acids

Dietary recommendations have been made by numerous government agencies and health care organizations for SFA. All recommendations consistently advocate reductions in SFA. In 2005, the DRI Report [12] recommended that SFA be a low as possible within the context of a nutritionally adequate diet. Specific targets have been recommended by the Dietary Guidelines for Americans, 2005 [22], the National Cholesterol Education Program (NCEP) ATP III, and the American Heart Association (AHA) in 2006. The Dietary Guidelines Report recommends that SFA be less than 10% of energy. Further reductions are recommended for individuals with high TC and LDL-C. Both the NCEP and the AHA recommend less than 7% of energy from SFA for the treatment of high LDL-C levels and for the prevention of CVD, respectively.

The Seven Countries Study [23], a landmark epidemiologic investigation, demonstrated that SFA intake (as a percent of energy) was positively correlated with serum cholesterol levels as well as with 5-year incidence of CHD. Many well-controlled clinical studies followed, resulting in the development of blood cholesterol predictive equations for estimating the changes in total cholesterol in response to changes in type of fat and amount of dietary cholesterol consumed. The original equations developed by Keys *et al.* [24] and Hegsted *et al.* [25] demonstrated that SFA was twice as potent in raising blood cholesterol levels as polyunsaturated fat (PUFA) was in lowering cholesterol levels. Monounsaturated fat (MUFA) was shown to have a neutral effect and dietary cholesterol raised the blood cholesterol level but less so than SFA. Other predictive equations have been developed for LDL-C and HDL-C [26–29]. The LDL-C response to fatty acid classes tracks with that reported for TC.

Figure 1 reports the results of a meta-analysis of 60 studies in which carbohydrates were isoenergetically replaced with different fatty acid classes (SFA, MUFA, PUFA, TFA) and shows the relative effects on LDL-C, HDL-C, and the TC:HDL-C ratio. SFA and TFA increase LDL-C, and MUFA and PUFA decrease LDL-C, the latter more so. All fatty acid classes except TFA increase HDL-C; SFA is the most potent, PUFA is least potent, and MUFA has an intermediate effect. Because SFA increases both LDL-C and HDL-C, there is a slight increase in the TC:HDL-C ratio. The TC:HDL-C ratio is most favorably affected by unsaturated fatty acids, and PUFA more so than MUFA because PUFA has a greater TC-lowering effect than MUFA [30].

A positive dose-response relationship between SFA intake, TC (Fig. 2), and LDL-C has also been reported in meta-analyses by several investigators [12, 26]. Figure 2 includes data from 395 studies and displays the linear relationship between SFA intake and total cholesterol concentrations.

There is a modest dose-response effect of SFA on the LDL:HDL-C ratio [31]. As shown in Figure 3, the increase in the LDL:HDL-C ratio elicited by SFA is less than that observed for TFA.

Recent studies also have evaluated the effects of individual SFA on plasma lipids and lipoproteins (Fig. 4) [32]. The cholesterolemic effects of the individual SFA vary. Lauric acid (C:12:0) has the most potent LDL-C and TC raising effect. Because lauric acid increases HDL-C proportionally more than it does LDL-C, a lowering of the TC:HDL-C ratio is observed [32]. Stearic acid has a neutral effect on LDL-C. However, results from the Nurses' Health Study have reported a high correlation between stearic acid and other SFA in the diet, and therefore, distinguishing

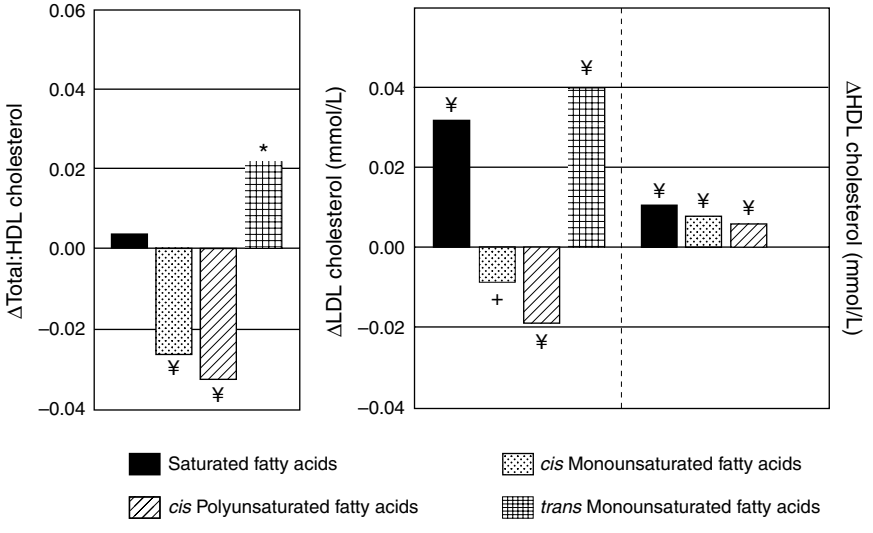

FIGURE 1 Predicted changes (△) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with saturated, *cis* monounsaturated, *cis* polyunsaturated, or *trans* monounsaturated fatty acids. $*p < 0.05$. $+p < 0.01$. $¥p < 0.001$ [32]. Reprinted with permission from the American Society of Nutritional Sciences.

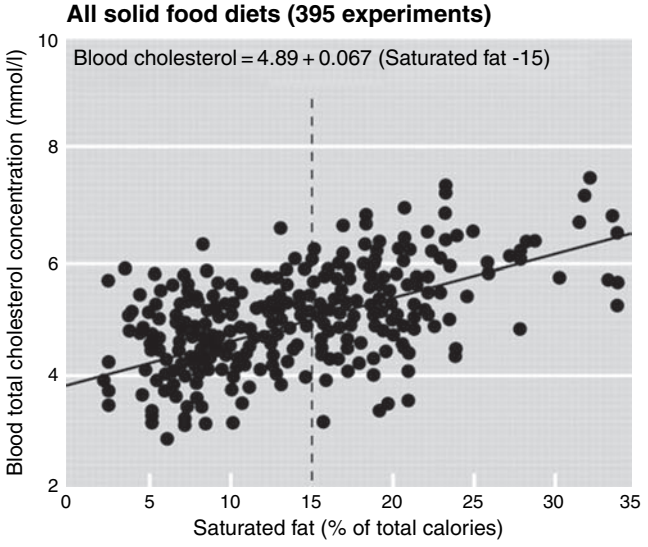

FIGURE 2 Univariate multilevel regression slopes of blood total cholesterol versus dietary saturated fat in metabolic ward experiments. (The equations take account of which experiments were part of the same study.) The dotted line represents a typical intake of saturated fat (15% of dietary energy), and this is used as an intercept for the regression equations. No adjustments are made for total energy intake or any other aspects of experimental diets [26]. Reprinted with permission from the *British Journal of Medicine*.

between individual SFA should not be a major dietary intervention in the treatment and prevention of CVD [33].

SFA also has been shown to have adverse effects on various emerging CVD risk factors such as flow-mediated dilation (FMD) of the brachial artery, cellular adhesion molecules, and hemostatic factors. FMD is a measurement of vascular reactivity commonly used to assess vascular endothelial function. Decreases in FMD are indicative of decreased vascular elasticity, which increases risk for CVD. Both acute and chronic consumption of SFA have been shown to adversely affect FMD. A single meal high in SFA has been shown to significantly decrease FMD for up to 6 hours [34]. With respect to chronic consumption of a diet high in SFA, a recent free-living crossover (3 weeks each diet period) study compared the effects of a diet that provided varying levels of energy from SFA (19% of energy), MUFA (19% of energy), PUFA (15% of energy), or carbohydrates (68% of energy) on FMD and found that the high-SFA diet significantly decreased FMD, indicating an adverse effect compared to the other diets, which had no appreciable effect [35].

Other important markers of vascular function are cellular adhesion molecules. Cellular adhesion molecules (ICAM-1, sICAM-1, VCAM-1, P-selectin, E-selectin) are compounds found on the luminal blood vessel epithelium that bind leukocytes and initiate the leukocyte-endothelial cell adhesion cascade [36]. Increased levels of adhesion molecules increase risk of myocardial infarction (MI) [37] and CVD [37, 38]. The effects of SFA on cellular adhesion molecules also have been examined in a postprandial setting. Subjects were given a high-fat milk shake (1 g fat/kg body weight) containing mainly SFA (89.6% SFA) or unsaturated fat (8.8% SFA). Increased consumption of SFA at this single meal significantly elevated the postprandial expression of the adhesion molecules ICAM-1 and VCAM-1 for up to 6 hours [34]. Levels of another adhesion molecule, P-selectin, which have been positively correlated with CVD, also have been shown to increase following a diet high in SFA [35]. Compared to individuals on a Mediterranean-style diet, the LDL-C particles from individuals on a high-SFA diet (20% of energy) induce increased expression of VCAM-1 and E-selectin [39]. Small reductions (–1.8% of total energy) in dietary SFA also significantly decreased sICAM-1 in hypercholesterolemic men and women [40].

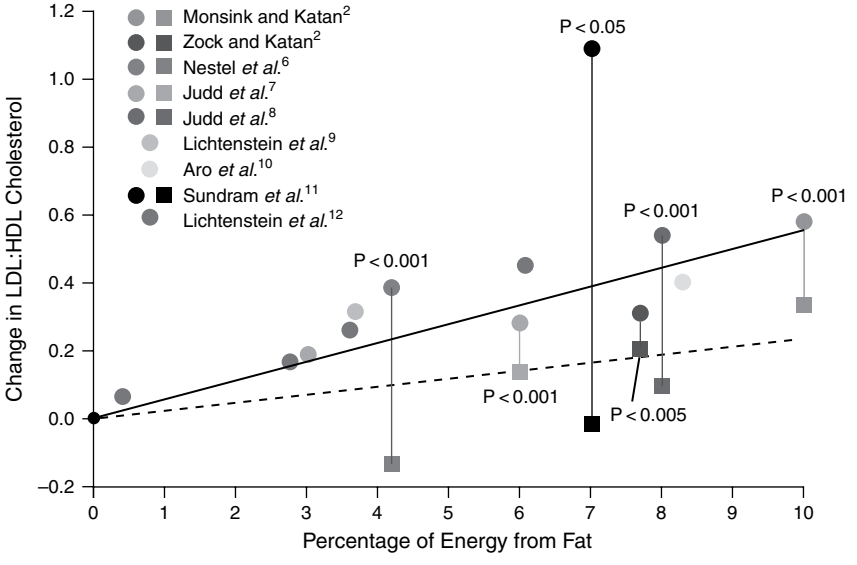

FIGURE 3 Results of randomized studies of the effects of a diet high in *trans* fatty acids (circles) or saturated fatty acids (squares) on the ratio of LDL cholesterol to HDL cholesterol. A diet with isoenergetic amounts of *cis* fatty acids was used as the comparison group. The solid line indicates the best-fit regression for *trans* fatty acids. The dashed line indicates the best-fit regression for saturated fatty acids [31].

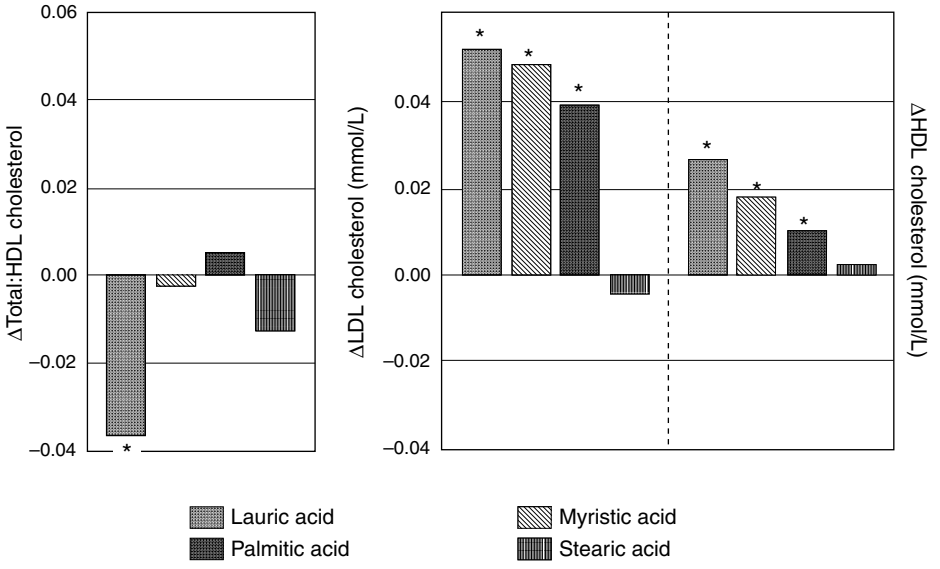

FIGURE 4 Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), or stearic acid (18:0). $^{*}p < 0.001$ [32]. Reprinted with permission from the American Society of Nutritional Sciences.

Epidemiologic evidence from the Atherosclerosis Risk in Communities Study [41] showed that a high intake of total fat, SFA, and cholesterol was associated with higher levels of factor VII and fibrinogen, two hemostatic factors that play a role in blood clot formation and are CVD risk factors. Likewise, in the Dietary Effects on Lipoproteins and Thrombogenic Activity (DELTA) Study, a well-controlled multicenter feeding study, investigators reported that reductions in SFA led to decreased factor VII levels [42]. Replacing SFA with MUFA has been shown to significantly decrease factor VII in mildly hypercholesterolemic subjects [43]. In a review on the topic of fatty acids and hemostasis, SFA (namely, C12–C16 SFA) was shown to be the main determinant of factor VII activation over time [44]. Collectively, the results from studies conducted to date provide a strong rationale for current dietary guidance to decrease SFA. The database for the recommendation to decrease TFA also is convincing. Decreasing these two fatty acid classes can be achieved in a variety of ways.

Strategies for reducing saturated fat that can be implemented singly or in combination are as follows:

1. *Replace energy from SFA and TFA with carbohydrate energy sources*—This is a common approach for reducing total fat. The potential downside to this approach is that replacing SFA with carbohydrate leads to a decrease in HDL-C and often an increase in TG [45–47], both of which increase risk of CVD. The increases in TG can be attenuated when whole grain carbohydrates are consumed, and when dietary fiber is increased [48].
2. *Replace energy from SFA and TFA with unsaturated fat energy sources*—The addition of PUFA and MUFA to the diet at the expense of SFA and TFA is an increasingly common approach that is consistent with a Mediterranean-style diet. When MUFA replace SFA, plasma TG is decreased and HDL-C remains unchanged or is decreased less compared with a high-carbohydrate, reduced-fat diet [47, 49, 50].
3. *Replace energy from SFA and TFA with protein energy sources*—There is a recent interest in replacing SFA and TFA energy with dietary protein to prevent some of the adverse effects that have been reported when dietary carbohydrate replaces SFA and TFA [51].
4. *Decrease energy from SFA and TFA*—Decreasing SFA and TFA without replacing energy with other macronutrients results in a reduction in total fat and energy, yielding a diet that is reduced in total fat.

The evidence is compelling that SFA has a potent and dose-response effect on TC and LDL-C. The individual SFA elicit different effects, with C12:0–C16:0 being hypercholesterolemic and stearic acid having a neutral effect. However, because these fatty acids track together in foods, the most prudent advice is to decrease total SFA to recommended levels. SFA intakes should meet current dietary recommendations within the context of a diet that achieves nutritional adequacy and is consistent with recommendations for total fat.

C. Unsaturated Fatty Acids

1. Monounsaturated Fatty Acids

MUFA along with PUFA provide great flexibility in diet planning because they are a vehicle for increasing total fat and can be used to replace energy from SFA, TFA, or carbohydrate. The current dietary recommendations from the National Academies do not include specific recommendations for MUFA, whereas the NCEP ATP III recommends that MUFA can make up to 20% of total energy

[13]. The average MUFA intake among the adult population provides about 15% of energy, whereas a high-MUFA diet typically provides about 20–22% of energy. During the past decade there has been a surge in research that examined the effects of using MUFA as a substitute for dietary carbohydrate and SFA because of beneficial effects: A moderate fat diet mediated CVD risk factors [47, 49]. MUFA have a slight LDL-C lowering effect, however, as noted in the meta-analysis conducted by Mensink *et al*. [32]; when MUFA are substituted for SFA and TFA, the expected decrease in TC and LDL-C will be significant. Replacing dietary carbohydrate with MUFA will decrease TG and increase HDL-C [32, 51]. Figure 5 shows an inverse-linear relationship between MUFA intake and TC:HDL-C levels [8].

Inclusion of MUFA in the diet is commonly achieved through the replacement of energy from SFA and/or carbohydrate. A meta-analysis of 60 controlled trials showed that the replacement of carbohydrate with MUFA resulted in significant decreases in TC:HDL-C ratio as well as LDL-C. This was accompanied by an increase in HDL-C [32]. These effects were examined more recently in the OmniHeart study. The OmniHeart study was a three-way crossover ($n = 164$), controlled-feeding trial that compared the effect of blood cholesterol-lowering diets that were either high in carbohydrate, protein, or unsaturated fats mostly MUFA on serum lipids and blood pressure (Table 1) [51, 52].

The high-unsaturated-fat (predominately MUFA) diet group experienced greater reductions in TG compared to the high-carbohydrate group (–9.3 mg/dl versus 0.1 mg/dl), LDL-C (–13.1 mg/dl versus –11.6 mg/dl), and TC (–15.4 mg/dl versus –12.4 mg/dl). The high-unsaturated-fat diet group also was the only diet group in which subjects did not experience a reduction in HDL-C [51].

TABLE 1 Macronutrient Comparisons of Three OmniHeart Diets [51]

	Diets		
	Carbohydrate	**Protein**	**Unsaturated Fat**
Diet composition, kcal%			
Fat	27	27	37
Saturated	6	6	6
Monounsaturated	13	13	21
Polyunsaturated	8	8	10
Carbohydrate	58	48	48
Protein	15	25	15
Meat	5.5	9	5.5
Dairy	4	4	4
Plant	5.5	12	5.5

Evidence also suggests that MUFA may decrease susceptibility of LDL particles to oxidative modification, an important initiating event in the development of atherosclerosis, thereby reducing the atherogenic potential of LDL [53, 54]. High-MUFA diets have been shown to increase the resistance of LDL to oxidation when compared to a high-PUFA diet, low-fat/high-carbohydrate diet, the average American diet, or the NCEP Step 1 diet (energy distributed as 55% carbohydrate, 30% fat, and 15% protein) [55, 56]. Moreover, a diet higher in total fat (and higher in MUFA) versus a lower-fat diet has been shown to maintain a larger LDL particle diameter [57, 58], which is important because small, dense LDL has been identified as a risk factor for CVD [59, 60].

There are conflicting views on the benefits of MUFA in the prevention and treatment of cardiovascular disease

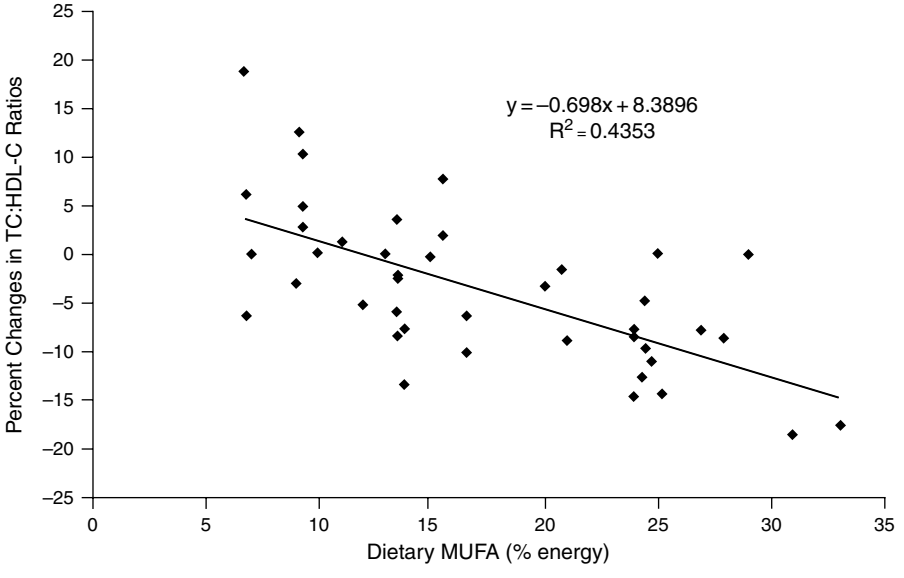

FIGURE 5 Relationship between monounsaturated fatty acid (MUFA) intake and total cholesterol (TC): high-density lipoprotein cholesterol (HDL-C) ratio. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations [12].

based on animal studies conducted by Rudel *et al.* [61]. Nonhuman primates were fed diets high in PUFA, MUFA, or SFA. The lipid and lipoprotein responses were similar to those reported for humans when diets high in PUFA, MUFA, or SFA were consumed. On the high-MUFA diet, nonhuman primates developed atherosclerosis similar to that observed for a high-SFA diet. The high-PUFA diet showed decreased atherosclerosis compared to the other two diet groups. More recently it was demonstrated in the mouse model that a diet high in MUFA leads to a greater formation of oleoyl-CoA and an increase in ACAT2-derived cholesteryl oleate. These results suggest that the potential atherogenic effects of a MUFA-rich diet are due to an increase in monounsaturated cholesterol esters in LDL particles [62].

In summary, the incorporation of MUFA into a heart-healthy diet appears to have favorable effects on some important risk factors for heart disease, including lipids and lipoproteins, oxidized lipids, and blood pressure in healthy individuals and persons with diabetes. On the other hand, results from some animal studies suggesting adverse effects indicate that more research comparing the effects of MUFA and PUFA is needed to determine the optimal ratio of these important unsaturated fats in relation to the total fat content of the diet to maximally reduce CVD risk.

2. *Trans* Fatty Acids

TFA are unsaturated fatty acids (mono- or poly- in the case of conjugated linoleic acid) with *trans* stereochemistry configuration of the double bonds. TFA have two main origins: ruminant animals and industrial production. The ruminant-produced TFA vaccenic acid (C18:1 Δ11t) is a precursor to conjugated linoleic acid (CLA). Because of the substantive evidence base, industrially produced TFA and their effects on CVD risk will be emphasized. The DRI report recommended that TFA intake be kept as low as possible as any increase in TFA intake will negatively impact CVD risk [12]. NCEP ATP III also recommends that TFA consumption be kept as low as possible while the AHA recommends that TFA intake be kept at 1% of energy or below [63].

Industrially produced TFA is made by the hydrogenation of unsaturated vegetable oils. The use of TFA became very popular in the mid-twentieth century when public health recommendations encouraged people to decrease their animal fat and tropical oil intakes. However, research that started in the early 1990s demonstrated numerous adverse effects of TFA [64, 65].

The adverse cardiovascular effects of TFA have been demonstrated in epidemiologic and clinical trials. In the Seven Countries Study, higher CHD mortality rates were observed in countries with greater TFA consumption (northern European countries versus Japan and Mediterranean countries) [66]. Other epidemiologic studies such as the Nurses' Health Study [67], a population-based case-control study [68], and Zutphen Elderly Study [69] also showed an increased risk of CHD with increased intake of TFA.

An analysis that included 140,000 subjects, pooled from several studies, concluded that a 2% increase in energy from TFA was associated with 23% increase in incidence of CHD [70]. One large case-control study found an association between erythrocyte TFA levels and sudden death (odds ratio = 1.47) [68].

TFA elicit both similar and different lipid and lipoprotein responses compared to SFA. SFA has consistently increased both LDL-C and HDL-C, whereas TFA increased LDL-C but decreased HDL-C, compared to SFA [65] (Fig. 4). Thus, SFA increase the LDL:HDL-C ratio modestly, whereas TFA increase the ratio appreciably, that is, towards a more atherogenic profile. Figure 1, from a meta-analysis of 60 controlled trials, displays the potent effect TFAs has on increasing LDL-C [32].

TFA intakes as low as 1–3% of total energy (current consumption is 2.6% of energy) adversely affect many CVD risk factors beyond increasing LDL-C [71] such as increasing inflammatory markers and decreasing endothelial function [70]. Thus, as a result of the evidence base, it is clear that TFA should be reduced in the diet. Because of the adverse effects that TFA has on CVD risk factors and positive association with CVD morbidity and mortality, the AHA has actively disseminated information about the health effects of TFA. Central to this is sharing information about the development of alternative fats and oils devoid of TFA that have acceptable functional properties and sensory characteristics and do not increase CVD risk [64].

D. Polyunsaturated Fatty Acids

Polyunsaturated fats are long-chain fatty acids that contain more than one double bond. There are two major classes of PUFA that are defined by the position of the first double bond relative to the methyl terminus; omega-6 (n-6 FA) and omega-3 (n-3 FA) fatty acids. There is a large evidence base demonstrating benefits of PUFA on CVD risk and risk factors.

1. Omega-6 Fatty Acids

Linoleic acid (LA) is an essential fatty acid. The major source of LA in the diet is vegetable oil. Intakes of LA have almost doubled from the 1930s (3% of energy) to the present (5–6% of energy) in the United States and Canada [72]. The adequate intake (AI) for LA is 17 g/day and 12 g/day for men and women, respectively, between 19 and 50 years of age [12]. The Acceptable Macronutrient Distribution Range (AMDR) for n-6 FA (LA) is 5–10% of total energy. The lower range of the AMDR for LA is the AI. The upper range of PUFA intake set by the DRI Committee and Dietary Guidelines [8] because it represents the upper range of PUFA consumption in the United States. The

NCEP ATP III guidelines also recommend up to 10% of energy from PUFA [13].

Predictive equations developed by Keys *et al.* [23] and Hegsted *et al.* [25] showed that a 1% increase in energy from PUFA resulted in a 0.9 mg/dl decrease in TC. Replacing of carbohydrate calories with PUFA increases HDL-C [32], but less than was observed for MUFA. PUFA intake also decreases the TC:HDL-C ratio. Three early controlled trials verified the cardioprotective effects of PUFA as observed by Keys *et al.* and Hegsted *et al.* [73]. The Oslo Heart Study [74], the Finnish Mental Hospital Study [75], and the Wadsworth Hospital and Veterans Administration Center in Los Angeles Study [76] all observed marked hypocholesterolemic effects of diets very high in PUFA from vegetable oils. Importantly, in two of these studies [75, 76], the cholesterol-lowering response was associated with a reduction in the incidence of CVD (16–34%).

The Nurses' Health Study reported a dose-response relationship regarding CVD risk and PUFA intake with the highest quintile of intake (6.4% of energy) conferring approximately a 30% reduction in risk [77]. A review [78] of the influence of PUFA on CVD concluded that there are beneficial effects of PUFA intakes above the recommended intake range (14–21% of energy); thus more research is needed to determine the optimal level of PUFA in the diet.

There is some concern that n-6 fatty acids may have adverse health effects because of their increased susceptibility to oxidation and the impact that high intakes have on n-3 fatty acid status and inflammation [79]. However, many long-term clinical studies have shown that increased PUFA intakes have a beneficial effect on CVD risk, and thus the impact of increased susceptibility to oxidation is unlikely if the diet provides ample antioxidants [73, 75, 80].

Concern also has been expressed because of the possibility that higher consumption of n-6 fatty acids will inhibit metabolism of n-3 fatty acids. This concern stems from n-3 and n-6 fatty acids sharing common enzymatic and metabolic pathways en route to eicosanoid synthesis (Fig. 6).

The impact of higher intakes of n-6 fatty acids on metabolism of n-3 fatty acids is hypothesized to occur in two areas. First, the increased LA levels can interfere with the formation of eicosapentaenoic acid from the alpha-linolenic acid because LA uses the same desaturase and elongase enzymes to form arachidonic acid. The second area is the direct formation of eicosanoids. Arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid all occupy space in the lipid bilayers of cellular membranes. It is hypothesized that increased levels of n-6 fatty acids and decreased levels of n-3 fatty acids will lead to more n-6 fatty acids being used for eicosanoid synthesis, leading to an increased production of proinflammatory molecules. However, it has been argued that the ratio of n-6 to n-3 fatty acids is not as important as the total amount of n-3 fatty acids [81]. A review of the results from the Health Professionals Follow-up Study based on information from 45,722 men concluded that irrespective of background n-6 fatty acid intake, increased consumption of n-3 fatty acids reduced risk of CVD [82].

n-6 fatty acids have been shown to have great benefit in reducing CVD risk factors and CVD events. The public health message regarding n-6 PUFA consumption should not be to decrease intake, but rather to achieve the recommended intake (5–10% of energy). More research is needed to examine the health effects and safety of PUFA intake above 10% of energy.

2. Omega-3 Fatty Acids

The two main sources of n-3 fatty acids are either plant derived or marine derived and have unique benefits with respect to CVD risk factors. Alpha-linolenic acid (ALA,

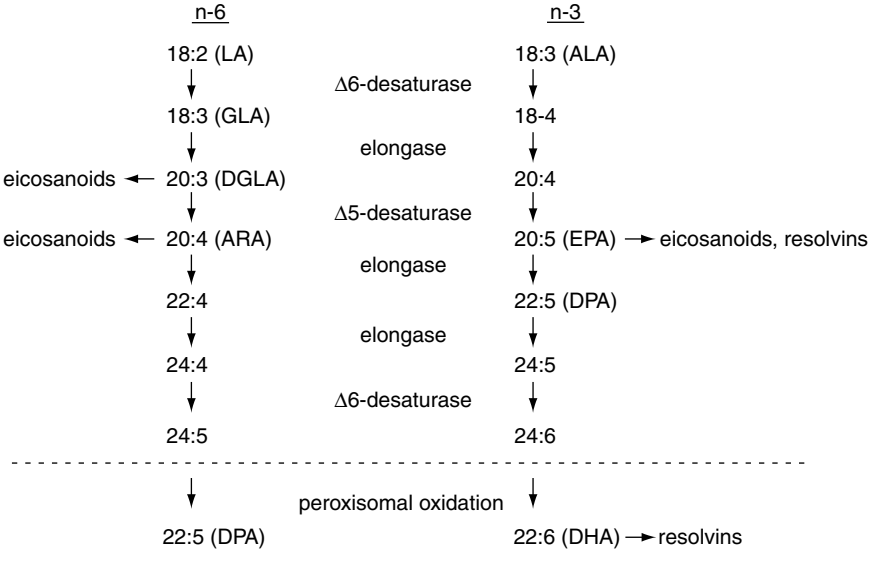

FIGURE 6 Biochemical pathway for the interconversion of n-6 and n-3 fatty acids. ALA, (alpha)-linolenic acid; ARA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GLA, (gamma)-linolenic acid; LA, linoleic acid [85]. Reprinted with permission from the American Society of Nutritional Sciences.

C18:3) is the major plant-derived n-3 fatty acid. The two major marine-derived omega-3 fatty acids are eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6). Fatty fish are the main source of EPA and DHA in the diet; these fatty acids are synthesized by cold water algae which are part of the food chain consumed by fish [83, 84]. ALA, commonly found in flax/flaxseed oil, canola oil, walnuts/walnut oil, and soybean oil, can undergo a series of elongations and desaturations by the body to yield both EPA and DHA (Fig. 6); however, these conversion rates are low, especially for DHA [85–88]. ALA is an essential fatty acid. The AI for individuals aged between 19 and 50 years for linolenic acid is 1.6 g/day and 1.1 g/day for men and women, respectively. The AMDR for ALA is 0.6–1.2% of total energy. It is recommended that up to 10% of the AMDR for ALA can be consumed as EPA and/or DHA [8]. Recommendations for EPA and DHA for the primary prevention of CVD from the United Kingdom Scientific Advisory Committee [89], Dietary Guidelines Advisory Committee [8], and the National Heart Foundation of Australia [90] are to consume 450–500 mg EPA and DHA per day.

The AHA has both food-based and nutrient-based recommendations (Table 2) [91] regarding n-3 FA, and specifically EPA and DHA. In a Science Advisory published in 2003, the AHA made recommendations for n-3 fatty acids for individuals without heart disease, patients with documented CHD, and patients with hypertriglyceridemia. The AHA Diet and Lifestyle Recommendations Revision 2006 recommend that people eat two servings (4 oz-each) of fatty fish weekly. This is the equivalent of 500 mg/day of EPA and DHA. The NCEP ATP III did not make specific n-3 fatty acid recommendations but endorsed those made by the AHA in 2002 [91].

TABLE 2 Summary of AHA Recommendations for Omega-3 Fatty Acid Intake [91]

Population	Recommendation
Patients without documented coronary heart disease (CHD)	Eat a variety of (preferably fatty) fish at least twice a week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseed and walnuts).
Patients with documented CHD	Consume about 1 g of EPA+DHA per day, preferably from fatty fish. EPA+DHA in capsule form could be considered in consultation with the physician.
Patients who need to lower triglycerides	2 to 4 g of EPA+DHA per day provided as capsules under a physician's care.

2.1. Alpha-Linolenic Acid

Observational studies have shown cardioprotective effects of ALA on risk of coronary morbidity and mortality. The Nurses' Health Study reported a 30% reduction in the relative risk of fatal coronary heart disease in individuals who consumed more than 1 gram of ALA per day [92]. In a subset of participants from the Cardiovascular Health Study, consumption of tuna or other broiled or baked fish assessed with a food frequency was found to correlate with plasma phospholipid long-chain n-3 fatty acid levels. Among the entire cohort of 4775 adults 65 years or older followed for 12 years, tuna and other fish consumption was associated with a 27% lower risk of ischemic stroke with intake of one to four times per week compared with an intake of less than once per month [93]. In the Iowa Women's Health Study, the highest tertile of ALA intake was associated with a 15% reduction in total mortality [94]. Finally, in a secondary analysis of the 24-hour recall data from the Multiple Risk Factor Intervention Trial (MRFIT), a primary prevention study that examined the effects of reducing elevated serum cholesterol and diastolic blood pressure along with smoking cessation on CHD mortality, observed that the highest quintile of ALA intake, 2.81 g/day, yielded a multivariate-adjusted relative risk for all-cause mortality of 0.67 [95].

The Lyon Diet Heart Study is the largest clinical trial to examine the effects of ALA on CVD [96, 97]. In this randomized secondary prevention trial, an AHA Step 1 Mediterranean dietary pattern (high in ALA) reduced cardiac death and nonfatal MI by approximately 70%, and all coronary events by about 50% despite no improvement in lipids and lipoproteins. The authors attributed the benefits to the 68% increase in ALA intake (~1.7 g/day) compared to the control group. On the other hand, the AHA Science Advisory suggested that other differences between the two diet groups could have played a role in the reduction in CVD risk observed in the Lyon Diet Heart Study [98]. For example, in the Lyon Diet Heart Study, subjects in the experimental group were instructed to adopt a Mediterranean-type diet that contained more bread, root vegetables, and green vegetables, fish, fruit at least once daily, less red meat (replaced with poultry), and margarine supplied by the Study to replace butter and cream.

Despite the beneficial effects of ALA on coronary disease risk seen in observational studies and in the Lyon Diet Heart Study, a recent review questioned the cardiovascular benefits of plant-derived n-3 fatty acids, stating that there "was no high quality evidence to support the beneficial effects of ALA" with respect to eliciting reductions in all-cause mortality, cardiac and sudden death, and stroke [99]. The majority of evidence comes from epidemiologic data, and the one controlled clinical study conducted to date did

not specifically evaluate ALA effects. More high-quality clinical trials are needed that examine the effects of ALA on CVD outcomes before definite conclusions can be drawn regarding its role in the treatment and prevention of heart disease.

2.2. Eicosapentaenoic Acid and Docosahexaenoic Acid

The 1970s marked the beginning of an extensive scientific evaluation of the role of n-3 fatty acids in the development of CVD. The seminal studies of Dyerberg *et al.* [100] noted that coronary atherosclerotic disease was rare in Greenland Eskimos and prevalent in a Danish population. These scientists attributed this difference in the incidence of CHD to the high intake of marine oils by the Eskimos and, in particular, EPA and DHA. During the past 30 years numerous studies have demonstrated that these fatty acids may confer cardioprotective effects via multiple mechanisms of action. As shown in Figure 7, the effects of EPA and DHA on clinical outcomes (e.g., antiarrhythmic, TG-lowering, BP-lowering) occur in a time-dependent manner. Of importance is that the antiarrhythmic effect is achieved at relatively low doses of EPA and DHA. This is clinically important as arrhythmias are the cause of sudden cardiac death, the leading cause of cardiac death in the United States [101]. The effects of EPA and DHA on lowering TG, heart rate, and blood pressure all occur within months to years at doses that are consistent with current dietary recommendations. Fish and/or fish oil consumption has consistently been shown to reduce CHD death (~35%), CHD sudden death (~50%), and ischemic stroke (~30%). Modest benefits of fish and/or fish oil consumption also have been observed in regard to nonfatal MI, delayed progression of atherosclerosis, recurrent ventricular tachyarrhythmias, and postangioplasty restenosis [102].

Several large epidemiologic studies have demonstrated EPA and DHA intakes of 250–500 mg/day yield significant reductions in CHD mortality and sudden death [102]. Researchers have suggested that there is a threshold of effect where intakes above 900 mg/day do not elicit a greater decrease in risk [93, 102, 103]. The beneficial effects of increased EPA and DHA intake in the prevention of CVD have been examined in both primary and secondary prevention populations.

The results from the MRFIT trial found that individuals in the highest quintile of EPA and DHA had a 40% reduction in risk from cardiac death [104]; Data from the Nurses' Health Study showed that women in the highest quintile of EPA and DHA intake had a 31% lower risk of heart attack than those in the lowest quintile [105]. Participants in the Physicians Health Study who consumed fatty fish at least once a month had a ~50% reduction in risk of sudden death from MI; however, no associations between fish intake and reduction in incidence of MI were found [106]. Not all primary prevention studies have found a benefit of an increased intake of EPA and DHA. A 6-year prospective study from Finland, which included 21,930 men, found no benefit to EPA and DHA or ALA in reducing cardiac death [107]. The researchers questioned the external validity of these findings because the subjects were mainly middle-aged, smoking men, with high intakes of dietary fat. Also, this study was conducted in an area in

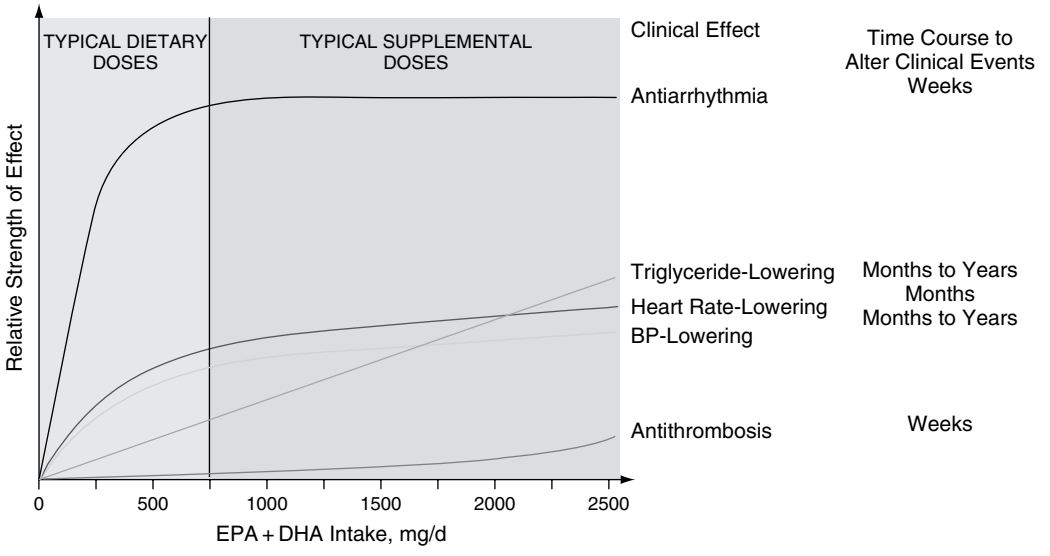

FIGURE 7 Schema of potential dose responses and time courses for altering clinical events of physiologic effects of fish or fish oil intake [102]. Reprinted with permission from the American Medical Association.

which mercury intake from fish is known to be high. Mercury levels can increase CVD risk and were not controlled for in the analysis.

There have been three large secondary prevention intervention studies where patients with CHD were given dietary advice to consume at least two servings of fatty fish a week (200–400 grams of fish) or given supplemental fish oil capsules (850 mg EPA and DHA and 1800 mg EPA). These interventions resulted in a 21–29% reduction in all-cause mortality [108], 45% reduction in sudden death from MI [108, 109], and 19% reduction in all coronary events [110].

Despite the significant evidence base reporting benefits of fish consumption in many populations, other studies have revealed that not all populations benefit from increased EPA and DHA consumption [111–114]. The Diet and Reinfarction Trial 2 (DART-2), a randomized clinical trial of patients with angina, was conducted to determine if fish or fish oil consumption would reduce risk of cardiac and sudden-death end points. The DART-2 Trial showed significantly higher mortality rates from sudden and cardiac death. The findings have been questioned because it is not clear how carefully subjects adhered to advice regarding increased fish consumption. In this trial, serum EPA levels were only measured in a small subset ($n = 39$) of the subjects at 6 months into the study [78].

The benefits of fish oil supplementation have been questioned in patients with implanted cardioverter/defibrillators (ICDs). Three fish-oil supplementation trials have been conducted in this population with mixed results. One trial found a significant trend favoring the use of fish-oil supplementation to prevent fatal ventricular arrhythmias; however, there was not enough statistical power to yield a significant result [115]. Another trial found that fish-oil supplementation did not reduce the risk of ventricular fibrillation/ventricular tachycardia and a potential adverse effect was seen in individuals with an ejection fraction less than 40% [114]. Finally, in the most recent trial, the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA), a protective effect attributed to fish-oil supplementation was not found in patients with ICDs [116]. Because of the discordant findings regarding increased EPA and DHA intake and patients with angina or ICDs, further studies are warranted.

Fish oil also has a marked hypotriglyceridemic effect in individuals with normal or elevated TG levels (≥ 2 mmol/l). A review of 21 studies that examined the effects of fish or fish oil on lipids and lipoproteins concluded that while the effects of EPA and DHA (0.1–5.4 g/day) on TC, LDL-C, and HDL-C are modest, TGs were reduced an average of 15%. TG were reduced with fish intakes as low as 0.9 servings per day, as high as 5.4 g/day, and with the greatest effect occurring when intake of EPA and DHA was greater than or equal to 2.6 g/day [117]. Also from this analysis, a dose-response relationship was reported. For every 1 g/day of fish oil, TG levels decreased 8 mg/dl. Individuals with elevated TG are more responsive to the TG-lowering effects of fish oil [118]; for every 10 mg/dl increase in baseline TG levels there was an additional 1.6 mg/dl decrease in TG with the consumption of EPA and DHA.

The effects of n-3 FA consumption on LDL-C levels were evaluated by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services. Data from 15 randomized clinical trials showed that n-3 FA consumption (ranging from 45 mg to 5.4 g of fish oil) led to a net increase of 10 mg/dl in LDL-C [119]. The increase in LDL-C levels may be due partly to an increase in LDL-C size as some [121, 122], but not all [120] studies have shown an increase in LDL-C particle size. It has been proposed that the change in LDL-C particle size relates to a patient's starting LDL-C particle size. Individuals with a Pattern B phenotype, defined as having a higher amount of small, dense LDL-C particles, will respond to fish oil supplementation with an increase LDL-C particle size, whereas individuals without this phenotype will not [120]. Fish-oil supplements can be an effective treatment for patients with hypertriglyceridemia, although monitoring by a physician is essential to ensure that LDL-C levels are closely observed [91].

One area of concern when recommending increased fish intake pertains to the issue of environmental contaminants such as mercury (Fig. 8). A majority of the fatty fish consumed are smaller with a shorter lifespan and thus have lower mercury concentrations than larger, longer-lived fish such as shark and swordfish [102]. It is also important to note that high consumption of certain lean fish high in mercury plays an important role in increased mercury accumulation in humans [123]. Therefore, emphasis on high omega-3 fatty acid fish (that is low in mercury) is recommended.

There have been two studies that observed higher risk of CVD with increased mercury intake; however, fish consumption in these situations still was cardioprotective [124, 125]. Moreover, recent reports describe the benefits of fish consumption far outweigh the risks [102, 124, 125]. Another strategy for increasing EPA and DHA consumption is fish-oil supplements as they are cost effective, convenient, and contain negligible quantities of environmental contaminants [126]. This is a strategy recommended for individuals who do not eat fish or those who need high doses of marine-derived omega-3 fatty acids. The best guidance is to follow FDA guidelines as well as state and local advisories for safe fish consumption.

In conclusion, long-chain n-3 fatty acids have been shown to have significant cardioprotective benefits in observational studies and secondary prevention trials. This research supports current dietary recommendations for two fish meals per week, preferably fatty fish. The efficacy of EPA and DHA in primary prevention along with the

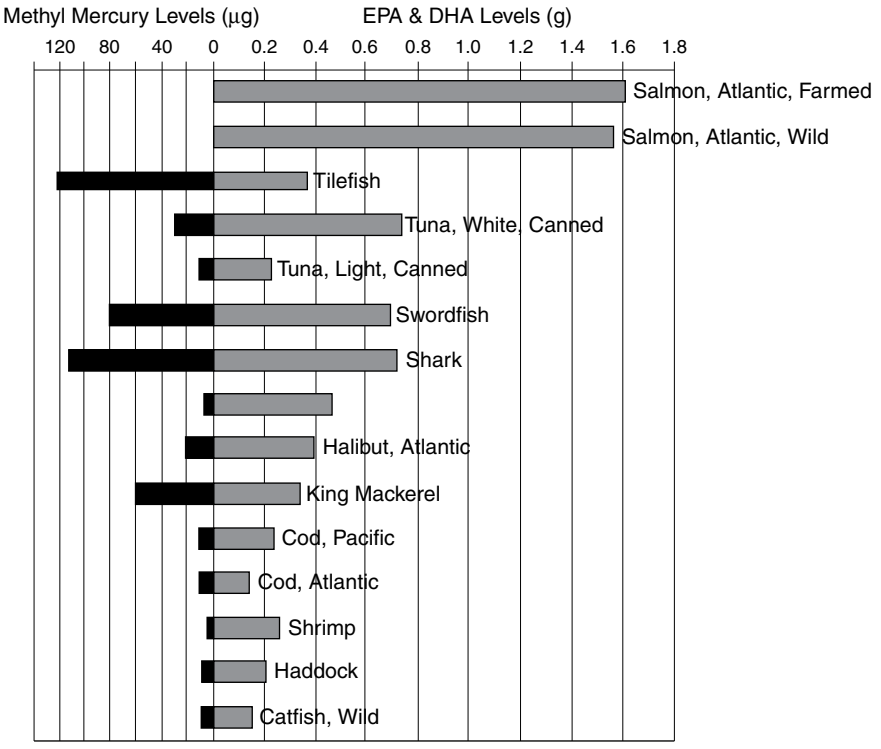

FIGURE 8 Comparison of EPA and DHA content of fish with methyl mercury levels (3-oz serving) [10, 288].

cardioprotective effects of ALA need to be clarified and explored further via randomized clinical trials.

III. DIETARY CARBOHYDRATE

The RDA for glucose is 130 g/day. This level of consumption is enough to prevent ketosis and provide enough glucose to the brain for proper function. The AMDR for carbohydrate is 45–65% of total energy, with no more than 25% of total energy coming from added sugar [12]. The 2005 Dietary Guidelines for Americans do not recommend specific intakes for added sugar, but rather recommend choosing and preparing foods and beverages with little added sugar; the Guidelines also suggest a discretionary allowance for various energy levels (e.g., 32 g/day [8 tsp] suggested for a 2000-kcal diet) [22]. The NCEP ATP III [13] recommends that 50–60% of energy come from carbohydrate.

When discussing different types of carbohydrates, scientists historically used the terms *complex* versus *simple* carbohydrates. We have some understanding of the role of some carbohydrate food sources in CVD risk; thus this simple terminology needs further explanation. Many foods that are included in a high-carbohydrate diet, such as fruits and vegetables, breads and cereals, and legumes, contain multiple compounds that could favorably affect CVD risk. In this section, a few of the active areas of scientific investigation associated with carbohydrate and reduction of CVD risk are covered, including low-carbohydrate diets and the role of glycemic index, dietary fiber, and soluble fiber.

A. High-Carbohydrate, Low-Fat Diets

Replacing energy from SFA with carbohydrate is one strategy for reducing SFA to decrease LDL-C. The resulting high-carbohydrate, low-fat diet, when not accompanied by weight loss, decreases HDL-C and typically increases TG, especially on low-fiber diets [127]. This is particularly problematic for people with insulin resistance and accompanying dyslipidemia characterized by low HDL-C and elevated TG [128]. A high-carbohydrate, low-fat diet also has been shown to increase plasma glucose and insulin in individuals with type 2 diabetes [129] and healthy women [130]. On the other hand, it can be argued that a high-carbohydrate, low-fat diet facilitates a reduction in energy intake [131] and promotes weight loss [132]. In the Women's Health Initiative Dietary Modification Trial [21], subjects in the intervention group who were instructed on a diet that provided 20% of energy from fat maintained a lower weight (1.9 kg, $p < 0.001$) during an average 7.5 years follow-up period than did women in the control group. In this study, it is important to point out that the women did not achieve the 20% energy as fat target and

consumed 29.8% of energy from fat. However, they did decrease total fat intake from 38.8% of energy. An extreme reduction in fat (10% energy) and thus a much higher carbohydrate (70–80%) diet has been advocated by some [134]. This latter approach has been shown to be effective when combined with other intensive lifestyle changes (e.g., stress management and aerobic exercise), in achieving athero-regression as measured by percent change in diameter stenosis [135]. Unfortunately, very low fat diets can be very hard to follow in free-living situations, and compliance with the diet significantly decreases over time (by 50%) [20].

A higher carbohydrate diet does not always increase TG levels. The OmniHeart Trial [51] and Dietary Approaches to Stop Hypertension (DASH) Diet studies [136, 137] both provided diets relatively high in carbohydrate (58% of energy), and no significant increase in TG was observed. This is most likely due to the type of carbohydrate consumed as well as dietary fiber. The diets tested in the OmniHeart Trial and DASH Diet studies were high in fruits, vegetables, and whole grains, which yielded diets containing at least 30 grams of fiber/day (2100-kcaldiet) [48].

B. Low-Carbohydrate Diets

Although low-carbohydrate diets have been around for decades, it has only been recently that their popularity has increased, principally for both weight loss and, in turn, prevention of cardiovascular disease. There is no standard definition of a low-carbohydrate diet, but it is generally accepted when a diet contains less than 50 grams of carbohydrate or less than 10% of energy from carbohydrate, it is considered a low-carbohydrate diet [138]. When compared to low-fat diets, the low-carbohydrate diets have been shown to elicit greater weight loss at 6 months (–7.3 lb versus −3.1 lb) but at 12 months weight loss is similar between diets [20, 139]. The mechanism by which low-carbohydrate diets promote greater weight loss at 6 months is unclear however several factors have been implicated. These include improved insulin/glucose control, increased thermic effect of food, enhanced maintenance of basal metabolic rate, ketosis-induced appetite suppression, and increased water loss [140]. The reduced weight loss in subjects on low-carbohydrate diets between months 6 and 12 is likely due to decreased dietary compliance [20].

Low-carbohydrate diets have been shown to reduce triglyceride levels and increase HDL-C [139]. The debate surrounding the effectiveness of low-carbohydrate diets in the treatment and prevention of cardiovascular disease centers on the effect of these diets on total cholesterol and LDL-C due to the increased intake of SFA that accompanies low-carbohydrate diets. Recent work by Krauss *et al.* [141] found that in overweight or obese men, reductions in carbohydrate intake (26% of total energy) versus 54% energy from carbohydrate along with controlled weight loss reduces the proportion of small, dense LDL-C particles. Importantly, this effect is primarily driven by changes in dietary carbohydrate. Of note also is that although there is an effect of dietary carbohydrate on LDL pattern B phenotype, this is attenuated after weight loss. Another dietary factor that affects the lipid and lipoprotein responses to a low-carbohydrate diet is soluble fiber. Wood *et al.* [142] found that the addition of 3 grams of supplemental soluble fiber (Konjac-mannan) to a low-carbohydrate diet reduced LDL-C by 14% while still reducing triglycerides and increasing HDL-C. Potentially one of the most important findings regarding a low-carbohydrate diet is the improved clearance of triglyceride-rich chylomicrons [138]. Chylomicron remnants increase risk for coronary disease [143]. Thus, low-carbohydrate diets appear to be of benefit for short-term weight loss (6 months). In addition, they beneficially affect triglycerides and HDL-C compared with higher carbohydrate diets, as well as postprandial TG clearance.

C. Glycemic Index and Glycemic Load

Carbohydrates differ in terms of their effects on glucose metabolism [144]. Carbohydrates can be classified according to their blood glucose-raising effects using the glycemic index (GI). Low-GI foods, such as mature beans and green vegetables, elicit less of a glycemic response than high-GI foods, such as potatoes and ready-to-eat cereals. Independent of weight loss, diets composed of low-GI foods increase insulin sensitivity [145, 146] and decrease total serum cholesterol [146] and LDL-C [145] in people with type 2 diabetes. LDL-C decreased 6% more in subjects following a low-GI diet compared to a high-GI diet [145]. These findings illustrate the importance of considering not only the macronutrient composition of the diet, but also the type of carbohydrate consumed within the context of a high-carbohydrate, low-fat diet.

A review of 13 intervention studies that examined the effects of glycemic index on triglycerides (5–20% reduction), LDL-C (>5% reduction), and total:HDL-C ratio (>5% reduction) consistently showed the benefit of a lower GI diet [147]. In general, foods high in soluble fiber have a low GI; however, this is an oversimplification because food preparation and consumption of a specific food in a mixed meal can alter the GI. Thus, a mixed meal can have a low GI with the selection of certain foods that elicit a high glycemic response when tested individually. Because of the complexity of implementing the GI, it likely will be difficult for consumers to adopt at the present time with currently available foods and contemporary lifestyle practices. Furthermore, the concept of glycemic index must also address the role of other nutrients in a way that is consistent with current dietary recommendations. For example, some low-GI foods are high in total fat, SFA,

and sugar and therefore should be limited. This example elucidates the importance of not just considering glycemic index but also considering other nutrient and dietary factors. Thus, it is apparent that many questions remain about implementation of glycemic index in practice.

The glycemic load is a measure of both type and amount of carbohydrates while the glycemic index is a measure of only carbohydrate type. Glycemic load is defined as the mathematical product of the carbohydrate amount and glycemic index. This has been shown to be a more effective classification method for carbohydrates. In a prospective analysis of carbohydrate intake using data from the Nurses' Health Study the glycemic load of the diet was directly associated with CHD. The upper two quintiles for glycemic load had relative risk ratings of 1.51 and 1.98. This relationship was most evident among women with a BMI above 23 [148]. An analysis [149] of 244 healthy women enrolled in the Women's Health Study (WHS) showed a strong correlation between high-sensitivity C-reactive protein (CRP) levels and glycemic load. This again suggests a relationship between type and amount of carbohydrate consumed and cardiovascular disease, specifically in middle-aged women. In contrast, the Zutphen Elderly Study [150] found no relationship between a high-GI diet and CHD in elderly men.

In a year randomized clinical trial, subjects with elevated insulin levels following a large oral dose of glucose lost more weight after 18 months on a low-glycemic-load diet compared with a high-glycemic-load weight-loss diet (12.76 lb versus 2.64 lb). Subjects with normal insulin levels lost similar amounts of weight with either low-glycemic-load or low-fat diets [151]. Changes in cardiovascular risk factors were diet specific. The low-glycemic-load diet resulted in greater reductions in TG (–21.2 mg/dl versus –4.0 mg/dl) and an increase in HDL-C (1.6 mg/dl versus –4.4 mg/dl), whereas the low-fat diet group experienced a much greater reduction in LDL-C (–5.8 mg/dl versus –16.3 mg/dl). However, another randomized clinical trial [152] that compared the effects of a low-glycemic-load diet versus a low-fat diet on lipids and lipoproteins found the only difference in lipid changes between diet groups to be TG, which decreased more in the low-glycemic-load group while LDL-C and HDL-C changes did not differ between diet groups. In this study, the low-glycemic-load group also experienced a 50% reduction in CRP, whereas CRP remained unchanged in the low-fat diet group. A 12-month randomized trial that compared low-glycemic-load compared to high-glycemic-load diets found no difference between diets with respect to TG, TC, LDL-C, and HDL-C [153]. Thus, further work is needed before conclusions are made regarding the importance of glycemic load for the treatment and prevention of CVD. Nonetheless, research to date suggests that a low-glycemic-load diet is more efficacious in individuals with insulin resistance.

D. Dietary Fiber

An abundance of evidence supports a beneficial association between dietary fiber intake and risk of CVD [154]. Dietary fiber is found naturally in fruits, vegetables, whole-grain cereals, and legumes. Fiber-fortified foods and supplements also are available that are intended to increase dietary fiber [155, 156]. The DRI Report on Macronutrients set the AI for dietary fiber at 38 g/day and 25 g/day for men and women, respectively [12]. This translates into 14 grams of fiber per 1000 kcal of energy consumed. Numerous epidemiologic studies support the cardioprotective effect of dietary fiber. A group of researchers recently pooled data from 10 prospective cohort studies in the United States and Europe and reported that each 10 g/day increment of dietary fiber yielded a 23% reduction in risk of coronary mortality and 14% reduction in all coronary events [157]. The association was strongest with cereal fiber compared to fruit/vegetable fiber. Increased fiber intake via whole grains also has been associated with improved insulin sensitivity [158].

E. Soluble Fiber

Soluble fiber, including oat bran, psyllium, guar gum, and pectin, has been shown to reduce CVD risk through its action on lipids and lipoproteins and glucose metabolism. Soluble fiber has numerous properties that mediate its cholesterol-lowering effects, such as binding bile acids, increasing gastrointestinal tract viscosity, and inhibiting cholesterol synthesis following fermentation in the colon [159, 160]. NCEP ATP III guidelines recommend 10–25 grams of soluble fiber each day using evidence that a dietary intake of 5–10 grams of soluble fiber per day has been shown to lower LDL-C levels by 5% [13]. Observational data from the Los Angeles Atherosclerosis Study showed that increased fiber intake (namely pectin) had a strong inverse relationship with intima-media thickness progression in otherwise healthy individuals [161].

A meta-analysis of 67 controlled human trials [162] determined that various soluble fibers (2–10 g/day) modestly reduced total and LDL-C and did not affect HDL-C cholesterol and TG levels. A randomized trial examining the effects of increased fiber in normolipidemic participants found that 3.5 g/day soluble fiber (29.5 g/day total fiber) yielded a 12.8% decrease in LDL-C. This effect was attributed to the differences in total and soluble fiber intake because no differences in intake of other macronutrients were found [163].

The effects of different food sources of soluble fiber on lipids and lipoproteins have been studied. Incorporating 15–115 grams of beans (navy or pinto) has been shown to reduce both total and LDL-C by 15–23% and 13–24%, respectively [160]. Arguably the most commercialized source of soluble fiber, oats (rolled or bran), are known for their cholesterol-lowering properties [164]. Oats contain

β-glucan, which has been shown to reduce total cholesterol along with fasting glucose and insulin [165]. In addition, soluble fiber has been shown to lower glucose and insulin levels in healthy individuals [166] and favorably affect insulin sensitivity in individuals with diabetes [167] and moderate hypercholesterolemia [168].

A diet that meets current recommendations for dietary fiber that is high in both total and soluble fiber can be achieved by consuming recommended amounts of fruits (four servings), vegetables (five servings), and whole grains (at least 3-oz, but preferably 6 oz equivalent servings). This level of dietary fiber has been shown in observational studies to reduce cardiovascular events and in clinical trials to reduce LDL-C.

IV. DIETARY PROTEIN

Epidemiologic and controlled clinical studies have shown benefits of dietary protein on CVD risk, although some studies suggest an adverse relationship. Data from the Nurses' Health Study found high protein intakes (up to 24% of total energy intake), which included animal and plant protein, were associated with a significantly reduced risk of CVD (RR = 0.75; 95% CI: 0.61, 0.92) [92]. Likewise, in the largest randomized controlled clinical trial to date, the OmniHeart Trial, found that a high-protein diet (25% of energy intake) reduced the estimated 10-year risk (5.8% lower) for CHD compared with a high-carbohydrate diet (58% of energy intake) [51]. However, in a 12-year follow-up study of middle-aged Swedish women participating in the Women's Lifestyle and Health Cohort, a diet low in carbohydrate and high in protein (assessed from protein and carbohydrate intakes according to deciles of individual energy intake) was associated with a higher total and CVD mortality [169]. In addition, in the Greek component of the European Prospective Investigation into Cancer and Nutrition, prolonged consumption of a low-carbohydrate, high-protein diet but not a high-protein diet alone was associated with an increase in total mortality [170]. This study suggests that marked reductions in carbohydrate together with an increase in dietary protein are problematic.

A. Animal Protein

There is uncertainty whether animal protein, particularly from meat, affects CVD risk. In a prospective study that examined whether overall dietary patterns derived from a food frequency questionnaire (FFQ) predicted risk of CHD in men found a dietary pattern including high intakes of red meat and processed meat was associated with a higher risk for CVD compared lower intakes (RR adjusted for lifestyle variables and fat intake: 1.43 [1.01, 2.01]) [171]. In contrast, the 2-year randomized Cholesterol Lowering Atherosclerosis Study found a reduction in new coronary artery lesions among those with increased dietary protein (lean meat and low-fat dairy) compared with subjects who decreased their protein intakes [172]. The early work that reported associations between animal protein and CVD mortality [173] likely was confounded by correlations between protein intake and dietary SFA and cholesterol [174].

The dietary guidance that recommends a reduction in SFA and cholesterol has been interpreted by some to restrict red meat consumption. Several studies, however, have been conducted to evaluate the effect of blood cholesterol-lowering diets containing lean red meat on lipids and lipoproteins. In three randomized controlled trials [287–289] conducted with hypercholesterolemic subjects, lean red meat, fish or lean poultry elicited similar effects on TC, LDL-C, and TG or HDL-C (Table 3). In addition, a small, recent, 8-week parallel study conducted in Australia found that markers of oxidative stress and inflammation were not elevated when energy from carbohydrate was partially replaced with 200 g/day of lean red meat [175]. These data suggest that lean red meat can be included in a blood cholesterol-lowering diet. Moreover, a diet that includes lean red meat also must meet current dietary recommendations.

B. Soy (Vegetable) Protein

Studies conducted in the 1970s and 1980s found that a diet rich in soy decreased TC by 20%–25% in hyperlipidemic patients [176–178]. In 1995, a meta-analysis of clinical trials of soy intakes (ranging between 31 and 47 g/day) reduced TC by 23.2 mg/dl (9.3%), LDL-C by 21.7 mg/dl (12.9%), and TG by 13.3 mg/dl (10.5%), with the greatest changes in serum TC and LDL-C related to initial serum cholesterol concentrations. There was a trend toward a 1.2 mg/dl (2.4%) increase in HDL-C [179]. Results of the 6 week randomized controlled OmniHeart trial, found that a high protein diet (25% energy (12 servings of plant protein/day)) reduced HDL-C (–2.6 mg/dal) over a six week period compared to a high carbohydrate (58% energy (5.5 servings of plant protein/day)) diet (–1.4 mg/dl) and a high unsaturated fat (31% energy (5.5 servings of plant protein/day)) diet (–0.3 mg/dl)) [51].

A reevaluation of the prior scientific evidence of soy protein effects on lipids and lipoproteins, as well as soy isoflavones, was conducted by Sacks *et al.* and published as an AHA Science Advisory [180]. Twenty-two randomized trials (conducted between 1998 and 2005) were included that evaluated isolated soy protein with isoflavones compared with casein or milk protein, wheat protein, or mixed animal protein. In these studies, soy protein intake ranged between 25 and 135 g/day with the range of soy isoflavones between 40 and 318 mg. A very modest 3% reduction in LDL-C was found due to soy proteins; soy isoflavones generally had no effect on LDL-C [180], despite large

TABLE 3 Dietary Cholesterol Changes Following Consumption of Varying Protein Food Sources

Author	Year	Subjects	Design		Results			
					TC	LDC-C	TG	HDL-C
Beauchesne-Rondeau, E. *et al*. [287]	2003	Hypercholesterolemic men (TC: >5.2 mmol/l; LDL-C: >3.4 mmol/l)	RCT: 26 days ($n = 17$ each; 50 years) of lean meat (~180 g) versus lean poultry (~180 g) versus fish (~270 g). 6-week washout period in between each diet. 69% animal protein and no milk products allowed: given 600 mg Ca + 125 IU vitamin D.	Lean beef	↓ 18%	↓ 7%	↓ 19%	
				Lean poultry	↓ 8%	↓ 9%	↓ 25%	
				Fish	↓ 5%	↓ 5%	↓ 20%	
Davidson, M. *et al*. [288]	1999	Hypercholesterolemic men and women (LDL-C: 3.37–4.92 mmol/l; TG: <3.96 mmol/l)	RCT: 36 days lean white meat ($n = 102$, 55 years) or lean red meat ($n = 89$, 57 years). 170 g (6 oz) for 5–7 days/week.	Lean red meat	NS	↓ 1.7%	—	↑ 2.3%
				Lean white meat	↓ 1.8%	↓ 3%	↓ 0.5%	↑ 2.4%
Hunninghake, D. *et al*. [289]	2000	Hypercholesterolemic men and women (LDL-C: 3.37–4.92 mmol/l; TG: <3.96 mmol/l)	RCT: 36 weeks lean red meat ($n = 72$, 57 years) versus lean white meat ($n = 73$, 56 years).	Lean red meat	↓ 0.9%	↓ 1.9%	NS	↑ 2.8%
				Lean white meat	↓ 1.2%	↓ 2%	NS	↑ 2.2%

RCT, randomized controlled trial.

increases in blood isoflavone concentrations. A recent report from Agency for Healthcare Research and Quality of the soy protein literature demonstrated a decrease in TC of 6 mg/dl (2.5%), with a median decrease in LDL-C of 5 mg/dl (3%). There was no effect of isoflavones [181]. Figure 9 presents the changes in LDL-C in response to soy protein and soy isoflavones as a function of baseline LDL-C. It can be seen in Figure 9 that those with high baseline LDL-C have a greater LDL-C lowering response, and there is a dose-response relationship between soy protein intake and LDL-C lowering.

A subsequent meta-analysis was published [182], including 11 trials on soy protein containing isoflavones, in addition to the effects of soy protein containing enriched and depleted isoflavones. Compared with animal protein (containing no isoflavones), soy protein (containing no isoflavones) decreased TC by 7.7 mg/dl (3.6%) and decreased LDL-C by 3.9 mg/dl (2.8%); soy protein (plus enriched isoflavones) lowered LDL-C by 7.0 mg/dl (5%) and increased HDL-C by 1.6 mg/dl (3%) [182]. The effects of isoflavones (after controlling for soy protein intake) were found to reduce TC by 3.9 mg/dl (1.8%) and decrease LDL-C by 5 mg/dl (3.6%) compared with soy protein (containing no isoflavones). Reductions in LDL-C were greatest in subjects with high versus normal cholesterol levels; however, there was no association between the changes in LDL-C levels and isoflavone intake. Although it was concluded that 102 mg ingested soy-derived isoflavones (independent of ingested soy protein) can lower TC and LDL-C, this intake is approximately double current intakes in Japan. Consuming 42 mg soy (which included 6 mg isoflavones—a very low content) also can improve LDL-C and HDL-C; however, this level of soy protein intake is quite large, representing at least 50% of the average daily total protein intake in the United States [182]. Moreover, ingestion of large amounts of isoflavones is necessary to identify any benefits on the lipid profile.

In addition to the effects on lipids, a recent 8-week crossover trial was conducted among postmenopausal women with metabolic syndrome comparing the DASH diet (17% energy from protein) versus soy protein (replaced one serving of red meat with soy protein—30 g) versus soy nut (replaced red meat with soy nuts—30 g) [183]. The soy nut and soy protein diets decreased the inflammatory markers E-selectin and CRP, compared with the DASH diet; IL-18 was lower on the soy nut diet, and nitric oxide production improved. In contrast, a recent randomized controlled trial in hypercholesterolemic patients found varying diets containing soybeans, soy flour, or soy milk (15% of energy as protein—7.5% of energy as experimental protein; 37.5 g/day) had no effect on blood pressure, vascular endothelial function, or CRP concentrations [184]. Previous

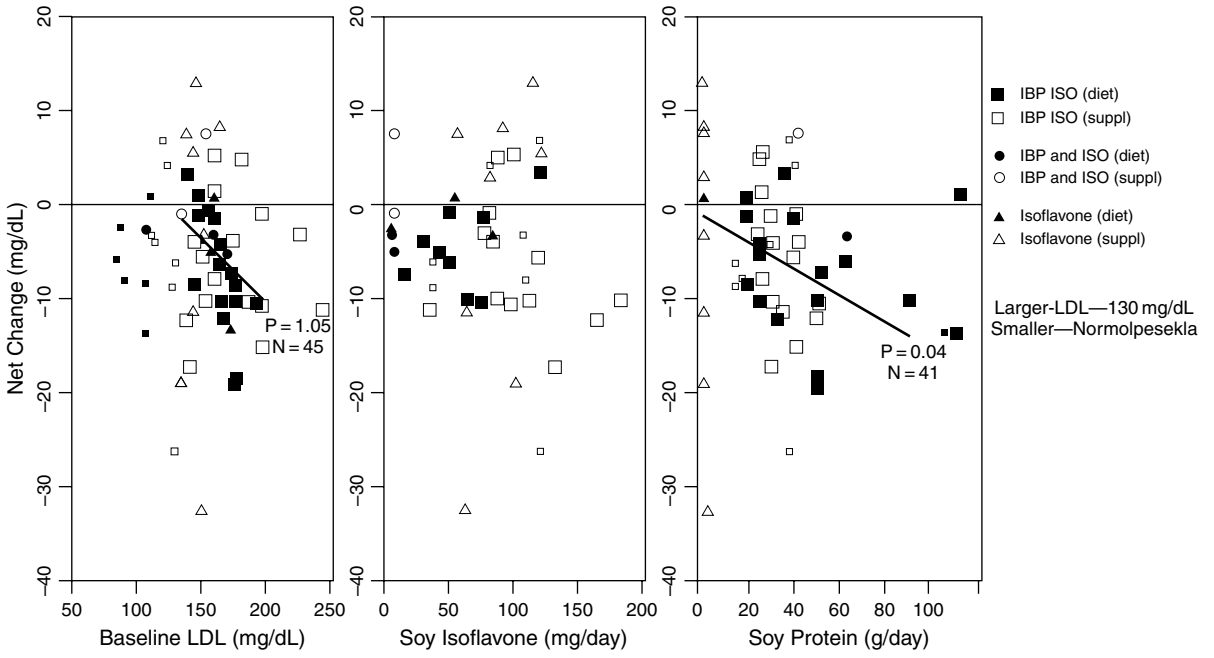

FIGURE 9 LDL changes after soy products consumption. (1) Net change of LDL-C with soy product consumption compared to control, by baseline level, isoflavone content, and soy protein content. Studies without non-soy control are not included. Studies without data on isoflavone or protein content are omitted from relevant graphs. (2) IBP w/ Iso, soy protein with isoflavones; IBP w/o Iso, soy protein without isoflavones; suppl, supplement. (3) Dashed lines represent adjusted regressions for studies with sufficient data for regression. Regression lines are drawn only within the range of independent variable (*x*-axis) data examined. *P*-values and number of studies included in regressions are shown. Both regression lines drawn are for all studies with abnormal baseline LDL. Reprinted with permission from [181].

controlled studies also have reported that soy intake inhibited LDL oxidative susceptibility [185, 186] and improved arterial compliance [187].

The evidence is conflicting about the role of soy protein in CVD risk reduction, and consumption of large amounts of isoflavones may be required to provide further benefits. Further trials are required investigating the isoflavone component on CVD mortality.

In summary, these studies highlight the favorable effect that both animal and plant proteins have on CVD risk factors. Of specific interest are their effects on TG and HDL-C, as well as inflammatory markers and blood pressure. A reduced-fat, high-protein (18–25% energy from protein) diet may be an alternative approach to the traditional reduced-fat, high-carbohydrate diets. With respect to soy protein, large intakes of soy protein (more than half the daily protein intake) may lower LDL-C by a few percent when it replaces dairy protein or a mixture of animal proteins [180]. Moreover, soy proteins with isoflavones do not appear to further benefit CVD risk reduction and therefore isoflavone supplement use is not recommended. In addition, soy protein also may be used to increase total dietary protein intake and to reduce carbohydrate and fat intake [180]. Soy products (e.g., tofu, soy butter, and soy nuts) may be beneficial to health because of their high unsaturated fat content, fiber, vitamins, minerals, and low content of saturated fat [180]. Further studies are required investigating the effect of high-protein diets on CVD risk factors. Studies are needed with both plant and animal protein sources to determine whether their effects on CVD risk and risk factors differ. This information will be important for future dietary guidance about protein.

V. ALCOHOL

There is accumulating evidence demonstrating that moderate alcohol consumption reduces CHD risk, and the pattern of drinking has important implications for various CVD risk factors [188–190], clinical outcomes [191–194], and mortality [195–197]. Consumption of one to three drinks a day has been shown to lower risk of CHD by 10–40% compared with those who abstain; the majority of studies have identified a lower risk with up to three alcoholic drinks a day [198–201]. The epidemiologic evidence suggests a J- or U-shaped relationship between alcohol and CHD [202–204], such that moderate alcohol consumption appears more beneficial than no alcohol or excessive alcohol consumption.

The mechanisms underlying alcohol and CVD risk have been a result of some beneficial effects in hemostatic factors [205, 206]; however, the putative benefits

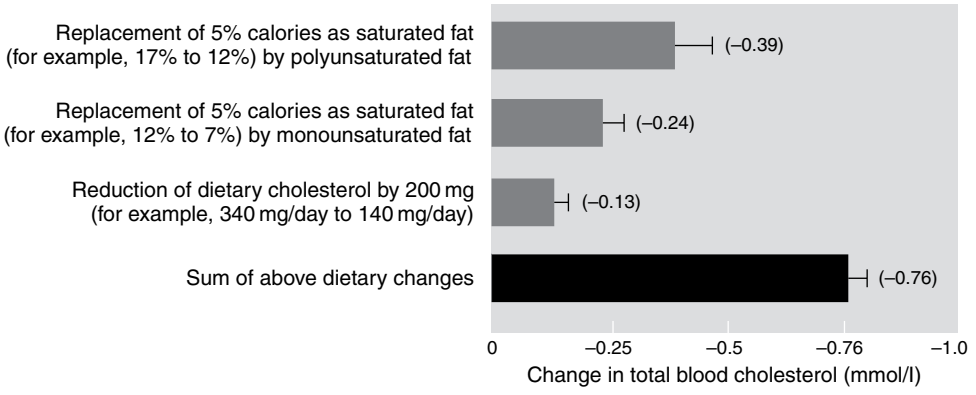

FIGURE 10 Mean (SE) changes in blood total cholesterol concentration associated with replacing dietary saturated fat by polyunsaturated and monounsaturated fats and with reducing dietary cholesterol [26]. Reprinted with permission from the *British Journal of Medicine*.

have been mainly credited to an increase in HDL-C [207–209], thus inhibiting LDL oxidation during the atherogenic process. In a meta-analysis of 42 trials investigating alcohol consumption and HDL-C, a 24.7% reduction in CHD was found following consumption of 30 g alcohol/day, directly attributable to increased HDL-C levels (3.99 mg/dl) [210].

With respect to specific beverage type, early studies have suggested that in wine-drinking countries, there was less coronary artery disease (CAD) incidence compared to beer- or liquor-drinking countries [211]; with later international comparison studies confirming this [212, 213]. Particularly in France, the markedly low incidence of CHD, despite intake of a high-fat diet, has been attributed to the consumption of red wine containing high levels of polyphenolic compounds. This was termed the ''French paradox,'' referring to the observation that France has the highest wine intake, the highest total alcohol intake, yet the second lowest CHD mortality rate [212, 213]. The mechanisms underlying this lower CHD incidence have been associated with antioxidant phenolic compounds or antithrombotic substances in red wine [213–215].

A recent review, however, reported that prospective population studies provide no consensus that wine has additional benefits, and various studies show benefit for all three major beverage types (wine, beer, and liquor) [216]. In contrast to this, controlled trials have found moderate consumption of red wine to inhibit oxidative modification of LDL-C [217, 218], improve coronary blood flow [219], and improve markers of inflammation [220], as well as reverse the impaired endothelial function caused by cigarette smoking [221].

Therefore, further randomized studies are required identifying benefits of other alcoholic beverages on CVD risk factors, and to assess whether moderate wine consumption is more protective than these beverages against cardiovascular risk.

Recommendations for alcohol consumption by the NCEP panel have stated that no more than two drinks per day for men and no more than one drink per day for women should be consumed. A drink is defined as 5 oz of wine, 12 oz of beer, or $1^1/_2$ oz of 80-proof whiskey. Persons who do not drink should not be encouraged to initiate regular alcohol consumption [13].

VI. DIETARY CHOLESTEROL

Cholesterol plays an important role in steroid hormone and bile acid biosynthesis and serves as an integral component of cell membranes. There is no biological requirement for dietary cholesterol because all tissues synthesize a sufficient amount of cholesterol to meet metabolic and structural needs. The DRI Report for Macronutrients recommended that cholesterol intake be as low as possible because of the dose-response relationship between dietary cholesterol and total and LDL-C [12, 26]. The Dietary Guidelines for Americans, 2005, as well as AHA, recommend less than 300 mg/day for normocholesterolemic individuals. NCEP ATP III recommends less than 200 mg/day for those with CHD or elevated LDL-C [13, 22].

There is some epidemiologic evidence demonstrating a relationship between dietary cholesterol and CVD risk [222]. Among Japanese women, one to two eggs per week was associated with a 12% lower all-cause death rate, with a trend toward a lower mortality due to stroke, ischemic heart disease (IHD), and cancer, compared with women consuming 1 egg per day [222]. In contrast, among 117,933 subjects in the United States, no relationship was found between consumption of 1 egg or fewer per day and the risk of IHD or stroke [33]. The Framingham Heart Study reported that egg consumption was not related to CHD [223] and was not related to serum cholesterol levels [224].

In normolipidemic healthy young men, subjects were randomized to consume either a low-cholesterol diet ($n = 15$, 3 egg whites: total intake of cholesterol 174 mg/day) or a high-cholesterol diet ($n = 12$, 3 whole eggs: total intake of

cholesterol 804 mg/day) for 15 days. Compared with the low-cholesterol diet group, the high-cholesterol diet group had higher serum TC (135 mg/dl versus 181 mg/dl), LDL-C (85 mg/dl versus 117 mg/dl), and HDL-C levels (35 mg/dl versus 50 mg/dl). Triglyceride and Lp(a) concentration did not differ [225].

In a meta-analysis of 395 metabolic ward trials investigating the importance of dietary fatty acids and dietary cholesterol in serum TC, LDL-C, and HDL-C, it was found that isoenergetic replacement of saturated fats (10% of dietary energy) by complex carbohydrates was associated with a decrease in TC by 20 mg/dl; replacing carbohydrates by PUFA (5% energy) would further reduce TC by 5 mg/dl. A reduction of 200 mg/day in dietary cholesterol was associated with a further reduction in TC of 5 mg/dl. The sum of these isoenergetic changes is displayed in Figure 1, indicating a reduction in TC by 29 mg/dl (99% CI: 0.67, 0.85) and LDL-C by 24 mg/dl and an increase in HDL-C by 4 mg/dl [26]. On the basis of this meta-analysis, dietary cholesterol elicits a small hypercholesterolemic effect that is less than that of saturated fat.

In another meta-analysis of 17 trials, consumption of dietary cholesterol increased the ratio of TC:HDL-C concentrations by 0.02 (95% CI: 0.010, 0.030). Furthermore, consuming approximately 200 mg/day of cholesterol (equivalent to one egg per day) increased the ratio of TC:HDL-C by 0.04 units, TC by 4.3 mg/dl, LDL-C by 3.9 mg/dl, and HDL-C by 0.6 mg/dl [226]. This effect was independent of other dietary factors such as type and amount of fat.

Collectively, the evidence shows that dietary cholesterol plays a role in modifying CVD risk; however, the effects on total and LDL-C are relatively modest. Nonetheless, decreasing dietary cholesterol would be expected to reduce the risk of CHD, especially in subgroups of individuals who are responsive to changes in cholesterol intake [227].

VII. PLANT STEROLS/STANOLS

Phytosterols are found in seed oil (e.g., sunflower oil and maize oil), fruits, vegetables, legumes, cereals, and some nuts. Although more than 40 phytosterols have been identified, β-sitosterol, campesterol, and stigmasterol are the most abundant and are the most effective at reducing cholesterol levels. Stanols are saturated molecules produced by the hydrogenation of sterols but are less abundant in nature [228]. The mechanisms by which plant sterols and stanols lower cholesterol levels involve the displacement of cholesterol from micelles, thus reducing intestinal cholesterol absorption and increasing fecal cholesterol excretion [229, 230].

Several nested case-control studies have found conflicting results between plasma sitosterol concentrations and CHD [231, 232]. Because nested case-control studies involve subsamples of participants in prospective studies, biological samples collected prior to onset of disease can be analyzed as a measure of exposure prior to onset of disease. Likewise, biological samples are analyzed in a matched group of disease-free controls. Thus, in these three nested case-control studies, the plasma for determination of sitosterol was collected prior to onset of disease for the cases. In the Prospective Cardiovascular Munster (PROCAM) study, men who suffered a coronary event within the previous 10 years had higher plasma sitosterol concentrations compared with those who had no event (0.19 mg/dl versus 0.17 mg/dl), with a 1.8-fold increased risk of coronary events in subjects with sitosterol levels above 0.21 mg/dl [231]. In contrast the Longitudinal Aging Study Amsterdam (LASA), plasma concentrations of all plant sterols were lower in those with CHD versus those free of CHD (e.g., sitosterol: 0.29 mg/dl versus 0.34 mg/dl); yet higher plasma concentrations of sitosterol were associated with a 28% reduction in CHD risk. The odds ratio with a twofold increase in sitosterol was associated with a 22% decrease in CHD risk [232]. On the other hand, the EPIC-Norfolk Population study, which compared 373 CAD cases with 758 controls, found that there was no difference in sitosterol between CAD cases and controls (0.21 mg/dl versus 0.21 mg/dl). However, there was a 21% lower risk (NS) for future CAD in the highest tertile of sitosterol concentration after adjusting for traditional risk factors [233]. Because these plasma sitosterol concentrations are similar to what was found in the PROCAM men, it appears that higher sitosterol concentrations, such as those found in the LASA study (approximately $>$0.34 mg/dl), may be necessary to achieve any sort of reduction in CHD risk in subjects initially free of the disease.

Numerous clinical studies conducted with hypercholesterolemic subjects, individuals with type 2 diabetes, and healthy adults and children have shown that consumption of 2–3 g/day of plant sterols or stanols lowers plasma LDL-C by 6–15% [13, 234]. Studies that examined sterol-enriched foods (spreads, low-fat yogurt, bakery products) in healthy subjects found that consumption of 1.6–3.2 g/day of sterols for 4 weeks to 1 year reduced TC 4–8.9% and LDL-C 6–14.7% [32, 235–238].

Some [236, 239], but not all [237, 240, 241], studies have found a decrease in serum antioxidant levels (corrected for TC and TG levels) (range of decrease ~6–14%) with sterol/stanol intakes ranging between 1.8 g and 3.4 g/day. Noakes *et al*., however, observed that the variations in plasma carotenoids are within observed seasonal and individual variations [239]. Increased consumption of one serving of carotene-rich fruit and vegetables has been effective in preventing this decline, after consumption of a sterol-rich spread [240].

Consumption of 2 g/day of plant sterols and stanols is recommended by the NCEP ATP III as a therapeutic option

for maximal LDL-C lowering (6–15%) [242]. The usual dietary intake of plant sterols and stanols ranges between 200 and 450 mg/day [228], but diets based on high intakes of vegetable fats, whole grains, fruits, and vegetables provide higher amounts but still fall far short of meeting the 2 g/day recommendation. Thus, fortified foods and/or supplements are needed to attain this level of intake. Plant stanols and sterols are now included in many foods such as margarine, low-fat milk, yogurt, cereal bars, and orange juice, as well as gel-capped sterol and stanol supplements to assist in increasing consumption.

VIII. SUPPLEMENTS

The dietary supplement market is one of the fastest growing industries [243]. Data from the Third National Health and Nutrition Examination Survey (NHANES III) and the more recent 1999–2002 NHANES found that approximately 55% of U.S. men and women aged 40 or older reported the use of some dietary supplement. Multivitamin use was most popular (38%) followed by single or combined antioxidant use (21%) and B vitamins (8%) [244]. The primary reason for using dietary supplements was to achieve self-care goals, as a means of ensuring good health, alleviating depression, and for ''medicinal'' purposes to treat and prevent various illnesses, including the common cold and flu [243].

Epidemiologic and clinical studies that have evaluated dietary supplements in the prevention or treatment of disease are inconsistent, showing little or no benefit. Nevertheless, the few beneficial results obtained in some studies likely influence the public's attitude toward the use of dietary supplements.

A. Niacin

High-dose niacin therapy is used in clinical practice mainly to increase HDL-C [245], and also favorably affect TC, LDL-C, and TG levels [246–248]. In men with a previous MI participating in the Coronary Drug Project, 5-year supplementation with 3 g/day niacin reduced incidence of nonfatal MI and cerebrovascular end points (stroke or transient ischemic attack [TIA]) by 26% and 24%, respectively, compared to placebo, with a reduction in TC and TG by 10% and 26% [249]. After 9 years of follow-up, all-cause mortality was 11% lower in the niacin group, primarily due to a reduction in CHD death [250]. Since then, numerous randomized studies have reported that niacin in doses ranging between 1 and 3 g/day decrease TC (8%), LDL-C (6–21%), and TG (16–29%) and increase HDL-C (17–30%) [246–248]. Several randomized controlled trials reported a reduced frequency of cardiovascular events and an improved lipid profile when niacin was taken alone or in combination with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) [251–255]. Of note in the study by Brown *et al*., however, was the inclusion of the ''antioxidant cocktail'' (800 IU vitamin E, 1000 mg vitamin C, 25 mg β-carotene, and 100 μg selenium) with drug therapy. The antioxidants blunted the effect of simvastatin/niacin treatment and did not reduce stenosis progression, unlike the simvastatin/niacin treatment.

It is recommended that niacin (1–3 g/day) be used to increase HDL-C levels, typically in patients with low HDL-C levels; they are also often prescribed with statins to treat patients with hypercholesterolemia or dyslipidemia. Although the use of niacin in clinical practice has been limited because of adverse side effects such as cutaneous flushing and hepatic toxicity [256], recently, dyslipidemia has been treated through the development of new niacin formulations that elicit less flushing and hepatic toxicity [257, 258].

B. Fish Oil

As mentioned previously, two meta-analyses have demonstrated benefits of EPA and DHA in the prevention of CHD mortality and stroke [259, 260] and improvements in the lipid profile (mainly TG) [261]. With respect to fish-oil supplements, however, a review published in 2006 reported increased consumption of omega-3 fatty acids from dietary fish intake or fish-oil supplements reduced the rates of all-cause mortality, cardiac and sudden death, and possibly stroke [99]. The evidence for the benefits of fish oil appeared stronger in secondary rather than primary-prevention settings, and adverse effects appeared to be minor [99].

Two servings per week of fatty fish are recommended (equivalent to 500 mg EPA+DHA) for primary prevention of CVD. For secondary prevention, 1 g/day is recommended; and for TG lowering, 2–4 g/day is recommended under a physician's supervision. For patients unable to meet these recommendations by consuming oily fish, fish-oil supplements are advised.

C. Fiber

Several cross-sectional and prospective studies have reported that an increased intake of dietary fiber is associated with a reduced risk of CHD and CVD [262–267]. In terms of supplemental fiber, however, in a randomized controlled trial, subjects with mild to moderate hypercholesterolemia were treated with a Step I diet for 12 weeks before receiving placebo or 3.4 g of psyllium (equivalent to 1 teaspoon) three times per day for eight weeks. Compared with placebo, psyllium decreased TC by a further 4.8%, LDL-C by 8.2%, and apolipoprotein (apo) B concentration by 8.8% [268]. A meta-analysis of eight trials also found supplementation with 10.2 g/day of psyllium (Metamucil),

adjunct to a low-fat diet in men and women with hypercholesterolemia, lowered serum TC by 4%, LDL-C by 7%, and the ratio of apo B to apo A-I by 6%, relative to placebo, with no effect on serum HDL or triacylglycerol concentrations [155]. Soluble fiber (psyllium—given as Metamucil supplement) appears to have an additive cholesterol-lowering effect when combined with statins. In a randomized clinical trial of hyperlipidemic subjects, 10 mg simvastatin plus 15 g psyllium decreased TC by 66 mg/dl (26%) and decreased LDL-C by 63 mg/dl (36%) [269].

The NCEP ATP III recommends that dietary supplementation with viscous soluble fiber is an effective therapeutic option to lower LDL-C. On average, an increase in viscous fiber of 5–10 g/day is accompanied by an approximate 5% reduction in LDL-C [270, 271]. To achieve the upper end of the ATP III soluble fiber recommendation, there must be a major emphasis on fruits, vegetables, cereal grains, and legumes. It is challenging to consume 25 g of soluble fiber each day, but a lower intake (5–10 g/day) will still reduce LDL-C by approximately 3% to 5%. Despite the availability of soluble fiber supplements, it is important to note that some provide energy and many do not deliver the same variety of nutrients that soluble-fiber-rich foods do.

D. Antioxidants

There has been controversy about whether antioxidant vitamins decrease CVD risk. In general, epidemiologic studies demonstrate a very modest beneficial association of antioxidants on CVD risk, whereas clinical studies have consistently not reported benefits. In a recent prospective report, the pooled analysis of 10 trials ($n = 227{,}443$) investigating dietary antioxidant intakes found that higher intakes of vitamin E (median intake in highest quartile: 8.2 mg) and β-carotene (median intake in highest quartile: 523 μg) were inversely associated with incidence of all major CHD events (vitamin E RR: 0.77 [0.64, 0.92]; β-carotene: 0.84 [0.74, 0.95]); whereas vitamin C was not (median intake highest quartile: 152 mg; 1.03 [0.91, 1.16]) [272]. When the intake of antioxidant supplements was combined with antioxidant intakes from food, no additional benefits were reported [272].

Relatively few [273] clinical studies have found beneficial effects on CVD reduction following antioxidant supplementation (ranging between 10 and 5000 IU vitamin E, 60 and 200 mg vitamin C, 15 and 50 mg β-carotene), compared with the majority that have not demonstrated beneficial effects [273–275]. Moreover, some have even found adverse effects [274–276].

The use of antioxidant supplements as a means to reduce CVD mortality is inconsistent and generally ineffective. The American Heart Association currently recommends consumption of antioxidant-rich foods such as fruits, vegetables, whole grains, and nuts [277, 278] to achieve recommended intakes, and supplementation is not recommended for CVD risk reduction. The increases in mortality rates following some supplementation studies further support not using antioxidant supplements to prevent or reduce CVD risk factors. Further studies are required assessing whether long-term dietary intakes of antioxidants are beneficial for CVD risk reduction, and whether excessive consumption of dietary intakes (from food and/or supplements) adversely affect health in the long term. Antioxidant supplements are therefore not recommended for the treatment or prevention of CVD.

E. B-Vitamins

The B-vitamins, in particular folate or folic acid, vitamin B_6, and vitamin B_{12}, decrease serum homocysteine levels [279–283], which is a risk factor for CVD. In the Norwegian Vitamin Trial (NORVIT), supplementation with folic acid 0.8 mg/day, vitamin B_{12} at a dosage of 0.4 mg/day, and vitamin B_6 at a dosage of 40 mg/day lowered plasma homocysteine levels by 27%, yet did not result in any reduction in the risk of MI or stroke in patients who have already had an MI [280]. Despite other studies also finding reductions in homocysteine, there was no substantial evidence indicating that B vitamins lowered CVD risk [281, 284]. Furthermore, supplemental doses that have been used (ranging between 20 μg and 2.5 mg folate; 200 μg and 50 mg vitamin B_6; and 0.4 mg and 1 mg vitamin B_{12}) are greater than what can be achieved through dietary sources alone and are far higher than current recommended intakes. Presently, the AHA does not recommend use of folic acid and B vitamin supplements to reduce the risk of CVD [63, 278], but rather recommends consumption of a healthy dietary pattern consisting of vegetables, fruits, legumes, nuts, lean meats, poultry, fatty fish, whole grains, and cereals to meet current recommendations for all nutrients.

IX. FOOD-BASED GUIDANCE

Food-based dietary guidance has been issued that translates energy and nutrient recommendations into healthful dietary patterns that can be implemented by individuals. There is great support for a food-based approach to meet nutrient needs, because certain dietary patterns deliver multiple, rather than single, nutrients to target CVD risk reduction, as well as risk of other chronic diseases, and to promote health and well-being. There are several models for designing dietary patterns. Although there are some subtle differences among them, they all recommend a diet that is high in fruits and vegetables, whole grains, low-fat and skim milk dairy products, lean meats, poultry and fish, legumes, and food sources of unsaturated fats including liquid vegetable oils, and nuts and seeds. All dietary patterns are low in SFA, TFA, and dietary cholesterol and high in dietary fiber. In addition, they all meet current recommendations for sodium

TABLE 4 USDA Food Guide

Daily Amount of Food from Each Group (vegetable subgroup amounts are per week)

Energy Level (kcal)	1000	1200	1400	1600	1800	2000	2200	2400	2600	2800	3000	3200
Fruits	1 c (2 srv)	1 c (2 srv)	1.5 c (3 srv)	1.5 c (3 srv)	1.5 c (3 srv)	2 c (4 srv)	2 c (4 srv)	2 c (4 srv)	2 c (4 srv)	2.5 c (5 srv)	2.5 c (5 srv)	2.5 c (5 srv)
Vegetables	1 c (2 srv)	1.5 c (3 srv)	1.5 c (3 srv)	2 c (4 srv)	2.5 c (5 srv)	2.5 c (5= srv)	3 c (6 srv)	3 c (6 srv)	3.5 c (7 srv)	3.5 c (7 srv)	4 c (8 srv)	4 c (8 srv)
Dark green veg.	1 c/wk	1.5c c/wk	1.5 c/wk	2 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk
Orange veg.	0.5 c/wk	1 c/wk	1 c/wk	1.5 c/wk	2 c/wk	2 c/wk	2 c/wk	2 c/wk	2.5 c/wk	2.5 c/wk	2.5 c/wk	2.5 c/wk
Legumes	0.5 c/wk	1 c/wk	1 c/wk	2.5 c/wk	3 c/wk	3 c/wk	3 c/wk	3 c/wk	3.5 c/wk	3.5 c/wk	3.5 c/wk	3.5 c/wk
Starchy veg.	1.5 c/wk	2.5 c/wk	2.5 c/wk	2.5 c/wk	3 c/wk	3 c/wk	6 c/wk	6 c/wk	7 c/wk	7 c/wk	9 c/wk	9 c/wk
Other veg.	3.5 c/wk	4.5 c/wk	4.5 c/wk	5.5 c/wk	6.5 c/wk	6.5 c/wk	7 c/wk	7 c/wk	8.5 c/wk	8.5 c/wk	10 c/wk	10 c/wk
Grains	3 oz eq	4 oz eq	5 oz eq	5 oz eq	6 oz eq	6 oz eq	7 oz eq	8 oz eq	9 oz eq	10 oz eq	10 oz eq	10 oz eq
Whole grains	1.5	2	2.5	3	3	3	3.5	4	4.5	5	5	5
Other grains	1.5	2	2.5	2	3	3	3.5	4	4.5	5	5	5
Lean meat and beans	2 oz eq	3 oz eq	4 oz eq	5 oz eq	5 oz eq	5.5 oz eq	6 oz eq	6.5 oz eq	6.5 oz eq	7 oz eq	7 oz eq	7 oz eq
Milk	2 c	2 c	2 c	3 c	3 c	3 c	3 c	3 c	3 c	3 c	3 c	3 c
Oils (g)	15 g	17 g	17 g	22 g	24 g	27 g	29 g	31 g	34 g	36 g	44 g	51 g
Discretionary energy allowance	165	171	171	132	195	267	290	362	410	426	512	648

Food group amounts shown in cup (c) or ounce equivalents (oz eq), with number of servings (srv) in parentheses when it differs from the other units.
srv, serving; c,cup; wk, week; oz eq, ounce equivalent; g, gram.

TABLE 5 Discretionary Energy Allowances for Various Age Groups as kcal

	Estimated Total Energy Need (kcal)[a]	Estimated Discretionary Energy Allowance (kcal)[a]	Estimated Total Energy Need (kcal)[b]	Estimated Discretionary Energy Allowance (kcal)[b]
Children 2–3 years old	1000	165[c]	1000–1400	165–170
Children 4–8 years old	1200–1400	170[c]	1400–1800	170–195
Girls 9–13 years old	1600	130	1600–2200	130–290
Boys 9–13 years old	1800	195	1800–2600	195–410
Girls 14–18 years old	1800	195	2000–2400	265–360
Boys 14–18 years old	2200	290	2400–3200	360–650
Females 19–30 years old	2000	265	2000–2400	265–360
Males 19–30 years old	2400	360	2600–3000	410–510
Females 31–50 years old	1800	195	2000–2200	265–290
Males 31–50 years old	2200	290	2400–3000	360–510
Females 51+ years old	1600	130	1800–2200	195–290
Males 51+ years old	2000	265	2200–2800	290–425

[a]These amounts are appropriate for individuals who get less than 30 minutes of moderate physical activity most days.

[b]These amounts are appropriate for individuals who get at least 30 minutes (lower energy level) to at least 60 minutes (higher energy level) of moderate physical activity most days.

[c]The level of discretionary energy is higher for children 8 and younger than it is for older children or adults consuming the same amount of energy, because younger children's nutrient needs are lower.

(<2300 mg/day). The specific food-based dietary recommendations that have been made are presented next.

A. USDA Food Guide

To complement the Dietary Guidelines, two examples of eating patterns have been developed, which include the U.S. Department of Agriculture (USDA) Food Guide and the Dietary Approaches to Stop Hypertension (DASH) Eating Plan (see below). These two similar eating patterns are designed to integrate dietary recommendations into a healthy way to eat and are presented in the Dietary Guidelines to provide examples of how nutrient-focused recommendations can be expressed in terms of food choices. (The Food Guide is available at http://www.health.gov/dietaryguidelines/dga2005/document/pdf/DGA2005.pdf.)

Table 4 displays food-based dietary recommendations from each of five food groups and liquid vegetable oil at 13 different energy levels. At each energy level, there is a discretionary energy allowance (Table 5) that can be included as solid fats, sugar, and/or both within a specified energy level. The discretionary energy allowance is based on estimated energy needs by age/sex group. The discretionary energy allowance is part of total estimated energy needs, not in addition to total energy needs. The chart gives a general guide (http://www.mypyramid.gov/pyramid/discretionary_calories_amount_table.html).

MyPyramid.gov (http://www.mypyramid.gov/) is the new online Food Guide that was developed to help Americans implement the Dietary Guidelines for Americans, 2005, and plan a healthful dietary pattern. The MyPyramid Plan offers a personal eating plan with the foods and amounts that are right for individuals. Using the MyPyramid Plan helps individuals make smart choices from every food group; find the appropriate balance between food and physical activity; achieve nutrient adequacy within energy needs; and identify daily energy needs.

B. Dietary Approaches to Stop Hypertension (DASH) Dietary Pattern

The DASH dietary pattern is rich in fruits, vegetables, and low-fat dairy foods. Whole grains, poultry, fish, and nuts also are emphasized and sweets are reduced. Table 6 displays the DASH eating plan with the recommended daily number of servings in a food group depending on energy needs.

C. Theraputic Lifestyle Changes (TLC) Diet

The TLC diet is a low SFA, TFA, and cholesterol diet aimed to reduce LDL-C. The TLC also includes two therapeutic diet options: plant stanol/sterol (add 2 g/day) and soluble fiber (add 10 to 25 g/day).

Table 7 details an example of the expected LDL-C lowering response to each dietary recommendation of the TLC diet, as well as the additive effects of all dietary strategies. The TLC diet recommendations are consistent with the AHA Diet and Lifestyle Recommendations (revised 2006). AHA recommendations designed specifically for daily energy needs, recommended range of total fat intake, and limits for SFA and TFA can be found at http://www.myfatstranslator.com/.

TABLE 6 The DASH Eating Plan at 1600, 2000, 2600, and 3100 kcal Levels[a]

Food Groups	1600 kcal	2000 kcal	2600 kcal	3100 kcal	Serving Sizes	Examples and Notes	Significance of Each Food Group to the DASH Eating Plan
Grains[b]	6 servings	7–8 servings	10–11 servings	12–13 servings	1 slice bread 1, oz dry cereal, 1/2 cup cooked rice, pasta, or cereal[c]	Whole wheat bread, English muffin, pita bread, bagel, cereals, grits, oatmeal, crackers, unsalted pretzels, and popcorn	Major sources of energy and fiber
Vegetables	3–4 servings	4–5 servings	5–6 servings	6 servings	1 cup raw leafy vegetable, 1/2 cup cooked vegetable, 6 oz vegetable juice	Tomatoes, potatoes, carrots, green peas, squash, broccoli, turnip greens, collards, kale, spinach, artichokes, green beans, lima beans, sweet potatoes	Rich source of potassium, magnesium, and fiber
Fruits	4 servings	4–5 servings	5–6 servings	6 servings	6 oz fruit juice, 1 medium fruit, 1/4 cup dried fruit, 1/2 cup fresh, frozen, or canned fruit	Apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	Important source of potassium, magnesium, and fiber
Low-fat or fat-free dairy foods	2–3 servings	2–3 servings	3 servings	3–4 servings	8 oz milk, 1 cup yogurt, 1 1/2 oz cheese	Fat-free or low-fat milk, fat-free or low-fat buttermilk, fat-free or low-fat regular or frozen yogurt, low-fat and fat-free cheese	Major sources of calcium and protein
Meat, poultry, fish	1–2 servings	2 or fewer servings	2 servings	2–3 servings	3 oz cooked meats, poultry, or fish	Select only lean; trim away visible fats; broil, roast, or boil instead of frying; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, legumes	3–4 servings/ week	4–5 servings/ week	1 serving	1 serving	1/3 cup or 1 1/2 oz nuts, 2 Tbsp or 1/2 oz seeds, 1/2 cup cooked dry beans or peas	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils, pistachios	Rich sources of energy, magnesium, potassium, protein, and fiber
Fat and oils[d]	2 servings	2–3 servings	3 servings	4 servings	1 tsp soft margarine, 1 Tbsp low-fat mayonnaise, 2 Tbsp light salad dressing, 1 tsp vegetable oil	Soft margarine, low-fat mayonnaise, light salad dressing, vegetable oil (such as olive, corn, canola, or safflower)	DASH has 27% of energy as fat (low in saturated fat), including fat in or added to foods
Sweets	0 servings	5 servings/ week	2 servings	2 servings	1 Tbsp sugar, 1 Tbsp jelly or jam, 1/2 oz jelly beans, 8 oz lemonade	Maple syrup, sugar, jelly, jam, fruit-flavored gelatin, jelly beans, hard candy, fruit punch sorbet, ices	Sweets should be low in fat

[a]NIH publication No. 034082; Karanja NM *et al. JADA* 8:S19–27, 1999.

[b]Whole grains are recommended for most servings to meet fiber recommendations.

[c]Equals 1/2 to 1 1/4 cups, depending on cereal type. Check the product's Nutrition Facts Label.

[d]Fat content changes serving counts for fats and oils: For example, 1 Tbsp of regular salad dressing equals 1 serving; 1 Tbsp of a low-fat dressing equals 1/2 serving; 1 Tbsp of a fat-free dressing equals 0 servings. Need to put reference number in. . . .

TABLE 7 Therapeutic Lifestyle Diet, Eating Pattern

Eating Pattern	TLC	Serving Sizes
Grains	7 servings/day[a]	1 slice bread; 1 oz dry cereal[b]; $^1/_2$ C cooked rice, pasta, or cereal
Vegetables	5 servings/day[a]	1 C raw leafy vegetable, $^1/_2$ C cut-up raw or cooked vegetable, $^1/_2$ C vegetable juice
Fruits	4 servings/day	1 medium fruit; $^1/_4$ C dried fruit; $^1/_2$ C fresh, frozen, or canned fruit; $^1/_2$ C fruit juice
Fat-free or low-fat milk and milk products	2–3 servings/day	1 C milk, 1 C yogurt, $1^1/_2$ oz cheese
Lean[c] meats, poultry, and fish	≤5 oz/day	
Nuts, seeds, and legumes	Counted in vegetable servings	$^1/_3$ C ($1^1/_2$ oz), 2 Tbsp peanut butter, 2 Tbsp or $^1/_2$ oz seeds, $^1/_2$ C dry beans or peas
Fats and oils	Amount depends on daily energy level	1 tsp soft margarine, 1 Tbsp mayonnaise, 2 Tbsp salad dressing, 1 tsp vegetable oil
Sweets and added sugars	No recommendation	1 Tbsp sugar, 1 Tbsp jelly or jam, $^1/_2$ C sorbet and ices, 1 C lemonade

[a]This number can be less or more depending on other food choices to meet 2000 kcal.
[b]Equals $^1/_2$ to $1^1/_4$ C, depending on cereal type. Check the product's Nutrition Facts Label.
[c]Lean cuts include sirloin tip, round steak, and rump roast; extra lean hamburger; and cold cuts made with lean meat or soy protein. Lean cuts of pork are center-cut ham, loin chops, and pork tenderloin. More information can be found at http://www.nhlbi.nih.gov/cgi-bin/chd/step2intro.cgi.

TABLE 8 Approximate and Cumulative LDL Cholesterol Reduction Achievable by Dietary Modification [13]

Dietary Component	Dietary Change	Approx. LDL-C Reduction
Major		
Saturated fat	<7% of energy	8–10%
Dietary cholesterol	<200 mg/d	3–5%
Weight reduction	Lose 10 lb	5–8%
Other LDL-Lowering Options		
Viscous fiber	5–10 g/d	3–5%
Plant sterol/stanol esters	2 g/d	6–15%
Cumulative estimate		**20–30%**

X. SUMMARY/CONCLUSION

Two very recent reviews have reinforced the importance of a dietary pattern that is low in SFA, TFA and cholesterol, and high in viscous fiber that beneficially affects lipids and lipoproteins, as well as other CVD risk factors that collectively decrease CVD risk [285, 286]. A dietary pattern that is low in SFA, TFA, and cholesterol, and high in viscous fiber beneficially affects lipids and lipoproteins, and other CVD risk factors that collectively decrease CVD risk. Table 8 shows the impact of these interventions, singly and collectively, on LDL-C lowering. Taken together, along with modest weight loss and inclusion of plant sterol/stanols, they can have a big impact on LDL-C lowering and, in turn, CVD risk reduction. Other dietary factors that beneficially affect CVD risk are omega-3 fatty acids, including fish/fish oil (to provide EPA and DHA), and ALA. These fatty acids act primarily through non-lipid-mediated mechanisms. A food-based dietary pattern that meets current nutrient goals is recommended because it delivers the full complement of nutrients and dietary factors that target a broad array of health benefits. This dietary pattern promotes consumption of fruits, vegetables, whole grains, low-fat/nonfat dairy products, lean meats, poultry and fish, and liquid vegetable oils, nuts, and seeds. Implementation of this dietary pattern will affect multiple, major CVD risk factors, including lipids and lipoproteins, blood pressure, and body weight, which can markedly decrease CVD risk. Thus, a healthful dietary pattern is an important tool for combating heart disease, and implementation of the food-based dietary recommendations that have been made by many organizations can have an important public health benefit.

References

1. Ford, E. S., Ajani, U.A, Croft, J.B, *et al.* (2007). Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N. Engl. J. Med.* **356**, 2388–2398.
2. Foot, D. K., Lewis, R. P., Pearson, T. A., and Beller, G. A. (2000). Demographics and cardiology, 1950-2050. *J. Am. Coll. Cardiol.* **35**, 66B–80B.
3. Pearson, T. A. (2007). The prevention of cardiovascular disease: Have we really made progress? *Health Aff.* **26**, 49–60.
4. Greenland, P., Knoll, M. D., Stamler, J, *et al.* (2003). Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* **290**, 891–897.
5. Khot, U. N., Khot, M. B., Bajzer, C. T., *et al.* (2003). Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* **290**, 898–904.
6. Castelli, W. P. (1996). Lipids, risk factors and ischaemic heart disease. *Atherosclerosis* **124**, S1–S9.

7. Page, I. H., Stare, F. J., Corcoran, A. C., Pollack, H., and Wilkinson, C. F. Jr, (1957). Atherosclerosis and the fat content of the diet. *JAMA* **164**, 2048–2051.
8. Dietary Guidelines Advisory Committee (2005). ''Dietary Guidelines for Americans.'' Retrieved July 2007 from http://www.health.gov/dietaryguidelines/.
9. Kris-Etherton, P. M. (2007). The Minnesota Heart Survey: Nutrition successes pave the way for strategic opportunities for food and nutrition professionals. *J. Am. Diet. Assoc.* **107**, 209–212.
10. United States Department of Agriculture (2007). USDA National Nutrient Database for Standard Reference. Retrieved July 2007 from http://www.nal.usda.gov/fnic/foodcomp/search/.
11. American Dietetic Association (2007). ''Disorders of Lipid Metabolism—Evidence Based Nutrition Practice Guideline.'' Retrieved August 2007 from http://www.adaevidencelibrary.com/topic.cfm?cat=2651&library=EBG.
12. OR Panel on Dietary Reference Intakes for Macronutrients. (2005). ''Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients).'' Retrieved July 2007 from http://www.nal.usda.gov/fnic/DRI//DRI_Energy/energy_full_report.pdf, The National Academies Press, Washington, DC.
13. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2002). Final report. *Circulation* **106**, 3143.
14. Bell, E. A., Castellanos, V. H., Pelkman, C. L., Thorwart, M. L., and Rolls, B. J. (1998). Energy density of foods affects energy intake in normal-weight women. *Am. J. Clin. Nutr.* **67**, 412–420.
15. Kendall, A., Levitsky, D. A., Strupp, B. J., and Lissner, L. (1991). Weight loss on a low-fat diet: Consequence of the imprecision of the control of food intake in humans. *Am. J. Clin. Nutr.* **53**, 1124–1129.
16. Kennedy, E., and Bowman, S. (2001). Assessment of the effect of fat-modified foods on diet quality in adults, 19 to 50 years, using data from the continuing survey of food intake by individuals. *J. Am. Diet. Assoc.* **101**, 455–460.
17. Lissner, L., Levitsky, D. A., Strupp, B. J., Kalkwarf, H. J., and Roe, D. A. (1987). Dietary fat and the regulation of energy intake in human subjects. *Am. J. Clin. Nutr.* **46**, 886–892.
18. Stubbs, R. J., Harbron, C. G., and Prentice, A. M. (1996). Covert manipulation of the dietary fat to carbohydrate ratio of isoenergetically dense diets: Effect on food intake in feeding men *ad libitum*. *Int. J. Obes. Relat. Metab. Disord.* **20**, 651–660.
19. van Stratum, P., Lussenburg, R. N., van Wezel, L. A., Vergroesen, A. J., and Cremer, H. D. (1978). The effect of dietary carbohydrate:fat ratio on energy intake by adult women. *Am. J. Clin. Nutr.* **31**, 206–212.
20. Dansinger, M. L., Gleason, J. A., Griffith, J. L., Selker, H. P., and Schaefer, E. J. (2005). Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. *JAMA* **293**, 43–53.
21. Howard, B. V., Van Horn, L., Hsia, J., *et al.* (2006). Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative randomized controlled dietary modification trial. *JAMA* **295**, 655–666.
22. Dietary Guidelines Advisory Committee Report. (2005). Retrieved July 2007 from http://www.health.gov/dietaryguidelines/dga2005/report/ Or U.S. Department of Health and Human Services and U.S. Department of Agriculture (2005). ''Dietary Guidelines for Americans'' Washington, DC. Retrieved June 2007 from www.healthierus.gov/dietaryguidelines.
23. Keys, A. (1970). Coronary heart disease in seven countries—American Heart Association monograph No. 29. *Circulation* **41–42**, I-1–I-211.
24. Keys, A., Anderson, J. T., and Grande, F. (1965). Serum cholesterol response to changes in the diets. IV. Particular saturated fatty acids in the diet. *Metabolism* **14**, 776–787.
25. Hegsted, D. M., McGandy, R. B., Myers, M. L., and Stare, F. J. (1965). Quantitative effects of dietary fat on serum cholesterol in man. *Am. J. Clin. Nutr.* **17**, 281–295.
26. Clarke, R., Frost, C., Collins, R., Appleby, P., and Peto, R. (1997). Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. *BMJ* **314**, 112–117.
27. Hegsted, D. M., Ausman, L. M., Johnson, J. A., and Dallal, G E. (1993). Dietary fat and serum lipids: An evaluation of the experimental data. *Am. J. Clin. Nutr.* **57**, 875–883.
28. Mensink, R. P., and Katan, M. B. (1992). Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. *Arterioscler. Thromb.* **12**, 911–919.
29. Yu, S., Derr, J., Etherton, T. D., and Kris-Etherton, P. M. (1995). Plasma cholesterol-predictive equations demonstrate that stearic acid is neutral and monounsaturated fatty acids are hypocholesterolemic. *Am. J. Clin. Nutr.* **61**, 1129–1139.
30. Muller, H., Lindman, A. S., Brantsaeter, A. L., and Pedersen, J. I. (2003). The serum LDL/HDL cholesterol ratio is influenced more favorably by exchanging saturated with unsaturated fat than by reducing saturated fat in the diet of women. *J. Nutr.* **133**, 78–83.
31. Ascherio, A., Katan, M. B., Zock, P. L., Stampfer, M. J., and Willett, W. C. (1999). Trans fatty acids and coronary heart disease. *N. Engl. J. Med.* **340**, 1994–1998.
32. Mensink, R. P., Zock, P. L., Kester, A. D., and Katan, M. B. (2003). Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: A meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.* **77**, 1146–1155.
33. Hu, F. B., Stampfer, M. J., Manson, J. E., *et al.* (1999). Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am. J. Clin. Nutr.* **70**, 1001–1008.
34. Nicholls, S. J., Lundman, P., Harmer, J. A., *et al.* (2006). Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function. *J. Am. Coll. Cardiol.* **48**, 715–720.
35. Keogh, J. B., Grieger, J. A., Noakes, M., and Clifton, P. M. (2005). Flow-mediated dilatation is impaired by a high-saturated fat diet but not by a high-carbohydrate diet. *Arterioscler. Thromb. Vasc. Biol.* **25**, 1274–1279.
36. Albelda, S. M., Smith, C. W., and Ward, P. A. (1994). Adhesion molecules and inflammatory injury. *FASEB J.* **8**, 504–512.
37. Ray, K. K., Morrow, D. A., Shui, A., Rifai, N., and Cannon, C. P. (2006). Relation between soluble intercellular adhesion molecule-1, statin therapy, and long-term risk of clinical cardiovascular events in patients with previous acute coronary

syndrome (from PROVE IT-TIMI 22). *Am. J. Cardiol.* **98**, 861–865.
38. Shai, I., Pischon, T., Hu, F. B., Ascherio, A., Rifai, N., and Rimm, E. B. (2006). Soluble intercellular adhesion molecules, soluble vascular cell adhesion molecules, and risk of coronary heart disease. *Obesity* **14**, 2099–2106.
39. Bellido, C., Lopez-Miranda, J., Perez-Martinez, P., *et al.* (2006). The Mediterranean and CHO diets decrease VCAM-1 and E-selectin expression induced by modified low-density lipoprotein in HUVECs. *Nutr. Metab. Cardiovasc. Dis.* **16**, 524–530.
40. Bemelmans, W. J. E., Lefrandt, J. D., Feskens, E. J. M., *et al.* (2002). Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1. *Atherosclerosis* **163**, 113–120.
41. Shahar, E., Folsom, A. R., Wu, K. K., *et al.* (1993). Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler. Thromb.* **13**, 1205–1212.
42. Ripsin, C. M., Keenan, J. M., Jacobs, D. R., Jr., *et al.* (1992). Oat products and lipid lowering. A meta-analysis. *JAMA* **267**, 3317–3325.
43. Allman-Farinelli, M. A., Gomes, K., Favaloro, E. J., and Petocz, P. (2005). A diet rich in high-oleic-acid sunflower oil favorably alters low-density lipoprotein cholesterol, triglycerides, and factor VII coagulant activity. *J. Am. Diet. Assoc.* **105**, 1071–1079.
44. Miller, G. J. (2005). Dietary fatty acids and the haemostatic system. *Atherosclerosis* **179**, 213–227.
45. Ginsberg, H. N., Kris-Etherton, P., Dennis, B., *et al.* (1998). Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: The Delta Study, protocol 1. *Arterioscler. Thromb. Vasc. Biol.* **18**, 441–449.
46. Kris-Etherton, P. M., Pearson, T. A., Wan, Y., *et al.* (1999). High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am. J. Clin. Nutr.* **70**, 1009–1015.
47. Kris-Etherton, P. M., Zhao, G., Pelkman, C. L., Fishell, V. K., and Coval, S. (2000). Beneficial effects of a diet high in mono-unsaturated fatty acids on risk factors for cardiovascular disease. *Nutr. Clin. Care* **3**, 153–162.
48. Griel, A. E., Ruder, E. H., and Kris-Etherton, P. M. (2006). The changing roles of dietary carbohydrates: From simple to complex. *Arterioscler. Thromb. Vasc. Biol.* **26**, 1958–1965.
49. Kris-Etherton, P. M. (1999). Monounsaturated fatty acids and risk of cardiovascular disease. *Circulation* **100**, 1253–1258.
50. Mensink, R. P., and Katan, M. B. (1987). Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women. *Lancet* **1**, 122–125.
51. Appel, L. J., Sacks, F. M., Carey, V. J., *et al.* (2005). Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. *JAMA* **294**, 2455–2464.
52. Carey, V. J., Bishop, L., Charleston, J., *et al.* (2005). Rationale and design of the Optimal Macro-Nutrient Intake Heart trial to prevent heart disease (OMNI-Heart). *Clin. Trials* **2**, 529–537.
53. Gumbiner, B., Low, C. C., and Reaven, P. D. (1998). Effects of a monounsaturated fatty acid-enriched hypocaloric diet on cardiovascular risk factors in obese patients with type 2 diabetes. *Diabetes Care* **21**, 9–15.
54. Reaven, P., Parthasarathy, S., Grasse, B. J., Miller, E., Steinberg, D., and Witztum, J. L. (1993). Effects of oleate-rich and linoleate-rich diets on the susceptibility of low density lipoprotein to oxidative modification in mildly hypercholesterolemic subjects. *J. Clin. Invest.* **91**, 668–676.
55. Lapointe, A., Couillard, C., and Lemieux, S. (2006). Effects of dietary factors on oxidation of low-density lipoprotein particles. *J. Nutr. Biochem.* **17**, 645–658.
56. Perez-Jimenez, F., Lopez-Miranda, J., and Mata, P. (2002). Protective effect of dietary monounsaturated fat on arteriosclerosis: Beyond cholesterol. *Atherosclerosis* **163**, 385–398.
57. Krauss, R. M., and Dreon, D. M. (1995). Low-density-lipoprotein subclasses and response to a low-fat diet in healthy men. *Am. J. Clin. Nutr.* **62**, 478S–487S.
58. Reaven, P. D., Grasse, B. J., and Tribble, D. L. (1994). Effects of linoleate-enriched and oleate-enriched diets in combination with alpha-tocopherol on the susceptibility of LDL and LDL subfractions to oxidative modification in humans. *Arterioscler. Thromb.* **14**, 557–566.
59. Austin, M. A. (1994). Small, dense low-density lipoprotein as a risk factor for coronary heart disease. *Int. J. Clin. Lab. Res.* **24**, 187–192.
60. Chait, A., Brazg, R. L., Tribble, D. L., and Krauss, R. M. (1993). Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am. J. Med.* **94**, 350–356.
61. Rudel, L. L., Parks, J. S., and Sawyer, J. K. (1995). Compared with dietary monounsaturated and saturated fat, polyunsaturated fat protects African green monkeys from coronary artery atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **15**, 2101–2110.
62. Bell, T. A., Wilson, M. D., Kelley, K., Sawyer, J. K., and Rudel, L. L. (2007). Monounsaturated fatty acyl-coenzyme A is predictive of atherosclerosis in human apoB-100 transgenic, LDLr–/– mice. *J. Lipid Res.* **48**, 1122–1131.
63. Lichtenstein, A. H., Appel, L. J., Brands, M., *et al.* (2006). Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association nutrition committee. *Circulation* **114**, 82–96.
64. Eckel, R. H., Borra, S., Lichtenstein, A. H., and Yin-Piazza, S. Y. (2007). Understanding the complexity of trans fatty acid reduction in the American diet: American Heart Association trans fat conference 2006: Report of the trans fat conference planning group. *Circulation* **115**, 2231–2246.
65. Mensink, R. P., and Katan, M. B. (1990). Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N. Engl. J. Med.* **323**, 439–445.
66. Kromhout, D., Menotti, A., Bloemberg, B., *et al.* (1995). Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: The Seven Countries Study. *Prev. Med.* **24**, 308–315.

67. Willett, W. C., Stampfer, M. J., Manson, J. E., *et al.* (1993). Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* **341**, 581–585.
68. Lemaitre, R. N., King, I. B., Raghunathan, T. E., *et al.* (2002). Cell membrane trans-fatty acids and the risk of primary cardiac arrest. *Circulation* **105**, 697–701.
69. Oomen, C. M., Ocke, M. C., Feskens, E. J., van Erp-Baart, M. A., Kok, F. J., and Kromhout, D. (2001). 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* **357**, 746–751.
70. Mozaffarian, D., Katan, M. B., Ascherio, A., Stampfer, M. J., and Willett, W. C. (2006). Trans fatty acids and cardiovascular disease. *N. Engl. J. Med.* **354**, 1601–1613.
71. Ascherio, A. (2006). Trans fatty acids and blood lipids. *Atheroscler. Suppl.* **7**, 25–27.
72. Loss, K., and Chow, C. K. (2000). ''Fatty Acids in Foods and Their Health Implications'' 2nd ed. Marcel Dekker, New York.
73. Sacks, F. M., and Katan, M. (2002). Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am. J. Med.* **113**(Suppl 9B), 13S–24S.
74. Leren, P. (1966). The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Med. Scand. Suppl.* **466**, 1–92.
75. Turpeinen, O., Karvonen, M. J., Pekkarinen, M., Miettinen, M., Elosuo, R., and Paavilainen, E. (1979). Dietary prevention of coronary heart disease: The Finnish Mental Hospital Study. *Int. J. Epidemiol.* **8**, 99–118.
76. Dayton, S., Pearce, M. L., Hashimoto, S., Fakler, L. J., Hiscock, E., and Dixon, W. J. (1962). A controlled clinical trial of a diet high in unsaturated fat. Preliminary observations. *N. Engl. J. Med.* **266**, 1017–1023.
77. Hu, F. B., Stampfer, M. J., Manson, J. E., *et al.* (1997). Dietary fat intake and the risk of coronary heart disease in women. *N. Engl. J. Med.* **337**, 1491–1499.
78. Kris-Etherton, P. M., and Harris, W. S. (2004). Adverse effect of fish oils in patients with angina? *Curr. Atheroscler. Rep.* **6**, 413–414.
79. Grundy, S. M. (1997). What is the desirable ratio of saturated, polyunsaturated, and monounsaturated fatty acids in the diet? *Am. J. Clin. Nutr.* **66**, 988S–990S.
80. Research, Committee (1968). Controlled trial of soya-bean oil in myocardial infarction. *Lancet* **2**, 693–699.
81. Harris, W. S., Assaad, B., and Poston, W. C. (2006). Tissue omega-6/omega-3 fatty acid ratio and risk for coronary artery disease. *Am. J. Cardiol.* **98**, 19i–26i.
82. Mozaffarian, D. D. (2005). Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern. Ther. Health Med.* **11**, 24–30.
83. Kris-Etherton, P. M., Taylor, D. S., Yu-Poth, S., *et al.* (2000). Polyunsaturated fatty acids in the food chain in the United States. *Am. J. Clin. Nutr.* **71**, 179S–188S.
84. Simopoulos, A. P. (1991). Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.* **54**, 438–463.
85. Arterburn, L. M., Hall, E. B., and Oken, H. (2006). Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am. J. Clin. Nutr.* **83**, S1467–S1476.
86. Burdge, G. C., Finnegan, Y. E., Minihane, A. M., Williams, C.M., and Wootton, S. A. (2003). Effect of altered dietary n-3 fatty acid intake upon plasma lipid fatty acid composition, conversion of [^{13}C]alpha-linolenic acid to longer-chain fatty acids and partitioning towards beta-oxidation in older men. *Br. J. Nutr.* **90**, 311–321.
87. Burdge, G. C., Jones, A. E., and Wootton, S. A. (2002). Eicosapentaenoic and docosapentaenoic acids are the principal products of alpha-linolenic acid metabolism in young men. *Br. J. Nutr.* **88**, 355–363.
88. Burdge, G. C., and Wootton, S. A. (2002). Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *Br. J. Nutr.* **88**, 411–420.
89. U.K. Scientific Advisory Committee on Nutrition. (2004). Paper FICS/04/02. Food Standards Agency, London. Retrieved August 2007.
90. National Heart Foundation of Australia. (1999). A review of the relationship between dietary fat and cardiovascular disease. *Aust. J. Nutr. Diet.* **56**, S5–S22.
91. Kris-Etherton, P. M., Harris, W. S., and Appel, L. J., American Heart Association Nutrition Committee (2002). Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* **21**, 2747–2757.
92. Hu, F. B., Stampfer, M. J., Manson, J. E., *et al.* (1999). Dietary protein and risk of ischemic heart disease in women. *Am. J. Clin. Nutr.* **70**, 221–227.
93. Mozaffarian, D., Longstreth, W. T., Jr., Lemaitre, R. N., Manolio, T. A., Kuller, L. H., Burke, G. L., and Siscovick, D. S. (2005). Fish consumption and stroke risk in elderly individuals: The Cardiovascular Health Study. *Arch. Intern. Med.* **165**, 200–206.
94. Folsom, A. R., and Demissie, Z. (2004). Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am. J. Epidemiol.* **160**, 1005–1010.
95. Dolecek, T., and Granditis, G. (1991). Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev. Nutr. Diet.* **66**, 205–216.
96. de Lorgeril, M., Renaud, S., Mamelle, N., *et al.* (1994). Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* **343**, 1454–1459.
97. de Lorgeril, M., Salen, P., Martin, J.-L., Monjaud, I., Delaye, J., and Mamelle, N. (1999). Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. *Circulation* **99**, 779–785.
98. Kris-Etherton, P., Eckel, R. H., Howard, B. V., St. Jeor, S., and Bazzarre, T. L. (2001). Lyon Diet Heart Study: Benefits of a Mediterranean-style, National Cholesterol Education Program/American Heart Association Step I dietary pattern on cardiovascular disease. *Circulation* **103**, 1823–1825.
99. Wang, C., Harris, W. S., Chung, M., *et al.* (2006). n-3 fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: A systematic review. *Am. J. Clin. Nutr.* **84**, 5–17.

100. Dyerberg, J., Bang, H. O., and Hjorne, N. (1975). Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am. J. Clin. Nutr.* **28**, 958–966.
101. Richter, S., Duray, G., Gronefeld, G., *et al.* (2005). Prevention of sudden cardiac death: Lessons from recent controlled trials. *Circ. J.* **69**, 625–629.
102. Mozaffarian, D., and Rimm, E. B. (2006). Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *JAMA* **296**, 1885–1899.
103. Siscovick, D. S., Lemaitre, R. N., and Mozaffarian, D. (2003). The fish story: A diet-heart hypothesis with clinical implications: n-3 polyunsaturated fatty acids, myocardial vulnerability, and sudden death. *Circulation* **107**, 2632–2634.
104. Multiple Risk Factor Intervention Trial Research Group. (1982). Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA* **248**, 1465–1477.
105. Hu, F. B., Bronner, L., Willett, W. C., *et al.* (2002). Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* **287**, 1815–1821.
106. Morris, M. C., Manson, J. E., Rosner, B., Buring, J. E., Willett, W. C., and Hennekens, C. H. (1995). Fish consumption and cardiovascular disease in the Physicians' Health Study: A prospective study. *Am. J. Epidemiol.* **142**, 166–175.
107. Pietinen, P., Ascherio, A., Korhonen, P., *et al.* (1997). Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: The alpha-tocopherol, beta-carotene cancer prevention study. *Am. J. Epidemiol.* **145**, 876–887.
108. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. (1999). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. *Lancet* **354**, 447–455.
109. Burr, M. L., Fehily, A. M., Gilbert, JF, *et al.* (1989). Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet* **2**, 757–761.
110. Yokoyama, M., Origasa, H., Matsuzaki, M., *et al.* (2007). Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* **369**, 1090–1098.
111. Brouwer, I. A., Heeringa, J., Geleijnse, J. M., Zock, P. L., and Witteman, J. C. (2006). Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. *Am. Heart J.* **151**, 857–862.
112. Burr, M. L., Ashfield-Watt, P. A., Dunstan, F. D., *et al.* (2003). Lack of benefit of dietary advice to men with angina: Results of a controlled trial. *Eur. J. Clin. Nutr.* **57**, 193–200.
113. Leaf, A., Albert, C. M., Josephson, M., *et al.* (2005). Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* **112**, 2762–2768.
114. Raitt, M. H., Connor, W. E., Morris, C., *et al.* (2005). Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: A randomized controlled trial. *JAMA* **293**, 2884–2891.
115. Leaf, A., Xiao, Y. F., Kang, J. X., and Billman, G. E. (2005). Membrane effects of the n-3 fish oil fatty acids, which prevent fatal ventricular arrhythmias. *J. Membr. Biol.* **206**, 129–139.
116. Brouwer, I. A., Zock, P. L., Camm, A. J., *et al.* (2006). Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* **295**, 2613–2619.
117. Balk, E. M., Lichtenstein, A. H., Chung, M., Kupelnick, B., Chew, P., and Lau, J. (2006). Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review. *Atherosclerosis* **189**, 19–30.
118. Harris, W. S. (1997). N-3 fatty acids and serum lipoproteins: Human studies. *Am. J. Clin. Nutr.* **65**, 1645S–1654S.
119. Balk, E., Chung, M., Lichtenstein, A., Chew, P., Kupelnick, B., Lawrence, A., DeVine, D., and Lau, J. (2004). Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evidence Report/Technology Assessment No. 93. AHRQ Publication No. 04-E010-2. Agency for Healthcare Research and Quality, Rockville, MD. March 2004. Retrieved August 2007 from http://www.ahrq.gov/downloads/pub/evidence/pdf/o3cardrisk/o3cardrisk.pdf.
120. Rivellese, A. A., Maffettone, A., Vessby, B., *et al.* (2003). Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. *Atherosclerosis* **167**, 149–158.
121. Minihane, A. M., Khan, S., Leigh-Firbank, EC, *et al.* (2000). ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. *Arterioscler. Thromb.* **20**, 1990–1997.
122. Mori, T. A., Burke, V., Puddey, I. B., *et al.* (2000). Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *Am. J. Clin. Nutr.* **71**, 1085–1094.
123. Salonen, J. T., Seppanen, K., Nyyssonen, K., *et al.* (1995). Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* **91**, 645–655.
124. Guillar, E., Sanz-Gallardo, M. I., van't Veer, P., *et al.* (2002). Mercury, fish oils, and the risk of myocardial infarction. *N. Engl. J. Med.* **347**, 1747–1754.
125. Virtanen, J. K., Voutilainen, S., Rissanen, T. H., *et al.* (2005). Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arterioscler. Thromb.* **25**, 228–233.
126. Foran, S. E., Flood, J. G., and Lewandrowski, K. B. (2003). Measurement of mercury levels in concentrated over-the-counter fish oil preparations: Is fish oil healthier than fish? *Arch. Pathol. Lab. Med.* **127**, 1603–1605.
127. Yu-Poth, S., Zhao, G., Etherton, T., Naglak, M., Jonnalagadda, S., and Kris-Etherton, P. M. (1999). Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: A meta-analysis. *Am. J. Clin. Nutr.* **69**, 632–646.
128. DeFronzo, R. A., and Ferrannini, E. (1991). Insulin resistance. A multifaceted syndrome responsible for NIDDM,

obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* **14**, 173–194.
129. Parillo, M., Rivellese, A. A., Ciardullo, A. V., *et al.* (1992). A high-monounsaturated-fat/low-carbohydrate diet improves peripheral insulin sensitivity in non-insulin-dependent diabetic patients. *Metabolism* **41**, 1373–1378.
130. Jeppesen, J., Schaaf, P., Jones, C., Zhou, M. Y., Chen, Y. D., and Reaven, G. M. (1997). Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. *Am. J. Clin. Nutr.* **65**, 1027–1033.
131. Hammer, V., and Rolls, B. (1997). Diet composition and the regulation of body weight. *In* ''Obesity and Weight Management: The Health Professional's Guide to Understanding and Treatment'' (S. Dalton, Ed.). Aspen, Gaithersburg, MD.
132. Bray, G. A., and Popkin, B. M. (1998). Dietary fat intake does affect obesity! *Am. J. Clin. Nutr.* **68**, 1157–1173.
133. Willett, W. C. (2002). Dietary fat plays a major role in obesity: No. *Obes. Rev.* **3**, 59–68.
134. Lichtenstein, A. H., and Van Horn, L. (1998). Very low fat diets. *Circulation* **98**, 935–939.
135. Ornish, D., Scherwitz, L. W., Billings, J. H., *et al.* (1998). Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* **280**, 2001–2007.
136. Harsha, D. W., Sacks, F. M., Obarzanek, E., *et al.* (2004). Effect of dietary sodium intake on blood lipids: Results from the DASH-sodium trial. *Hypertension* **43**, 393–398.
137. Obarzanek, E., Sacks, F. M., Vollmer, W. M., *et al.* (2001). Effects on blood lipids of a blood pressure-lowering diet: The Dietary Approaches to Stop Hypertension (DASH) Trial. *Am. J. Clin. Nutr.* **74**, 80–89.
138. Volek, J. S., Sharman, M. J., and Forsythe, C. E. (2005). Modification of lipoproteins by very low-carbohydrate diets. *J. Nutr.* **135**, 1339–1342.
139. Nordmann, A. J., Nordmann, A., Briel, M., *et al.* (2006). Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: A meta-analysis of randomized controlled trials. *Arch. Intern. Med.* **166**, 285–293.
140. St. Jeor, S. T., Howard, B. V., Prewitt, T. E., Bovee, V., Bazzarre, T., and Eckel, R. H. (2001). Dietary protein and weight reduction: A statement for healthcare professionals from the nutrition committee of the council on nutrition, physical activity, and metabolism of the American Heart Association. *Circulation* **104**, 1869–1874.
141. Krauss, R. M., Blanche, P. J., Rawlings, R. S., Fernstrom, H. S., and Williams, P. T. (2006). Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am. J. Clin. Nutr.* **83**, 1025–1031.
142. Wood, R. J., Fernandez, M. L., Sharman, M. J., *et al.* (2007). Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk. *Metabolism* **56**, 58–67.
143. Ginsberg, H. N. (2002). New perspectives on atherogenesis: Role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation* **106**, 2137–2142.
144. Wolever, T. M. S. (1999). Dietary recommendations for diabetes: High carbohydrate or high monounsaturated fat. *Nutr. Today* **34**, 73–77.
145. Jarvi, A. E., Karlstrom, B. E., Granfeldt, Y. E., Bjorck, I. E., Asp, N. G., and Vessby, B. O. (1999). Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* **22**, 10–18.
146. Wolever, T. M., Jenkins, D. J., Vuksan, V., Jenkins, A. L., Wong, G. S., and Josse, R. G. (1992). Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. *Diabetes Care* **15**, 562–564.
147. Ludwig, D. S. (2002). The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* **287**, 2414–2423.
148. Liu, S., Manson, J. E., Stampfer, M. J., *et al.* (2000). A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in U.S. women. *Am. J. Public Health* **90**, 1409–1415.
149. Liu, S., Manson, J. E., Buring, J. E., Stampfer, M. J., Willett, W. C., and Ridker, P. M. (2002). Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am. J. Clin. Nutr.* **75**, 492–498.
150. van Dam, R. M., Visscher, A. W., Feskens, E. J., Verhoef, P., and Kromhout, D. (2000). Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur. J. Clin. Nutr.* **54**, 726–731.
151. Ebbeling, C. B., Leidig, M. M., Feldman, H. A., Lovesky, M. M., and Ludwig, D. S. (2007). Effects of a low-glycemic load vs low-fat diet in obese young adults: A randomized trial. *JAMA* **297**, 2092–2102.
152. Pereira, M. A., Swain, J., Goldfine, A. B., Rifai, N., and Ludwig, D. S. (2004). Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA* **292**, 2482–2490.
153. Das, S. K., Gilhooly, C. H., Golden, J. K., *et al.* (2007). Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: A 1-y randomized controlled trial. *Am. J. Clin. Nutr.* **85**, 1023–1030.
154. Anderson, J. W., and Hanna, T. J. (1999). Impact of nondigestible carbohydrates on serum lipoproteins and risk for cardiovascular disease. *J. Nutr.* **129**, 1457.
155. Anderson, J. W., Davidson, M. H., Blonde, L., *et al.* (2000). Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. *Am. J. Clin. Nutr.* **71**, 1433–1438.
156. Davidson, M. H., Maki, K. C., Kong, J. C., *et al.* (1998). Long-term effects of consuming foods containing psyllium seed husk on serum lipids in subjects with hypercholesterolemia. *Am. J. Clin. Nutr.* **67**, 367–376.
157. Pereira, M. A., O'Reilly, E., Augustsson, K., *et al.* (2004). Dietary fiber and risk of coronary heart disease: A pooled analysis of cohort studies. *Arch. Intern. Med.* **164**, 370–376.
158. Liese, A. D., Roach, A. K., Sparks, K. C., Marquart, L., D'Agostino, R. B., and Jr., Mayer-Davis, E. J. (2003). Whole-grain intake and insulin sensitivity: the insulin resistance atherosclerosis study. *Am. J. Clin. Nutr.* **78**, 965–971.

159. Fernandez, M. L. (2001). Soluble fiber and nondigestible carbohydrate effects on plasma lipids and cardiovascular risk. *Curr. Opin. Lipidol.* **12**, 35–40.
160. Glore, S. R., Van Treeck, D., Knehans, A. W., and Guild, M. (1994). Soluble fiber and serum lipids: A literature review. *J. Am. Diet. Assoc.* **94**, 425–436.
161. Wu, H., Dwyer, K. M., Fan, Z., Shircore, A., Fan, J., and Dwyer, J. H. (2003). Dietary fiber and progression of atherosclerosis: the Los Angeles Atherosclerosis Study. *Am. J. Clin. Nutr.* **78**, 1085–1091.
162. Brown, L., Rosner, B., Willett, W. W., and Sacks, F. M. (1999). Cholesterol-lowering effects of dietary fiber: A meta-analysis. *Am. J. Clin. Nutr.* **69**, 30–42.
163. Aller, R., de Luis, D. A., Izaola, O., *et al.* (2004). Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: A randomized clinical trial. *Diabetes Res. Clin. Pract.* **65**, 7–11.
164. de Groot, A., Luyken, R., and Pikaar, N. A. (1963). Cholesterol-lowering effect of rolled oats. *Lancet* **2**, 303–304.
165. Biorklund, M., van Rees, A., Mensink, R. P., and Onning, G. (2005). Changes in serum lipids and postprandial glucose and insulin concentrations after consumption of beverages with beta-glucans from oats or barley: A randomised dose-controlled trial. *Eur. J. Clin. Nutr.* **59**, 1272–1281.
166. Fukagawa, N. K., Anderson, J. W., Hageman, G., Young, V. R., and Minaker, K. L. (1990). High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. *Am. J. Clin. Nutr.* **52**, 524–528.
167. Anderson, J. W., Zeigler, J. A., Deakins, D. A., *et al.* (1991). Metabolic effects of high-carbohydrate, high-fiber diets for insulin- dependent diabetic individuals. *Am. J. Clin. Nutr.* **54**, 936–943.
168. Hallfrisch, J., Scholfield, D. J., and Behall, K. M. (1995). Diets containing soluble oat extracts improve glucose and insulin responses of moderately hypercholesterolemic men and women. *Am. J. Clin. Nutr.* **61**, 379–384.
169. Lagiou, P., Sandin, S., Weiderpass, E., *et al.* (2007). Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J. Intern. Med.* **261**, 366–374.
170. Trichopoulou, A., Psaltopoulou, T., Orfanos, P., Hsieh, C. C., and Trichopoulos, D. (2007). Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur. J. Clin. Nutr.* **61**, 575–581.
171. Hu, F. B., Rimm, E. B., Stampfer, M. J., Ascherio, A., Spiegelman, D., and Willett, W. C. (2000). Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am. J. Clin. Nutr.* **72**, 912–921.
172. Blankenhorn, D. H., Johnson, R. L., Mack, W. J., el Zein, H. A., and Vailas, L. I. (1990). The influence of diet on the appearance of new lesions in human coronary arteries. *JAMA* **263**, 1646–1652.
173. Terpstra, A. H., Hermus, R. J., and West, C. E. (1983). The role of dietary protein in cholesterol metabolism. *World Rev. Nutr. Diet.* **42**, 1–55.
174. Stamler, J., (1979). Population studies. *In* "Nutrition, Lipids and Coronary Heart Disease," Raven, New York.
175. Hodgson, J. M., Ward, N. C., Burke, V., Beilin, L. J., and Puddey, I. B. (2007). Increased lean red meat intake does not elevate markers of oxidative stress and inflammation in humans. *J. Nutr.* **137**, 363–367.
176. Descovich, G. C., Ceredi, C., Gaddi, A., *et al.* (1980). Multicentre study of soybean protein diet for outpatient hypercholesterolaemic patients. *Lancet* **2**, 709–712.
177. Sirtori, C. R., Gatti, E., Mantero, O., *et al.* (1979). Clinical experience with the soybean protein diet in the treatment of hypercholesterolemia. *Am. J. Clin. Nutr.* **32**, 1645–1658.
178. Sirtori, C. R., Zucchi-Dentone, C., Sirtori, M., *et al.* (1985). Cholesterol-lowering and HDL-raising properties of lecithinated soy proteins in type II hyperlipidemic patients. *Ann. Nutr. Metab.* **29**, 348–357.
179. Anderson, J. W., Johnstone, B. M., and Cook-Newell, M. E. (1995). Meta-analysis of the effects of soy protein intake on serum lipids. *N. Engl. J. Med.* **333**, 276–282.
180. Sacks, F. M., Lichtenstein, A., Van Horn, L., Harris, W., Kris-Etherton, P., and Winston, M. (2006). Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* **113**, 1034–1044.
181. Balk, E., Chung, M., Chew, P., Ip, S., Raman, G., Kupelnick, B., Tatsioni, A., Sun, Y., Wolk, B., DeVine, D., and Lau, J. (2005). Effects of soy on health outcomes. Evidence Report/Technology Assessment No. 126. AHRQ Publication No. 05-E024-2. Agency for Healthcare Research and Quality, Rockville, MD. Retrieved August 2007 from http://www.ahrq.gov/downloads/pub/evidence/pdf/soyeffects/soy.pdf
182. Taku, K., Umegaki, K., Sato, Y., Taki, Y., Endoh, K., and Watanabe, S. (2007). Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am. J. Clin. Nutr.* **85**, 1148–1156.
183. Azadbakht, L., Kimiagar, M., Mehrabi, Y., Esmaillzadeh, A., Hu, F. B., and Willett, W. C. (2007). Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care* **30**, 967–973.
184. Matthan, N. R., Jalbert, S. M., Ausman, L. M., Kuvin, J. T., Karas, R. H., and Lichtenstein, A. H. (2007). Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am. J. Clin. Nutr.* **85**, 960–966.
185. Tikkanen, M. J., Wahala, K., Ojala, S., Vihma, V., and Adlercreutz, H. (1998). Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance. *Proc. Natl. Acad. Sci. USA* **95**, 3106–3110.
186. Wiseman, H., O'Reilly, J. D., Adlercreutz, H., *et al.* (2000). Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. *Am. J. Clin. Nutr.* **72**, 395–400.
187. Nestel, P. J., Yamashita, T., Sasahara, T., *et al.* (1997). Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler. Thromb. Vasc. Biol.* **17**, 3392–3398.
188. Russell, M., Cooper, M. L., Frone, M. R., and Welte, J. W. (1991). Alcohol drinking patterns and blood pressure. *Am. J. Public Health* **81**, 452–457.

189. Stranges, S., Wu, T., Dorn, J. M., *et al.* (2004). Relationship of alcohol drinking pattern to risk of hypertension: a population-based study. *Hypertension* **44**, 813–819.
190. Trevisan, M., Krogh, V., Farinaro, E., Panico, S., and Mancini, M. (1987). Alcohol consumption, drinking pattern and blood pressure: Analysis of data from the Italian National Research Council Study. *Int. J. Epidemiol.* **16**, 520–527.
191. Dorn, J. M., Hovey, K., Williams, B. A., *et al.* (2007). Alcohol drinking pattern and non-fatal myocardial infarction in women. *Addiction* **102**, 730–739.
192. Kabagambe, E. K., Baylin, A., Ruiz-Narvaez, E., Rimm, E. B., and Campos, H. (2005). Alcohol intake, drinking patterns, and risk of nonfatal acute myocardial infarction in Costa Rica. *Am. J. Clin. Nutr.* **82**, 1336–1345.
193. Mukamal, K. J., Jensen, M. K., Gronbaek, M., *et al.* (2005). Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation* **112**, 1406–1413.
194. Tolstrup, J., Jensen, M. K., Tjonneland, A., Overvad, K., Mukamal, K. J., and Gronbaek, M. (2006). Prospective study of alcohol drinking patterns and coronary heart disease in women and men. *BMJ* **332**, 1244–1248.
195. Jackson, R., Scragg, R., and Beaglehole, R. (1991). Alcohol consumption and risk of coronary heart disease. *BMJ* **303**, 211–216.
196. Tolstrup, J. S., Jensen, M. K., Tjonneland, A., Overvad, K., and Gronbaek, M. (2004). Drinking pattern and mortality in middle-aged men and women. *Addiction* **99**, 323–330.
197. Trevisan, M., Schisterman, E., Mennotti, A., Farchi, G., and Conti, S. (2001). Drinking pattern and mortality: The Italian Risk Factor and Life Expectancy Pooling Project. *Ann. Epidemiol.* **11**, 312–319.
198. Doll, R., Peto, R., Hall, E., Wheatley, K., and Gray, R. (1994). Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ* **309**, 911–918.
199. Fuchs, C. S., Stampfer, M. J., Colditz, G. A., *et al.* (1995). Alcohol consumption and mortality among women. *N. Engl. J. Med.* **332**, 1245–1250.
200. Rimm, E. B., Giovannucci, E. L., Willett, W. C., *et al.* (1991). Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* **338**, 464–468.
201. Thun, M. J., Peto, R., Lopez, A. D., *et al.* (1997). Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N. Engl. J. Med.* **337**, 1705–1714.
202. Agarwal, D. P. (2002). Cardioprotective effects of light-moderate consumption of alcohol: A review of putative mechanisms. *Alcohol Alcohol.* **37**, 409–415.
203. Marmot, M. G., Rose, G., Shipley, M. J., and Thomas, B. J. (1981). Alcohol and mortality: A U-shaped curve. *Lancet* **1**, 580–583.
204. Shaper, A. G., Wannamethee, G., and Walker, M. (1988). Alcohol and mortality in British men: Explaining the U-shaped curve. *Lancet* **2**, 1267–1273.
205. Renaud, S. C., and Ruf, J. C. (1996). Effects of alcohol on platelet functions. *Clin. Chim. Acta* **246**, 77–89.
206. Ridker, P. M., Vaughan, D. E., Stampfer, M. J., Glynn, R. J., and Hennekens, C. H. (1994). Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA* **272**, 929–933.
207. De Oliveira, E., Silva, E. R., Foster, D., McGee Harper, M., Seidman, C. E., Smith, J. D., Breslow, J. L., and Brinton, E. (2000). Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. *Circulation* **102**, 2347–2352.
208. Srivastava, L. M., Vasisht, S., Agarwal, D. P., and Goedde, H. W. (1994). Relation between alcohol intake, lipoproteins and coronary heart disease: The interest continues. *Alcohol Alcohol.* **29**, 11–24.
209. Roussell, M., and Kris-Etherton, P. (2007). Effects of lifestyle interventions on high-density lipoprotein cholesterol levels. *J. Clin. Lipid.* **1**, 65–73.
210. Rimm, E. B., Williams, P., Fosher, K., Criqui, M., and Stampfer, M. J. (1999). Moderate alcohol intake and lower risk of coronary heart disease: Meta-analysis of effects on lipids and haemostatic factors. *BMJ* **319**, 1523–1528.
211. St. Leger, A. S., Cochrane, A. L., and Moore, F. (1979). Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet* **1**, 1018–1020.
212. Criqui, M. H., and Ringel, B. L. (1994). Does diet or alcohol explain the French paradox? *Lancet* **344**, 1719–1723.
213. Renaud, S., and de Lorgeril, M. (1992). Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* **339**, 1523–1526.
214. Booyse, F. M., and Parks, D. A. (2001). Moderate wine and alcohol consumption: Beneficial effects on cardiovascular disease. *Thromb. Haemost.* **86**, 517–528.
215. Frankel, E. N., Kanner, J., German, J. B., Parks, E., and Kinsella, J. E. (1993). Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* **341**, 454–457.
216. Klatsky, A. L. (2007). Alcohol, cardiovascular diseases and diabetes mellitus. *Pharmacol. Res.* **55**, 237–247.
217. Gorelik, S., Ligumsky, M., Kohen, R., and Kanner, J. (2007). A novel function of red wine polyphenols in humans: Prevention of absorption of cytotoxic lipid peroxidation products. *FASEB J.* (in press).
218. Pignatelli, P., Ghiselli, A., Buchetti, B., *et al.* (2006). Polyphenols synergistically inhibit oxidative stress in subjects given red and white wine. *Atherosclerosis* **188**, 77–83.
219. Kiviniemi, T. O., Saraste, A., Toikka, J. O., *et al.* (2007). A moderate dose of red wine, but not de-alcoholized red wine increases coronary flow reserve. *Atherosclerosis* (in press).
220. Avellone, G., Di Garbo, V., Campisi, D., *et al.* (2006). Effects of moderate Sicilian red wine consumption on inflammatory biomarkers of atherosclerosis. *Eur. J. Clin. Nutr.* **60**, 41–47.
221. Karatzi, K., Papamichael, C., Karatzis, E., *et al.* (2007). Acute smoking induces endothelial dysfunction in healthy smokers. Is this reversible by red wine's antioxidant constituents? *J. Am. Coll. Nutr.* **26**, 10–15.
222. Nakamura, Y., Okamura, T., Tamaki, S., *et al.* (2004). Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: The National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (1980, NIPPON DATA80). *Am. J. Clin. Nutr.* **80**, 58–63.

223. Dawber, T. R., Nickerson, R. J., Brand, F. N., and Pool, J. (1982). Eggs, serum cholesterol, and coronary heart disease. *Am. J. Clin. Nutr.* **36**, 617–625.
224. Kannel, W. B., and Gordon, T. (1970). The Framingham Diet Study: Diet and the regulations of serum cholesterol (Section 24). Department of Health, Education and Welfare, Washington, DC.
225. Cesar, T. B., Oliveira, M. R., Mesquita, C. H., and Maranhao, R. C. (2006). High cholesterol intake modifies chylomicron metabolism in normolipidemic young men. *J. Nutr.* **136**, 971–976.
226. Weggemans, R. M., Zock, P. L., and Katan, M. B. (2001). Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am. J. Clin. Nutr.* **73**, 885–891.
227. Kratz, M. (2005). Dietary cholesterol, atherosclerosis and coronary heart disease. *Handb. Exp. Pharmacol.* **2005**, 195–213.
228. Perisee, D. M. (2005). Food fortification with plant sterol/stanol for hyperlipidemia: Management in free-living populations. *J. Am. Diet. Assoc.* **105**, 52–53.
229. Gylling, H., Puska, P., Vartiainen, E., and Miettinen, T. A. (1999). Serum sterols during stanol ester feeding in a mildly hypercholesterolemic population. *J. Lipid Res.* **40**, 593–600.
230. Miettinen, T. A., Vuoristo, M., Nissinen, M., Jarvinen, H. J., and Gylling, H. (2000). Serum, biliary, and fecal cholesterol and plant sterols in colectomized patients before and during consumption of stanol ester margarine. *Am. J. Clin. Nutr.* **71**, 1095–1102.
231. Assmann, G., Cullen, P., Erbey, J., Ramey, D. R., Kannenberg, F., and Schulte, H. (2006). Plasma sitosterol elevations are associated with an increased incidence of coronary events in men: results of a nested case-control analysis of the Prospective Cardiovascular Munster (PROCAM) study. *Nutr. Metab. Cardiovasc. Dis.* **16**, 13–21.
232. Fassbender, K., Lutjohann, D., Dik, M. G., *et al.* (2006). Moderately elevated plant sterol levels are associated with reduced cardiovascular risk—The LASA study. *Atherosclerosis* (in press).
233. Pinedo, S., Vissers, M. N., von Bergmann, K., *et al.* (2007). Plasma levels of plant sterols and the risk of coronary artery disease: The prospective EPIC-Norfolk Population Study. *J. Lipid Res.* **48**, 139–144.
234. Devaraj, S., and Jialal, I. (2006). The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutr. Rev.* **64**, 348–354.
235. Hendriks, H. F., Brink, E. J., Meijer, G. W., Princen, H. M., and Ntanios, F. Y. (2003). Safety of long-term consumption of plant sterol esters-enriched spread. *Eur. J. Clin. Nutr.* **57**, 681–692.
236. Homma, Y., Ikeda, I., Ishikawa, T., Tateno, M., Sugano, M., and Nakamura, H. (2003). Decrease in plasma low-density lipoprotein cholesterol, apolipoprotein B, cholesteryl ester transfer protein, and oxidized low-density lipoprotein by plant stanol ester-containing spread: A randomized, placebo-controlled trial. *Nutrition* **19**, 369–374.
237. Ntanios, F. Y., Homma, Y., and Ushiro, S. (2002). A spread enriched with plant sterol-esters lowers blood cholesterol and lipoproteins without affecting vitamins A and E in normal and hypercholesterolemic Japanese men and women. *J. Nutr.* **132**, 3650–3655.
238. Quilez, J., Rafecas, M., Brufau, G., *et al.* (2003). Bakery products enriched with phytosterol esters, alpha-tocopherol and beta-carotene decrease plasma LDL-cholesterol and maintain plasma beta-carotene concentrations in normocholesterolemic men and women. *J. Nutr.* **133**, 3103–3109.
239. Noakes, M., Clifton, P. M., Doornbos, A. M., and Trautwein, E. A. (2005). Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. *Eur J. Nutr.* **44**, 214–222.
240. Noakes, M., Clifton, P., Ntanios, F., Shrapnel, W., Record, I., and McInerney, J. (2002). An increase in dietary carotenoids when consuming plant sterols or stanols is effective in maintaining plasma carotenoid concentrations. *Am. J. Clin. Nutr.* **75**, 79–86.
241. Plat, J., van Onselen, E. N., van Heugten, M. M., and Mensink, R. P. (2000). Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. *Eur. J. Clin. Nutr.* **54**, 671–677.
242. Grundy, S. M. (2005). Stanol esters as a component of maximal dietary therapy in the National Cholesterol Education Program Adult Treatment Panel III report. *Am. J. Cardiol.* **96**, 47D–50D.
243. Levitt, J. A. (2001). Center for Food Safety and Applied Nutrition, Food and Drug Administration. Statement to the U.S. House of Representatives Committee on Government Reform, U.S. Food and Drug Administration. Accessed August 2007. http://www.cfsan.fda.gov/~1rd/st010320.html/
244. Buettner, C., Phillips, R. S., Davis, R. B., Gardiner, P., and Mittleman, M. A. (2007). Use of dietary supplements among United States adults with coronary artery disease and atherosclerotic risks. *Am. J. Cardiol.* **99**, 661–666.
245. Carlson, L. A. (2005). Nicotinic acid: The broad-spectrum lipid drug. A 50th anniversary review. *J. Intern Med.* **258**, 94–114.
246. Goldberg, A., Alagona, P., Jr., Capuzzi, D. M., *et al.* (2000). Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. *Am. J. Cardiol.* **85**, 1100–1105.
247. Knopp, R. H., Alagona, P., Davidson, M., *et al.* (1998). Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism* **47**, 1097–1104.
248. Morgan, J. M., Capuzzi, D. M., Guyton, J. R., *et al.* (1996). Treatment effect of Niaspan, a controlled-release niacin, in patients with hypercholesterolemia: A placebo-controlled trial. *J. Cardiovasc. Pharmacol. Ther.* **1**, 195–202.
249. The Coronary Drug Project Research Group. (1975). Clofibrate and niacin in coronary heart disease. *JAMA* **231**, 360–381.
250. Canner, P. L., Berge, K. G., Wenger, N. K., *et al.* (1986). Fifteen year mortality in coronary drug project patients: Long-term benefit with niacin. *J. Am. Coll. Cardiol.* **8**, 245–1255.
251. Birjmohun, R. S., Kastelein, J. J., Poldermans, D., Stroes, E. S., Hostalek, U., and Assmann, G. (2007). Safety and

tolerability of prolonged-release nicotinic acid in statin-treated patients. *Curr. Med. Res. Opin.* **23**, 1707–1713.
252. Blankenhorn, D. H., Nessim, S. A., Johnson, R. L., Sanmarco, M. E., Azen, S. P., and Cashin-Hemphill, L. (1987). Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* **257**, 3233–3240.
253. Brown, B. G., Hillger, L., Zhao, X. Q., Poulin, D., and Albers, J. J. (1995). Types of change in coronary stenosis severity and their relative importance in overall progression and regression of coronary disease. Observations from the FATS Trial. Familial Atherosclerosis Treatment Study. *Ann. N. Y. Acad. Sci.* **748**, 407–417, discussion 417–418.
254. Brown, B. G., Zhao, X. Q., Chait, A., *et al.* (2001). Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N. Engl. J. Med.* **345**, 1583–1592.
255. Hunninghake, D. B., McGovern, M. E., Koren, M., *et al.* (2003). A dose-ranging study of a new, once-daily, dual-component drug product containing niacin extended-release and lovastatin. *Clin. Cardiol.* **26**, 112–118.
256. Berra, K. (2004). Clinical update on the use of niacin for the treatment of dyslipidemia. *J. Am. Acad. Nurse Pract.* **16**, 526–534.
257. Brown, B. G. (2007). Expert commentary: Niacin safety. *Am. J. Cardiol.* **99**, 32C–34C.
258. Tavintharan, S., and Kashyap, M. L. (2001). The benefits of niacin in atherosclerosis. *Curr. Atheroscler. Rep.* **3**, 74–82.
259. He, K., Song, Y., Daviglus, M. L., *et al.* (2004). Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* **109**, 2705–2711.
260. He, K., Song, Y., Daviglus, M. L., *et al.* (2004). Fish consumption and incidence of stroke: A meta-analysis of cohort studies. *Stroke* **35**, 1538–1542.
261. Panagiotakos, D. B., Zeimbekis, A., Boutziouka, V., *et al.* (2007). Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med. Sci. Monit.* **13**, CR307–CR312.
262. Bazzano, L. A., He, J., Ogden, L. G., Loria, C. M., and Whelton, P. K. (2003). Dietary fiber intake and reduced risk of coronary heart disease in US men and women: The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch. Intern. Med.* **163**, 1897–1904.
263. Liu, S., Buring, J. E., Sesso, H. D., Rimm, E. B., Willett, W. C., and Manson, J. E. (2002). A prospective study of dietary fiber intake and risk of cardiovascular disease among women. *J. Am. Coll. Cardiol.* **39**, 49–56.
264. Merchant, A. T., Hu, F. B., Spiegelman, D., Willett, W. C., Rimm, E. B., and Ascherio, A. (2003). Dietary fiber reduces peripheral arterial disease risk in men. *J. Nutr.* **133**, 3658–3663.
265. Mozaffarian, D., Kumanyika, S. K., Lemaitre, R. N., Olson, J. L., Burke, G. L., and Siscovick, D. S. (2003). Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA* **289**, 1659–1666.
266. Rimm, E. B., Ascherio, A., Giovannucci, E., Spiegelman, D., Stampfer, M. J., and Willett, W. C. (1996). Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* **275**, 447–451.
267. Wolk, A., Manson, J. E., Stampfer, M. J., *et al.* (1999). Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* **281**, 1998–2004.
268. Bell, L. P., Hectorne, K., Reynolds, H., Balm, T. K., and Hunninghake, D. B. (1989). Cholesterol-lowering effects of psyllium hydrophilic mucilloid. Adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. *JAMA* **261**, 3419–3423.
269. Moreyra, A. E., Wilson, A. C., and Koraym, A. (2005). Effect of combining psyllium fiber with simvastatin in lowering cholesterol. *Arch. Intern. Med.* **165**, 1161–1166.
270. U.S. Department of Health and Human Services. Food and Drug Administration. (1997). Food labeling: health claims. Soluble fiber from certain foods and coronary heart disease: Proposed rule. *Fed. Register* **62**, 28234–28245.
271. U.S. Department of Health and Human Services. Food and Drug Administration. (1998). Food labeling: health claims. Soluble fiber from certain foods and coronary heart disease: Final rule. *Fed. Register* **63**, 8103–8121.
272. Knekt, P., Ritz, J., Pereira, M. A., *et al.* (2004). Antioxidant vitamins and coronary heart disease risk: A pooled analysis of 9 cohorts. *Am. J. Clin. Nutr.* **80**, 1508–1520.
273. Virtamo, J., Rapola, J. M., Ripatti, S., *et al.* (1998). Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. *Arch. Intern. Med.* **158**, 668–675.
274. Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G., and Gluud, C. (2007). Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. *JAMA* **297**, 842–857.
275. Vivekananthan, D. P., Penn, M. S., Sapp, S. K., Hsu, A., and Topol, E. J. (2003). Use of antioxidant vitamins for the prevention of cardiovascular disease: Meta-analysis of randomised trials. *Lancet* **361**, 2017–2023.
276. Cook, N. R. (2007). A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study. *Arch. Intern. Med.* **167**, 1610–1618.
277. Lichtenstein, A. H., Appel, L. J., Brands, M., *et al.* (2006). Summary of the American Heart Association diet and lifestyle recommendations revision 2006. *Arterioscler. Thromb. Vasc. Biol.* **26**, 2186–2191.
278. Mosca, L., Banka, C. L., Benjamin, E. J., *et al.* (2007). Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *J. Am. Coll. Cardiol.* **49**, 1230–1250.
279. Homocysteine Lowering Trialists' Collaboration (1998). Lowering blood homocysteine with folic acid based supplements: Meta-analysis of randomised trials. *BMJ* **316**, 894–898.
280. Bonaa, K. H., Njolstad, I., Ueland, P. M., *et al.* (2006). Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N. Engl. J. Med.* **354**, 1578–1588.

281. Toole, J. F., Malinow, M. R., Chambless, L. E., *et al.* (2004). Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: The Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* **291**, 565–575.
282. Wang, X., Demirtas, H., and Xu, X. (2006). Homocysteine, B vitamins, and cardiovascular disease. *N. Engl. J. Med.* **355**, 207–209.
283. Zee, RY, Mora, S., Cheng, S., *et al.* (2007). Homocysteine, 5,10-methylenetetrahydrofolate reductase 677C > T polymorphism, nutrient intake, and incident cardiovascular disease in 24,968 initially healthy women. *Clin. Chem.* **53**, 845–851.
284. Bazzano, L. A., Reynolds, K., Holder, K. N., and He, J. (2006). Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. *JAMA* **296**, 2720–2726.
285. Kris-Etherton, P. M., Innis, S., American Dietetic Association, and Dietitians of Canada. (2007). Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. *J. Am. Diet. Assoc.* **9**, 1599–1611.
286. Van Horn, L. V., McCoin, M., Kris-Etherton, P. M., *et al.* The evidence for dietary prevention and treatment of cardiovascular disease. *J. Am. Diet Assoc.* (in press).
287. Beauchesne-Rondeau, E., Gascon, A., and Bergeron, J., Jacques, H. (2003). Plasma lipids and lipoproteins in hypercholesterolemic men fed a lipid-lowering diet containing lean beef, lean fish, or poultry. *Am. J. Clin. Nutr.* **3**, 587–593.
288. Davidson, M. H., Hunninghake, D., Maki, K. C., Kwiterovich, P. O. Jr, and Kafonek, S. (1999). Comparison of the effects of lean red meat vs. lean white meat on serum lipid levels among free-living persons with hypercholesterolemia: a long-term, randomized clinical trial. *Arch Intern Med.* **12**, 1331–1338.
289. Hunninghake, D. B., Maki, K. C., Kwiterovich, P. O. Jr, Davidson, M. H., Dicklin, M. R., and Kafonek, S. D. (2000). Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: a long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J. Am. Coll. Nutr.* **3**, 351–60.