Review

Meets Learning Need Codes 5000, 5160, 9000, and 9020

The Evidence for Dietary Prevention and Treatment of Cardiovascular Disease

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ABSTRACT

During the past few decades numerous studies have reported the atherogenic potential of saturated fatty acids, *trans*-fatty acids, and cholesterol, and beneficial effects of fiber, phytostanols/phytosterols, n-3 fatty acids, a Mediterranean diet, and other plant-based approaches. The purpose of this article is to provide a comprehensive and systematic review of the evidence associated with key dietary factors and risk of cardiovascular disease—an umbrella term encompassing diseases that affect the heart and blood vessels, including coronary heart disease, coronary artery disease, dyslipidemia, and hypertension—in conjunction with the work of the American Dietetic Association Evidence Analysis Library review on diet and lipids, updated with new evidence from the past 2 years. The criteria used and results cited provide scientific rationale for food and nutrition professionals and other health professionals for counseling patients. Details of these searches are available within the American Dietetic Association Evidence Analysis Library online (http://adaevidencelibrary.com). Potential mechanisms and needs for future research are summarized for each relevant nutrient, food, or food component.
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During the past 50 years, much evidence has documented a relationship between diet and cardiovascular disease (CVD) risk (1). Specifically, epidemiologic, experimental, and clinical trial evidence have demonstrated a relationship between diet, nutrients, and blood lipid levels; blood pressure; and coronary heart disease (CHD). Evidence from prospective studies have shown that dietary patterns are associated with risk and, specifically, that dietary patterns high in saturated fatty acids, cholesterol, and animal fat increase low-density lipoprotein (LDL) cholesterol levels (2). Clinical trials involving dietary interventions to reduce total fat, saturated fatty acids (SFAs), and cholesterol have further demonstrated favorable responses among dyslipidemic and normolipidemic individuals (3-7). Many (if not most) of these studies focused on single nutrients, such as SFAs and/or dietary cholesterol, or individual fatty acids (ie, n-3 fatty acids, *trans*-fatty acids [TFAs], and α-linolenic acid [ALA]). The National Cholesterol Education Program Adult Treatment Panel III (ATP III) reviewed the evidence in 1999 and recommended the Therapeutic Lifestyle Changes diet and lifestyle (1). Since 2000 research has shifted to other dietary factors, including whole foods and favorable dietary patterns that likewise appear to affect blood lipid levels. As potential nonlipid biomarkers for CVD have also been identified (ie, blood pressure, thrombogenecity, and inflammation) research interest

about how diet might influence these factors has increased (8,9). A review of this research and its strengths is presented here.

METHODS

An expert panel was formed to identify and evaluate current research to develop the American Dietetic Association (ADA) Hyperlipidemia Evidence Analysis Library online entry (www.adaevidencelibrary.com). This review builds on previous works of Van Horn and Ernst (10) and the ADA Hyperlipidemia Guide for Practice (originally presented in 2001 and currently available as the ADA Disorders of Lipid Metabolism Evidence Based Nutrition Practice Guideline, available at https://www.adaevidencelibrary.com/topic.cfm?cat=2651), which encompassed a literature search from 1991-2001 and included 67 primary and 30 review articles. A comprehensive literature search was conducted using PubMed MEDLINE, the Database of Abstracts of Reviews of Effects, and the Agency for Healthcare Research and Quality (AHRQ). Additional articles were identified from bibliographies of recent review articles and personal communication. The ADA Evidence Analysis Library search was limited to human subjects, English language articles, and initially articles published from 2001-2004. Articles were excluded if the sample size was <10 in each treatment group and the dropout rate was >20%. Due to vast numbers of articles identified, additional inclusion and exclusion criteria were applied to each topic. Approximately 1,000 articles were identified initially. After reviewing these articles for relevance and inclusion and exclusion criteria, 83 primary and 19 review articles were accepted and included. The expert panel also identified major studies published after the completion of the original literature search through 2006. More than 50 articles were added. These findings provide the foundation for the ADA Disorders of Lipid Metabolism Guides for Practice (https://www.adaevidencelibrary.com/topic.cfm?cat=2651), which is a more expansive and detailed resource for clinicians. This review is an executive summary that documents relevant evidence, lists conclusion statements, and identifies limitations and gaps in knowledge that requires further research.

REVIEW OF MAJOR FACTORS

Dietary Fat-Related Components that Modify LDL Cholesterol Levels: SFAs, Unsaturated Fatty Acids (UFAs), TFAs, and Dietary Cholesterol

Population studies provide evidence of associations between diets high in SFA and increased total cholesterol (TC) and LDL cholesterol levels, as well as increased risk of both CHD and CVD. Decreasing SFAs, TFAs, and cholesterol in a diet that provides 20% to 35% of energy from fat reduces risk of CHD and CVD. The average per capita consumption of TFA in the United States approximates 5.3 g TFA, or 2.6% of total energy; upper levels of intake are of greater concern (11).

SFA, TFA, and dietary cholesterol increase TC and LDL cholesterol levels in a dose-dependent manner, with SFA and TFA having greater cholesterol-raising effects than dietary cholesterol. Unlike SFA, which raises serum levels of high-density lipoprotein (HDL) cholesterol, TFA decreases HDL cholesterol levels vs SFA, and increases the TC/HDL cholesterol ratio in a dose-dependent manner. Polyunsaturated fatty acids (PUFAs) lower TC and LDL cholesterol levels, whereas monounsaturated fatty acids (MUFAs) mainly have a neutral effect. Isocaloric replacement of SFA with PUFA and MUFA decreases TC and LDL cholesterol levels and the TC/HDL cholesterol ratio (sometimes in response to changes in HDL cholesterol level), which collectively reduces CHD/CVD risk (1).

Status of Current Research

Total Fat Reduction. Recent results from the landmark Women's Health Initiative reported that after 8.1 years there were no statistically significant differences in cardiovascular mortality among participants in the diet modification intervention (<20% of energy from total fat and increased fruit, vegetable, and grain intake) compared to the control diet (12). Because this study's primary outcome measure was breast cancer, there was no specific intervention aimed at reducing SFA, TFA, or blood cholesterol. Total fat intake was reduced by 8.2% based on self-reported food frequency questionnaire data, with small decreases in SFA (2.9% of energy), TFA (0.6% of energy), MUFA (3.3% of energy), and PUFA (1.5% of energy). Adherence data showed that those consuming the lowest levels of SFA (6.1% of energy) had reduced risk of CHD, stroke, and CVD compared to the control group (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.69 to 0.96, $P<0.001$; adjusted HR 0.82, 95% CI 0.67 to 0.99, $P=0.05$). Similarly, those with the lowest TFA intake (1.1% of energy) had reduced risk compared to controls (HR 0.81, 95% CI 0.69 to 0.95, $P<0.001$; adjusted HR 0.84, 95% CI 0.69-1.02, $P=0.10$). These data are supported by the accompanying patterns of LDL cholesterol level reductions in participants stratified by changes in SFA at Year 1 (−10.1 mg/dL* 95% CI −13.5 to −6.6 mg/dL in the quartile with greatest reduction in SFA; $P=0.005$ for trend) and TFA (−9.0 mg/dL, 95% CI. −12.5 to −5.6 mg/dL in the quartile with the greatest reduction; $P=0.03$). Overall, the Women's Health Initiative results suggest that focusing on total fat led to reductions in intake of all fatty acids with subsequent modest improvement in LDL cholesterol level, but no improvement in HDL cholesterol level or other lipid levels (12). It is evident that dietary advice regarding both qualitative and quantitative aspects of fatty acid intake is needed to maximize blood cholesterol lowering.

Saturated Fat- and Cholesterol-Restricted Diets. It has long been known that diets containing <10% kcal from SFA and <300 mg/day cholesterol lower TC and LDL cholesterol levels. Reducing SFA to <7% of total energy and dietary cholesterol to <200 mg/day results in further LDL cholesterol lowering (10). Three randomized controlled trials (RCTs) found that diets containing <7% SFA and <200 mg/day cholesterol reduced LDL cholesterol level by 9% to 12% compared to baseline values or to

**To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L choleseterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.*

Table 1. Blood lipid–lipoprotein level responses to reduced saturated fatty acid (SFA) and cholesterol intake across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Ginsberg (1998) (16)	n=103; healthy adults/ 8 wk on each diet	6.1% SFA; ≈ 275 mg/d cholesterol; 25% total fat vs AAD (15% SFA, ≈ 275 mg/d cholesterol; 34% total fat) (RCT[a], crossover design)	11%↓ LDL[b] cholesterol ($P<0.01$); 11%↓ HDL[c] cholesterol ($P<0.01$); 9%↑ TG[d] (NS[e])
Obarazanek (2001) (15)	n=290; adults; some stage 1 hypertension; some high LDL cholesterol/8 wk on each diet	DASH[f] diet (7% SFA; 141 mg/d cholesterol; 27% total fat vs control diet (14% SFA, 246 mg/d cholesterol; 37% total fat) (RCT)	9%↓ in LDL cholesterol ($P<0.0001$); 7.3%↓ in TC[g] ($P<0.0001$); 7.5%↓ HDL cholesterol ($P<0.0001$); no change in TG; greater decreases in LDL cholesterol and HDL cholesterol in subjects with higher baseline levels
Lichtenstein (2002) (13)	n=36; adults; moderate hypercholesterolemia/ 32 d on each diet	Step 2 diet (7% SFA; 66 mg/1,000 kcal cholesterol; 28% total fat) vs Western diet (15% SFA; 164 mg/1,000 kcal cholesterol; 39% total) (RCT, crossover design)	11%↓ in LDL cholesterol ($P<0.001$); 7%↓ HDL cholesterol ($P<0.001$); no change in TG
Jenkins (2003) (14)	n=25; healthy adults/4 wk	4.4% SFA; 34 mg/1,000 kcal cholesterol; 22% total fat vs baseline (RCT, feeding trial); Portfolio diet discussed in text	12%↓ in LDL cholesterol ($P<0.001$) vs baseline
Appel (2005) (18)	n=164; Adults; prehypertension or stage 1 hypertension; 6 wk each diet	Carbohydrate diet (6% SFA; 58% carbohydrate; 27% total fat) vs protein diet (6% SFA; 25% protein; 27% total fat) vs MUFA[h] diet (6% SFA; 21% MUFA; 37% total fat) (RCT, crossover design, feeding trial)	11.6, 14.2, 13.1 mg/dL[i]↓ in LDL cholesterol level on the carbohydrate, protein, and MUFA diets, respectively vs baseline (1.4, −2.6, −0.3 mg/dL[i]↓ in HDL cholesterol level, respectively; +0.1, −16.4, −9.3 mg/dL[i]↓ in TG, respectively); *P* values not reported for ↓ from baseline

[a]RCT=randomized controlled trial.
[b]LDL=low-density lipoprotein.
[c]HDL=high-density lipoprotein
[d]TG=triglycerides.
[e]NS=not significant
[f]DASH=Dietary Approaches to Stop Hypertension.
[g]TC=total cholesterol.
[h]MUFA=monounsaturated fatty acid.
[i]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.

a Western-type diet (13-15). Other RCTs with <300 mg/day cholesterol report similar LDL cholesterol-lowering response to SFA reduction (13-16). A meta-analysis of the National Cholesterol Education Program Step 2 diet studies (<7% SFA, <200 mg/day cholesterol) with weight loss (3 to 6 kg) reported a 16% decrease in LDL cholesterol level (17).

The OmniHeart Randomized Trial (18) recently evaluated the effects of three reduced SFA and dietary cholesterol diets that varied in macronutrients: one diet high in dietary carbohydrates, one rich in protein, and one high in UFAs and MUFAs. All diets provided 6% SFA. The carbohydrate-rich diet provided 58% of energy from carbohydrate and 27% of energy from total fat, the protein-rich diet provided 25% of energy from protein and 27% of energy from total fat, and the UFA-rich diet provided 37% of energy from total fat (21% MUFA). LDL cholesterol levels decreased 11.6, 14.2, and 13.1 mg/dL on the carbohydrate-rich, protein-rich, and UFA-rich diets, respectively, vs baseline. HDL cholesterol level changed by −1.4, −2.6, −0.3 mg/dL*, respectively. Triglyceride (TG) levels changed by +0.1, −16.4, −9.3 mg/dL† respectively. Compared to the carbohydrate-rich diet, both the protein-rich and UFA-rich diets significantly lowered TG levels. The UFA-rich diet increased HDL cholesterol levels compared to the carbohydrate-rich diet. Therefore, partial substitution of carbohydrate for protein or UFA favorably affects TG and HDL cholesterol levels (Table 1).

Portfolio Diet. The Therapeutic Lifestyle Changes diet recommended by ATP III is low in SFA (<7% energy) and cholesterol (<200 mg/day) and also includes viscous fiber (10 to 25 g/day) and plant sterols/stanols (2 g/day). The portfolio diet is a vegetarian approach that meets these recommendations and includes soy protein (21 g/1,000 kcal) and almonds (14 g/1,000 kcal) (14). In one small study (n=25), this diet under controlled conditions re-

†To convert mg/dL triglycerides to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.6. Triglycerides of 159 mg/dL=1.80 mmol/L.

duced LDL cholesterol levels by 35% after 1 month ($P<0.001$) (14). A longer-term (1 year) study of the portfolio diet (n=66) reported that individuals who adhered well (31.8% of participants) to the diet reduced LDL cholesterol levels by 29.7% (no P value given) (19). Larger studies across different age and ethnic groups are needed.

Individual Fatty Acid Modifications/Substitutions. Several types of trials have evaluated the effect of different fatty acids on LDL cholesterol levels and found consistent positive correlations with total dietary SFA. For every 1% change in total energy from SFA, a 1.8 mg/dL change in LDL cholesterol level was expected (20). For every 1% increase in PUFA, a 0.50 mg/dL decrease in LDL cholesterol level was predicted. Replacing SFA with MUFA (diets provided 4% to 12% and 17% to 33%, respectively) decreased LDL cholesterol between 2.2% and 21.6% (21). A randomized crossover trial that substituted carbohydrate or oleic acid for LDL cholesterol-raising SFA (eg, lauric, myristic, and palmitic fatty acids [LMPs] at 8% of energy), decreased LDL cholesterol levels 4.8% and 8%, respectively (22). Isocalorically replacing dietary carbohydrate with MUFA and PUFA lowered the TC/HDL cholesterol ratio compared to SFA as reported in a meta-analysis of 60 RCTs (23). Moreover, LMP raised LDL cholesterol and HDL cholesterol levels whereas stearic acid had a neutral effect. The authors emphasized that risk reduction is most effective when SFA and TFA are replaced with cis-UFA.

Replacing SFAs with TFAs. The meta-analysis (23) also reported that *trans* MUFA (intake ranged from 0% to 10.9% of energy) increased the TC/HDL cholesterol ratio almost twice that of SFA at a comparable dose. Previously, it was reported that replacing 10% of energy from butter with stick margarine (high in TFA) lowered TC by 7.3 mg/dL*, LDL cholesterol by 4.2 mg/dL, and HDL cholesterol by 0.77 mg/dL, respectively, with no effect on TC and HDL cholesterol (24). Replacement with soft-tub margarine low in TFA decreased TC by 9.7 mg/dL and LDL cholesterol by 7.7 mg/dL, respectively, did not affect HDL cholesterol levels, and decreased TC/HDL cholesterol ratio by 7.7 mg/dL. The authors emphasized the importance of reducing both SFA and TFA and replacing them with UFA for the most favorable response (23).

RCTs with TFAs. Three RCTs with small sample sizes involving either mildly hypercholesterolemic or healthy men and women were reviewed (Table 2). A study of 30 mildly hypercholesterolemic men and women (LDL cholesterol >130 mg/dL) compared the effects of diets containing soybean oil, semiliquid margarine, soft-margarine, shortening, and stick margarine (TFA=0.55%, 0.91%, 3.3%, 4.15%, and 6.72% of total energy, respectively) on lipids and lipoproteins (25). LDL cholesterol level decreased by 12%, 11%, 9%, 7%, and 5%, respectively, compared to a diet rich in butter (TFA=1.25% of total energy) ($P<0.05$). HDL cholesterol level was 6% lower only on the stick margarine diet (highest level of TFA; $P<0.05$). TC/HDL cholesterol ratio was lowest on the soybean-oil or semiliquid margarine diets and highest on the stick margarine diet. In addition, TFA decreased LDL cholesterol particle size in a dose-dependent manner ($P<0.001$) (25). In 32 healthy men and women (26), a diet high in TFA (9.3% of energy; SFA=12.9% of energy) vs a diet high in SFA (TFA=0.3% of energy, SFA=22.9% of energy) evoked a similar LDL cholesterol response, TC was 12 mg/dL lower ($P=0.0007$), and HDL cholesterol was 16.6 mg/dL lower ($P<0.0001$), whereas the LDL/HDL cholesterol ratio was higher ($P<0.0001$) after the TFA diet. The third study utilized six diets and mildly hypercholesterolemic adults. Each diet period was 5 weeks and the diets differed by 8% in the energy provided by either carbohydrate or different fatty acids (22). Two diets high in TFA (4% or 8% energy) were compared to a diet rich in LMP. LDL cholesterol was 4.8% higher after the 8% TFA diet and HDL cholesterol significantly lower (10% and 11%, respectively) compared to LMP. These results demonstrate that dietary TFA should be avoided.

Replacing Carbohydrates with TFAs. Mensink and Katan (23) reported that when carbohydrates were isocalorically replaced (for every 1% of energy) with *trans* MUFA, TC (coefficient 0.031; 95% CI 0.02 to 0.042), LDL cholesterol (coefficient 0.04; 95% CI 0.02 to 0.06), and TC/HDL cholestrol (coefficient 0.022; 95% CI 0.005 to 0.038) increased, and HDL cholesterol and TG were unaffected. Also, Judd and colleagues (22) reported that in 50 men, diets high in TFA (4% and 8% of energy) increased TC, LDL cholesterol level, and TC/HDL cholesterol ratio vs dietary carbohydrate. There was no effect of TFA on HDL cholesterol level or HDL cholesterol subfractions.

Published Research on Effect of TFAs on Lipid Levels Since Completion of ADA Evidence Analysis Library

Consistent with earlier results reporting increases in LDL cholesterol with *trans* fat compared to dietary carbohydrate, a recent study found an LDL cholesterol-raising effect with partially hydrogenated soybean oil (PHSO) containing 2.5% of energy from TFA compared to standard soybean oil or low SFA soybean oil (27). Compared to the standard soybean oil diet, the difference in LDL cholesterol was −3.2% for the soybean oil compared to an increase of 5.6% for the PHSO ($P<0.05$). A high oleic acid soybean oil and low linolenic acid soybean oil also showed a similar LDL cholesterol-lowering effect. Compared to the standard soybean oil diet, LDL cholesterol levels did not change on the high oleic soybean oil diet or the low linolenic acid soybean oil diet (141.3 mg/dL vs 142.8 mg/dL, and 143.2 mg/dL, respectively). The TC/HDL cholesterol ratio was significantly higher after the PHSO vs standard, low SFA, and high oleic soybean oils (183 mg/dL vs 176 mg/dL, 171 mg/dL, and 169 mg/dL, respectively). All nonhydrogenated soybean oils resulted in more favorable lipid profiles than PHSO.

Two studies evaluated ruminant TFAs on blood lipid profiles of healthy men (28,29). One study (28) evaluated the effects of dairy products enriched in cis-9, *trans*-11 conjugated linoleic acid *trans*-11, 18:1 in healthy middle-aged men. After consumption of 1.42 g/day ruminant *trans* fat there was no effect on TC, LDL cholesterol, and HDL cholesterol levels. The LDL/HDL cholesterol ratio increased by 4% ($P=0.023$) compared to baseline. A study conducted by Tholstrup and colleagues (29) evaluated the effects of test diets high (3.6 g/day) or low (0.4 g/day) in vaccenic acid (provided by butter) on lipids and lipoproteins. The high vaccenic acid diet decreased TC levels −6% ($P=0.05$) and HDL cholesterol levels −9%

Table 2. Blood lipid-lipoprotein level responses to changes in *trans*-fatty acid (TFA) intake across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Lichtenstein (1999) (25)	N=36; adults; hypercholesterolemic (LDL[a] cholesterol >130 mg/dL[b])/35 d each	Soybean oil (TFA=0.55% of total energy); semiliquid margarine (TFA=0.91% of total energy); soft-margarine (TFA=3.3% of total energy); shortening (TFA=4.15% of total energy); and stick margarine (TFA=6.72% of total energy) vs butter (TFA=1.25% of total energy) (RCT[c], crossover design, feeding study)	↓ LDL cholesterol 12%, 11%, 9%, 7%, 5% ($P<0.05$), no ↓ HDL[d] cholesterol except stick margarine ↓ HDL cholesterol 6% ($P<0.05$), TC[e]/ HDL cholesterol was lowest with the soybean-oil and semiliquid margarine and highest with stick margarine, TFA ↓ particle size in a dose-dependant manner ($P<0.001$)
de Roos (2002) (26)	N=32; healthy adults/4 wks each	*Trans*-diet (TFA 9.3% of energy; SFA[f] 12.9% of energy) vs sat-diet (TFA 0.3% of energy, SFA 22.9% of energy) (RCT, crossover design, feeding study)	Compared to the diet rich in SFA, the diet rich in TFA ↓ TC 0.31 mmol/L[b] ($P=0.0007$), ↓ HDL cholesterol 0.36 mmol/L[b] ($P<0.0001$), with nonsignificant effects on LDL cholesterol and triacylglycerols.
Judd (2002) (22)	N=50; men; normocholesterolemic/ 5 wk each	TFA 4% or 8% energy vs diet rich in LMP[g] or carbohydrate (RCT, crossover design, feeding study)	Compared to LMP, 8% TFA diet ↑ LDL cholesterol 4.8% ($P<0.01$), ↓ HDL cholesterol 11.1% ($P<0.01$); 4% TFA ↓ HDL cholesterol 9.9%
Lemaitre (2006) (34)	N=214; subjects with IHD[h] and 214 controls/6 y (1992-1998)	Cardiovascular Health Study of subjects with fatal IHD; study of TFAs in plasma (case-control nested study)	Higher levels of plasma phospholipid *trans* 18:2 fatty acids associated with higher risk of IHD (odds ratio for interquintile range 1.68, 95% confidence interval 1.21 to 2.33) after adjustment for risk factors and *trans* 18:1 levels. *Trans* 18:1 levels above the 20th percentile associated with lower risk (odds ratio 0.34, 95% confidence interval 0.18 to 0.63)
Colon-Ramos (2006) (33)	1,797 incident cases of first nonfatal MI[i] matched with 1,797 population controls/ between 1994 and 2004	Comparison of adipose tissue TFA (observational study)	Total TFA positively associated with ↑ MI risk after adjusting for established risk factors (odds ratio by quintiles of total TFA: 1.00, 1.37, 1.91, 1.86, 3.28; *P* for trend <0.001). The association was mostly due to 18:2 *trans*
Lichtenstein (2006) (36)	30 moderately hyperlipidemic adults /5 experimental diets consumed for 35 d each	Subjects fed diets at 30% energy from fat, soybean oils with different fatty acid profiles: regular, low-sat fat, high-oleic, low-α-linoleic, or partially hydrogenated (controlled feeding study)	Favorable LDL cholesterol level was associated with all varieties of soybean oil, except the partially hydrogenated form ($P<0.05$)
Tricon (2006) (28)	Healthy middle-aged men (N=32)/2 diets consumed for 6 wk each with a 7-wk washout between periods	Consumption of ultra heat-treated milk, butter, and cheese that provided 0.151 g/d (control) or 1.421 g/d (modified) *cis*-9,*trans*-11 conjugated linoleic acid (randomized, double-blind, placebo-controlled, crossover design, feeding study)	LDL/HDL cholesterol from baseline to end of phase ↓ −0.10 in control condition; ↑ 0.11 in modified condition ($P=0.023$). Other changes not significant. Dairy products naturally enriched (modified condition) do not appear to have a significant effect on blood lipid profile.
Tholstrup (2006) (29)	Healthy young men (N=42)/5 wk	Consumption of test butter high in vaccenic acid (3.6 g/d) or a control butter with low content of vaccenic acid (double-blind, randomized, parallel intervention study)	Butter high in ruminant *trans* or vaccenic acid ↓ TC by 6% ($P=0.005$) and ↓ plasma HDL cholesterol by 9% ($P=0.002$) compared to controls. Ratio of total to HDL cholesterol did not differ significantly between groups.

[a]LDL=low-density lipoprotein.
[b]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
[c]RCT=randomized controlled trial.
[d]HDL=high-density lipoprotein.
[e]TC=total cholesterol.
[f]SFA=saturated fatty acid.
[g]LMP=lauric, myristic, and palmitic fatty acids.
[h]IHD=ischemic heart disease.
[i]MI=myocardial infarction.

(P=0.002). The TC/HDL cholesterol ratio was unchanged. The available data indicate that the isomeric structure of TFA affects the cholesterolemic response.

Effect of TFAs on Coronary Events

A case-control study (30) (N=964) reported that the highest (4.40 g/100 g) vs lowest (1.84 g/100 g) quintile of adipose tissue TFA was associated with an approximate threefold increased risk of myocardial infarction (MI) (P<0.05). Adipose tissue TFA is considered a reasonable objective marker of long-term TFA intake, but cost, discomfort, and inconsistent sensitivity of measures precludes routine use for clinical screening.

A prospective cohort study of 667 male participants noted a 2% energy increase in TFA was associated with a 1.3-fold increased risk of MI in 98 cases within 10 years (P=0.0001) (31). The Nurses' Health Study (32) reported that the highest (5.7 g/day) vs the lowest (2.4 g/day) quintile of TFA intake was associated with an increase in CHD risk (121,700 female participants, relative risk (RR) 1.50, 95% CI 1.12 to 2.00, P for trend=0.001). Studies continue to provide compelling reasons to avoid TFA.

Published Research on Effect of TFAs on Coronary Outcomes since Completion of the ADA Evidence Analysis Library

In an observational study conducted in Costa Rica (33), total adipose tissue TFA was positively associated with increased MI risk after adjusting for established risk factors. By adipose tissue total TFA quintiles, the odds ratio (OR) values were 1.00, 1.37, 1.91, 1.86, and 3.28 (P for trend <0.001). The association was due mainly to adipose tissue C18:2 TFA. Similiar findings were reported in a case-control study with 214 subjects with fatal ischemic heart disease (34). In this study, higher levels of plasma phospholipid *trans* 18:2 fatty acids were associated with higher risk of fatal ischemic heart disease (IHD). Interestingly, higher levels of *trans* 18:2 fatty acids were associated with higher risk whereas *trans* 18:1 fatty acids were associated with lower risk. A recent analysis of Nurses' Health Study data (35) showed that total TFA (measured in red blood cells, a good biomarker of intake) was associated with an elevated risk of CHD. Thus, on the basis of the clinical trial evidence and much observational data, reducing elaidic acid as well as other synthetic TFA is appropriate. The limited evidence for *trans* 18:2 fatty acid suggests that targeted efforts are needed to also reduce this trans isomer. With respect to the *trans* isomers in ruminant fat, it is clear that more research is needed before definitive recommendations can be made.

Summary of Research-Based Dietary Recommendations and Fat-Related Components that Modify LDL Cholesterol Level

The Therapeutic Lifestyle Changes diet, providing 25% to 35% of energy from total fat, <7% from SFA and TFA combined, and <200 mg/day dietary cholesterol is recommended by ATP III (1). The American Heart Association recommends a diet that contains <7% from SFA and <1% of energy from TFA. Tailoring the diet to meet individual needs is encouraged. Based on energy needs and risk factors, SFA and TFA should be replaced isocalorically with complex carbohydrates and/or UFA, including both MUFA (not to exceed 20% of energy) and PUFA (not to exceed 10% of energy). This approach involves shifting the food pattern to include more plant-based and fewer animal foods. Detailed guidance on how best to achieve this eating pattern is provided in the 2006 American Heart Association Diet and Lifestyle Recommendations revision (36). A recent publication from an American Heart Association Conference on *Trans* Fat Alternatives summarizes the complexities of completely reducing dietary TFA and discusses the significant progress that has been (and is being) made to achieve this goal (37).

Additional Research Needed

Table 1 summarizes recent high-quality studies regarding the effects of reducing SFA on lipid and lipoprotein levels based on RCT data. Research is needed to further define the optimal macronutrient substitutions qualitatively and quantitatively for SFA, TFA, UFA, protein, and carbohydrate to attain the most beneficial lipid and lipoprotein profile in the general population and in patients at increased risk for CVD. Effects of the specific TFA isomers on lipid and lipoprotein levels remain unclear.

NUTS AND LIPID LOWERING

General Relationship

Observational studies reported that nut consumption is associated with a reduced CHD risk (38). A dose-dependent relationship has been reported but controlling for confounders is challenging in these studies. The reported cardioprotective effects may be due, in part, to the unique nutrient profile of nuts.

Potential Mechanisms

Nuts are high in UFA and low in SFA. Some nuts, like walnuts, are high in ALA. Nuts are also a source of vegetable protein and plant sterols. Because of their nutrient profile, nuts favorably affect lipid and lipoprotein levels. In addition, nuts may displace foods high in SFA and cholesterol thereby further favorably affecting plasma lipid and lipoprotein levels.

Status of Current Research

Five controlled studies conducted from 2000 to 2003 were included in this review (Table 3). Sample sizes were small (mostly) and subjects studied were healthy; one study evaluated subjects with type 2 diabetes. After 2 to 8 weeks, daily consumption of 50 to 113 g nuts (walnuts, almonds, almond oil, and pecans) decreased TC (4% to 22%) and LDL cholesterol (6% to 30%) levels (39-43). Only one study (43) found no change in TC, but LDL cholesterol level was 10% lower (43). Findings regarding HDL cholesterol levels were mixed. Eleven clinical trials confirmed these findings when 18% to 20% of energy is consumed as walnuts, almonds, peanuts, macadamia and pistachios (44). One study (40) reported no effect on insulin sensitivity. Long-term effects are unknown.

Despite beneficial effects of nuts, it should be noted that three studies (39,41,42) were confounded by higher SFA and cholesterol content of the reference diets compared to the nut-rich diets, which may partially explain the observed reductions in TC and LDL cholesterol levels.

Table 3. Blood lipid–lipoprotein level responses to nuts across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major finding[a]
Iwamoto (2002) (39)	40 healthy men and women/2 wk	50-54 g walnuts daily; SFA[b] was ~7% on the reference diet and ~5% on the walnut diet (randomized crossover design)	↓ TC[c] 4.5%, ↓ apo B[d] 7.7%, ↓ LDL[e]/HDL[f] cholesterol ratio 10.3% vs control diet ($P<0.05$)
Lovejoy (2002) (40)	20 healthy men and women/4 wk	100 g almonds daily	↓ TC 21%, ↓ LDL cholesterol 29% vs baseline ($P<0.001$)
Sabate (2003) (41)	25 healthy men and women; multiethnic/4 wk	20% of fat from almonds (~68 g) vs Step 1 diet. High almond diet provided 6% less energy from SFA vs Step 1 diet (randomized crossover design)	↓ TC 4.4%, ↓ LDL cholesterol 7.0% vs Step 1 diet ($P<0.001$)
Hyson (2002) (42)	22 healthy men and women/6 wk	66 g almonds daily or 35 g almond oil daily. SFA intake was 8% on almond diets and 10% at baseline (randomized crossover design)	Both diets produced comparable lowering of serum lipids: ↓ TC 4%, ↓ LDL cholesterol 6%, ↓ TG[g] 14%, ↑ HDL cholesterol 5% vs baseline ($P<0.05$)
Morgan (2000) (43)	19 healthy men and women/8 wk	68 g pecans daily. SFA intake did not differ between the experimental and baseline diet (randomized controlled trial)	↓ LDL cholesterol 6% vs baseline ($P<0.05$) and ↓ LDL cholesterol 19% vs control group ($P<0.05$)
Zibaeenezhad (2006) (45)	52 subjects with hyperlipidemia/8 wk	Persian walnuts (20 g/d) for 8 wk (randomized case-control parallel arm study)	↓ TG 17% ($P<0.02$), ↑ HDL cholesterol 9% ($P<0.03$)
Tapsell (2004) (47)	58 men and women with type 2 diabetes/6 mo	Walnuts (30 g/d) for 6 mo (randomized case-control parallel arm study)	↓ LDL cholesterol 10% ($P=0.03$), ↑ HDL cholesterol (from 1.10 to 1.30 mmol/L[h]) ($P=0.05$)
Zhao (2004) (46)	20 men and 3 women with moderately elevated LDL cholesterol level/6 wk	Walnuts (37g/d) and walnut oil (15 g/d) that provided a high linoleic acid diet for 6 wk (randomized crossover study)	↓ TC 11%, ↓ LDL cholesterol 12%, ↓ TG 18%, ↓ apo B 9% vs average American diet ($P<0.05$ for all)

[a]All significant findings reported.
[b]SFA=saturated fatty acid.
[c]TC=total cholesterol.
[d]apo B=apolipoprotein B.
[e]LDL=low-density lipoprotein.
[f]HDL=high-density lipoprotein
[g]TG=triglycerides.
[h]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7.Cholesterol of 193 mg/dL=5.00 mmol/L.

In these studies (39,41,42), the nut diets provided 2% to 6% fewer SFA kilocalories compared to the reference diet. In addition, one study (42) fed four different diets with varying levels of total fat (37% or 25%) and found dietary fat level had more of an effect on serum lipid levels than did fat source (almonds vs olive or canola oil). TC level was 3% lower with lower fat intake, while TG was 16% lower and TC/HDL cholesterol ratio was 4% lower with the higher fat intake (42). One walnut study reported an inverse association between ALA intake and LDL cholesterol level in women (Table 3) (39).

Published Research on Nuts Since Completion of the ADA Evidence Analysis Library

Since the ADA Evidence Analysis Library review was conducted, three studies have been published evaluating the effects of walnuts on lipid and lipoprotein levels in hypercholesterolemic subjects (45,46) and subjects with type 2 diabetes (47). Subjects received 20 g walnuts (45), 30 g walnuts (47), or 37 g walnuts plus 15 g walnut oil per day (46) for 8 weeks, 6 months, and 6 weeks, respectively. The test diets with walnuts significantly decreased LDL cholesterol 10% ($P=0.03$) (47) and 12% ($P<0.05$) (46). Triglyceride levels decreased in two studies by 17% ($P<0.05$) (45) and 18% ($P<0.05$) (46). In addition, HDL cholesterol levels increased in two studies by 9% ($P<0.03$) (45) and approximately 18% ($P=0.05$) (47).

Effects of Nut Consumption on CHD Events: Observational Data

The Nurses' Health Study (48) evaluated the association between nut consumption and relative risk of CHD in 86,016 women. After 14 years of follow-up, 1,255 CHD events were reported. After adjusting for age, smoking, and other known CHD risk factors, women who ate more than 5 oz nuts/week had a significantly lower CHD risk than those who rarely or never ate nuts. In 1980, 5% of women reported

eating nuts ≥5 times/week but this level dropped by 1990 where only 3% reported eating nuts this often ($P=0.0009$). Whether other confounders may influence these results is difficult to assess from food frequency data.

Summary of Research-Based Dietary Recommendations and Nut Consumption

Consumption of ¾ oz to 1 oz unsalted nuts daily or up to 5 oz weekly, isocalorically substituted for other foods (to prevent excessive energy intake and weight gain), is suggested to confer cardiovascular benefits (44). Table 3 summarizes current research evidence from RCTs.

SOY AND LDL CHOLESTEROL LEVEL LOWERING

General Relationship

Controlled clinical studies as well as meta-analyses have evaluated the effects of soy on lipid and lipoprotein levels. Interpretation of the results of these studies has been complicated by numerous factors, such as the amount and various forms of soy used, including soy protein, soy protein isolate, soy flour, and soy oil, and more specifically the isoflavones comprising soy protein, genestein, and daidzein. Differences in baseline lipid levels have further confounded results because subjects with higher baseline values are generally more responsive. Other limitations in study design and nonstandardized methodology often preclude generalizability and further reduce strength of evidence.

Potential Mechanisms

Soy has a modest LDL cholesterol-level lowering effect possibly via substitution for other animal protein-rich foods with higher saturated fat content or a potentially favorable effect on LDL-receptor status, which lowers serum LDL cholesterol levels. Soy isoflavones also may have beneficial vascular effects, but these results are inconclusive.

Status of Current Research

Two meta-analyses and five clinical trials were reviewed to examine the effects of soy protein on lipids and lipoproteins (Table 4). Of these studies, one meta-analysis and five clinical studies evaluated isoflavones as well as soy protein.

In a 1995 meta-analysis of 29 studies, a soy protein diet (mean 47 g/day) compared to a control diet, reduced TC by 9.3%, LDL cholesterol by 12.9%, and TG by 10.5% (49). Initial cholesterol value was the primary predictor of cholesterol response because the higher the initial cholesterol, the greater the cholesterol-lowering diet effect.

A more recent meta-analysis of 10 studies with a total of 959 participants found soy protein plus isoflavones (26 g soy protein and 52 mg isoflavones, on average) in place of animal or dairy protein did not significantly lower LDL cholesterol level; however, it increased HDL cholesterol levels by 3% (50). The recent RCTs have also reported conflicting results when 26 to 50 g soy protein with 80 to 165 mg isoflavones were evaluated (Table 4). All studies involved patients with type 2 diabetes and/or hypercholesterolemic participants and reported decreases in TC (4% to 12.5%) and LDL cholesterol (7% to 18%) (51-54). One study in postmenopausal women with hypercholesterolemia reported improved endothelial function but no effect on blood lipid levels (55). TG level was reduced in one study (51), whereas four studies found no effect (52-55).

One of the five RCTs assessed a potential dose-response relationship between soy protein and isoflavones and changes in lipid levels. This study reported no difference between a commercial product containing 30 g isolated soy protein with 81 mg aglycone isoflavones or 50 g isolated soy protein with 135 mg aglycone isoflavones (108 male, 22 female participants; $P=0.01$) (54).

Published Research on Soy and CVD Since Completion of the ADA Evidence Analysis Library

More recent studies demonstrate little effect of soy protein with and without isoflavones on lipid and lipoprotein levels in healthy subjects (56-58). Subjects consumed similar amounts of soy protein daily: 31.5 g soy protein and 120 mg isoflavones in the aglycone form; 32 g soy protein isolate either low or high in isoflavones (ie, 1.64 mg or 61.7 mg aglycone isoflavone); and 30 g soy protein, 100 mg isoflavones, and 9 g cotyledon fiber, respectively. The study by Ma and colleagues (56) used water-washed (which preserves the isoflavone content) not alcohol-washed soy protein. All three studies reported no significant effects on lipid and lipoprotein levels in normocholesterolemic (57) or hypercholesterolemic subjects (56,58). However, McVeigh and colleagues (57), despite no effects on lipids and lipoprotein levels, reported that both soy protein treatments similarly and significantly lowered the ratios of TC/HDL cholesterol (5%; $P<0.05$); LDL/HDL cholesterol (8.6%; $P<0.05$); and apolipoprotein B (apo B):apolipoprotein A (6.3%; $P<0.05$) (57). In addition, when equol excretion status was included as a covariate in the statistical model, LDL cholesterol level was significantly lower after consumption of both low and high isoflavone soy protein isolate. Some people form and excrete equol, which is a measure of biotransformation of soy isoflavones to the more potent estrogenic isoflavone, equol (59). In the study by Hermansen and colleagues (58), a subset of subjects (postmenopausal women) who participated in a substudy to evaluate the vascular effects of soy protein plus cotyledon and isoflavones, the soy supplement decreased LDL cholesterol levels 7.6% compared to the placebo.

Soy protein (30 g/day) (60) or soybean β-conglycinin (5 g/day; one of the major soy storage proteins in soy protein isolate) (61) was studied in two different subject cohorts: dialysis patients with hypercholesterolemia (60) or subjects with elevated LDL cholesterol and TG levels (61). In patients undergoing hemodialysis (n=27), soy protein substitution for milk protein decreased TC 17%, LDL cholesterol 15%, and apo B 14% ($P=0.05$ for all) (60). In the study by Kohno and colleagues (61), subjects with hypertriglyceridemia were given β-conglycinin for 4, 8, and 12 weeks and TG levels decreased by 13.6% compared to baseline. In another experiment in that article (61) with subjects with visceral obesity, β-conglycinin had no effect on lipid and lipoprotein levels after 20 weeks of treatment.

As discussed earlier, Jenkins and colleagues (19) conducted a 1-year study to test the effectiveness of implementation of the Portfolio Diet by hyperlipidemic, free-living subjects (N=66). Subjects were instructed to consume a low-fat diet with 22.5 g soy protein per 1,000 kcal from soy milk and soy meat analogs with: 1.0 g plant

Table 4. Blood lipid–lipoprotein responses to soy intake across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Hermansen (2001) (51)	n=14 men with type 2 diabetes n=6 women with type 2 diabetes; 15 wk	Supplement with 50 g isolated soy protein, total isoflavones 165 mg, and 20 g soy cotyledon fiber vs placebo supplement. Controlled double-blind crossover with 23-wk washout	LDL[a] cholesterol −10% ($P<0.05$) LDL/HDL[b] ratio −12 % ($P<0.05$) TG[c] −22% ($P<0.05$) HDL no change
Jayagopal (2002) (52)	N=32 postmenopausal women with diet-controlled type 2 diabetes; 12 wk per treatment plus 2-wk washout	Soy treatment: 30 g isolated soy protein with 132 mg isoflavones. The product was completely devoid of soluble fiber and each sachet provided 243 kcal vs control treatment, of an identical sachet containing 30 g pure microcrystalline cellulose of no significant caloric content. Randomized controlled trial, double-blind, placebo-controlled.	Serum insulin HOMA-IR[d] and HbA1c[e] decreased (−8.09%, $P=0.006$%, -6.47%, $P=0.003$, −0.064%, $P=0.048$, respectively)/12 wk soy. TC[f] −4.07%, $P=0.004$, LDL cholesterol −7.09%, $P=0.001$; no changes in HDL or TG
Puska (2002) (53)	N=60 men and women; 6 wk	Randomized controlled trial, double-blind, parallel, single-center trial. Isolated soy protein supplement added to regular diet.	LDL cholesterol level reduced 0.27 mmol/L[g]; $P=0.049$
Tonstad (2002) (54)	N=130 men and women with hyperlipidemia	Fed 30 g isolated soy protein vs casein	No significant differences in any lipid–lipoprotein measure
Cuevas (2003) (55)	N=18 postmenopausal women with hyperlipidemia	Low-fat diet randomized to isolated soy protein vs casein 4 wk then alternate treatment	No significant differences in LDL cholesterol level; flow-mediated dilation was improved
Ma (2005) (56)	N=159 men and women	Randomized double-blind placebo controlled trial; soy with isoflavones vs milk protein; 5 wk	No significant differences in soy based LDL cholesterol level reduction, regardless of isoflavone content
McVeigh (2006) (57)	N=35 males	Randomized to soy protein isolate vs milk protein isolate; 57 d each	No significant differences in individual serum lipid levels, ratios were favorably enhanced
Hermansen 2005 (58)	N=100 participants with hypercholesterolemia	Randomized double-blind parallel intervention; 24 wk soy supplement with isoflavones vs dairy protein	No significant changes in lipid levels observed
Jenkins (2006) (19)	N=66 men and women with hyperlipidemia	Randomized controlled trial/12 mo; low-saturated-fat diet plus almonds, plant sterols, fiber and 22.5 g soy protein	LDL cholesterol level reduced −14.0% and −12.8 ($P<0.001$) respectively at 3 mo and 1 y. Better adherence to all diet constituents yielded best results
Chen (2006) (60)	N=26 patients on hemodyalisis with hypercholesterolemia	Randomized double blind clinical trial; 4 wk run-in phase Isolated soy protein vs milk protein	Significant changes in TC, LDL cholesterol levels: −17.2% and −15.3%, respectively ($P=0.03$ and $P<0.05$, respectively)
Kohno (2006) (61)	N=138 age 26-69 y with TG >1.69 mmol/L[g]	Randomized into β-conglycinin vs casein; 12 wk/ 4-wk washout	Serum TG reduced by 0.31±0.08, 0.26±0.09, and 0.36±0.09 mmol/L[b] respectively after 4, 8, and 12 wk intervention, respectively

[a]LDL=low-density lipoprotein.
[b]HDL=high-density lipoprotein.
[c]TG=triglycerides.
[d]HOMA-IR=homeostasis model assessment insulin resistance.
[e]HbA1c=hemoglobin A1c.
[f]TC=total cholesterol.
[g]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.

sterols per 1,000 kcal, 10 g viscous fiber per 1,000 kcal, and 23 g whole almonds per 1,000 kcal. After 1 year, LDL cholesterol levels decreased 12.8% ($P<0.001$). Of note, is that 32% of participants had LDLcholesterol level reductions >20% after 1 year (these were subjects who adhered best to the diet) (19).

In 2006 the American Heart Association published a critical summary of the literature regarding soy and reported that LDL cholesterol levels lowered about 3% in RCTs of isolated soy protein with isoflavones vs milk or other proteins. On the basis of study design and strength of evidence, the American Heart Association concluded that soy offered no particular advantages in lipid lowering but served as an excellent vegetable protein source for low-SFA diets (62).

US Food and Drug Administration (FDA) Health Claim for Soy Protein

In 1999, the FDA issued a health claim stating that 25 g/day soy protein was associated with reduced risk of CHD. The current research does not support the earlier findings that were the basis for the FDA health claim. Soy foods can be used as a plant protein substitute for animal protein foods high in SFA (62), but expected LDL cholesterol lowering may be modest and most likely in subjects with hypercholesterolemia.

Additional Research Needed

As recommended by the American Heart Association Science Advisory Committee on soy protein (62), studies are needed to assess and compare the influence of higher protein intake from plant vs animal sources on CVD risk factors. In the meantime, soy protein foods could provide a useful strategy for decreasing saturated fat intake when substituted for animal foods.

PHYTOSTEROLS AND LDL CHOLESTEROL LEVEL LOWERING

General Relationship

Plant sterols (phytosterols) are chemically related and structurally similar to cholesterol. The most common phytosterols include β-sitosterol, campesterol, and stigmasterol. Sitostanol is the most common plant stanol, which is a saturated derivative of sitosterol. Sterol/stanol esters are esterified to UFA to facilitate maximal incorporation into small amounts of fat.

Potential Mechanisms

Plant sterols and stanols decrease TC and LDL cholesterol levels by reducing dietary and biliary cholesterol absorption via the displacement of cholesterol from micelles resulting in reduced cholesterol solubility in the intestine.

Status of Current Research

RCTs have demonstrated cholesterol-lowering effects of esterified plant sterols and stanols in normocholesterolemic and hypercholesterolemic individuals (Table 5).

Three studies examined sterol-enriched foods (eg, spreads, low-fat yogurt, and bakery products) in normocholesterolemic participants and found that after 4 weeks to 1 year of consumption, 1.6 to 3.2 g/day sterols reduced TC 4% to 8.9%, and LDL cholesterol 6% to 14.7% (23,63,64). Similar results were reported in two studies conducted with Japanese adults given 2 or 3 g/day plant stanol or sterols (65,66). One study did not report a significant decease in TC and LDL cholesterol levels with 0, 3, 6, or 9 g/day sterol ester-enriched spreads and salad dressings (67). Recent research with plant stanols and sterols used low-fat hard cheese (68) as the food source and different population groups, including subjects with hypercholesterolemia taking statin drugs (69,70) and postmenopausal women with and without CAD (71). The results consistently show a similar LDL cholesterol level reduction as reported in earlier studies (ie, 5.8%, 9.1%, and 7.9% reduction respectively, in response to 1.8 to 2.0 g plant stanols (68-70). Plant sterol esters decreased TC by 8.7% in the coronary group and 11% in the noncoronary group (71). These results are consistent with a recent meta-analysis of six studies conducted in normo- and hypercholesterolemic subjects that evaluated cholesterol-lowering effects of phytosterols/stanols and reported 7% to 11% decrease in LDL cholesterol after 4 weeks to 3 months of intervention (72).

Seven studies evaluated the cholesterol lowering effectiveness of esterified and nonesterified plant sterols and stanols in adults with hypercholesterolemia (73-79). Four studies with 36 to 115 subjects found that 1.5 g to 5 g esterified and non-esterified plant sterols (in margarine, fortified orange juice, bread, meat products, and jam) consumed for 5 weeks to 1 year lowered TC 7.2% to 10.2% and LDL cholesterol 11.3% to 14.1% (73-76,79). In three other studies, 1.6 g to 3.2 g/day esterified and nonesterified stanols (in enriched bread, cereals, and spreads) reduced TC 2.8% to 11.9% and LDL cholesterol 1.7% to 13.4% (77-79). Thus, both sterols and stanols either esterified or nonesterified lower TC and LDL cholesterol levels similarly.

Questions have been raised about whether or not phytosterols are effective in persons consuming low-fat, low-cholesterol diets. Evidence from RCTs show that consumption of sterols/stanols for 3 to 8 weeks lowers TC and LDL cholesterol levels, 5.2% to 11.2% and 7.6% to 15.6%, respectively, in subjects with hypercholesterolemia consuming a low-fat diet (<30% of energy from fat, 10% of energy from SFA, and 300 mg/day cholesterol) (80-82).

The effectiveness of plant sterols and stanols among individuals on diet and drug therapy is of interest. In a study of 22 women with CAD, 3 g/day sitostanol ester-enriched margarine for 7 weeks reduced TC 13% ($P<0.05$) and LDL cholesterol 20% ($P<0.01$) (83). Addition of sitostanol to simvastatin therapy reduced TC and LDL cholesterol an additional 11% and 16%, respectively. The combination of sitostanol ester margarine and statins may reduce the dose of the cholesterol-lowering drug needed (83). In a larger study with 67 women and 100 men receiving statin therapy with LDL cholesterol levels ≥130 mg/dL and TG level ≤350 mg/dL, consuming 3 g/day plant stanols for 8 weeks reduced TC level 12% ($P=0.001$) and LDL cholesterol level 17% ($P=0.001$) (84). Phytosterols, as part of a fat-modified diet, may decrease TC and LDL cholesterol levels beyond statin therapy alone.

Three population studies, two using a nested-case con-

Table 5. Blood lipid–lipoprotein level responses to sterols/stanol consumption and carotenoid/tocopherol concentrations across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Miettinen (1995) (74)	N=153; participants with mild hypercholesterolemia;1 y	Margarine with sitostanol ester, 1.8 or 2.6 g/d. Subjects followed an average Finnish diet (randomized double-blind design)	TC[a] and LDL[b] cholesterol decreased 24 mg/dL[c] and 14%, respectively ($P<0.001$). HDL[d] cholesterol and TG[e] levels did not change
Blair et al (2000) (84)	n=67 women and n=100 men with LDL cholesterol level ≥130 mg/dL[c], and TG level ≤350 mg/dL[f] using a statin drug; 8 wk	5.1 g/d plant stanol ester provided in 3 servings/d (each serving provided 8 g spread that contained 1.7 g stanol sterol of which 1 g was the plant stanol). 3 g plant stanol/d was consumed. Subjects followed usual diet (randomized, double-blind, placebo controlled design)	TC decreased 7% compared to control ($P<0.0001$) LDL cholesterol level decreased 10% ($P<0.0001$). HDL cholesterol and TG levels did not change
Hallikainen (2000) (78)	N=22 men and women with hypercholesterolemia; 4 wk	0, 0.8, 1.6, 2.3, and 3.0 g/d stanol ester in 25 g margarine in 2-3 portions with meals. Subjects followed a standardized background diet (34% of energy from fat and <12% of energy from saturated fat) (randomized, single-blind design)	LDL cholesterol level decreased 1.7% ($P=0.89$), 5.6% ($P< 0.05$), 9.7% ($P<0.001$), and 10.4% ($P<0.001$), respectively. The LDL cholesterol-lowering effect of the 1.6 g/d dose did not differ from larger doses. HDL cholesterol and TG levels did not change.
Nestle (2001) (77)	n=22 subjects with hypercholesterolemia in Study 1; n=15 subjects in Study 2. Study 1: LDL cholesterol 184 mg/dL[c]; Study 2: 178 mg/dL[c]; 4 wk	In Study 1, 2.4 g plant sterol esters or 2.4 g plant stanols per day. In Study 2, 2.4 g sterols esters were consumed. In Study 1, the sterol ester/sterol was incorporated in breakfast cereal, wholemeal bread, and soft margarine. In Study 2, sterol esters were incorporated in a dairy spread. All subjects followed low-saturated fat, low-cholesterol diet (randomized, single-blind, crossover design)	In Study 1, LDL cholesterol level was reduced by sterol esters by 14% ($P<0.001$). LDL cholesterol level was decreased by 8% by stanols ($P=0.003$). In Study 2, LDL cholesterol level decreased 12% with a sitosterol ester spread ($P=0.03$). HDL cholesterol and TG levels did not change in either study. Plasma carotenoid and tocopherol levels were not decreased
Maki (2001) (80)	N=219 participants with mild to moderate primary hypercholesterolemia; 5 wk	1.1 or 2.2 g/d sterol esters. Subjects followed a Step I diet (randomized double-blind, parallel arm design)	In subjects who consumed ≥80% of dose, TC was 5.2% and LDL cholesterol level was 7.6% lower on the 1.1. g/d dose and 6.6% and 8.1% lower, respectively, on the higher dose ($P<0.001$). HDL cholesterol and TG levels did not change.
Tikkanen (2001) (76)	N=71 participants with primary hypercholesterolemia; 15 wk	Bread, meat products, and jam-flavored yogurt enriched with 1.25 (for first 5 wk), 2.5 (for second 5 wk), and 5.0 g/d plant sterols (for third 5 wk). Subjects followed a diet that provided 31% of energy from fat (randomized, double-blind, placebo-controlled design).	LDL cholesterol level decreased 10%, 10%, and 13% at Week 5, 10, and 15, respectively. Across 15 wk, TC decreased 8% ($P=0,007$), and LDL cholesterol decreased 13% ($P=0.007$).
Christiansen (2001) (73)	N=134 patients with hypercholesterolemia; 6 mo	Spreads with plant sterols, 1.5 or 3.0 g/d (randomized double-blind, placebo-controlled design)	TC and LDL cholesterol levels decreased 7.5% and 11.6%, respectively ($P<0.002$) with no differences between sterol doses. HDL cholesterol and TG levels did not change.
Volpe (2001) (82)	N=30 participants with moderate hypercholesterolemia treated 4 wk. 11 of these went on to drink 2 g/d plant sterols; 8 wk.	A yogurt-based drink enriched with 1 g/d plant sterols for 4 wk; a yogurt-based drink enriched with 2 g/d plant sterols for 8 wk. Subjects followed Step I diet (randomized, crossover design for 4-wk study; randomized, parallel arm design for 8-wk study)	On the 1 g/d dose for 4 wks, TC and LDL cholesterol levels decreased 6.7% and 11.1%, respectively ($P=0.0005$ and $P=0.0009$). On the 2 g/d dose for 8 wk, TC and LDL cholesterol levels decreased 11.2% and 15.6% ($P<0.001$). HDL cholesterol and TG levels did not change.

(continued)

Table 5. Blood lipid–lipoprotein level responses to sterols/stanol consumption and carotenoid/tocopherol concentrations across recent trials (continued)

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Davidson et al (2001) (67)	N=84 men and women with mildly elevated LDL cholesterol level (130 mg/dL[c]); 8 wk	0, 3.0, 6.0, and 9.0 g/d plant sterol esters were provided in 14 g reduced-fat spread and 46 g reduced-fat salad dressing per day. Subjects followed usual diet (randomized, double-blind, controlled design)	LDL cholesterol level decreased by 5%, 2.6% and 9% in the 3, 6, and 9 g/d groups, respectively, vs 1.3% in the 0 g/d group. The changes were not statistically significant. TC and HDL cholesterol levels did change. TG level increased in the control group, which was significantly different from the 3.0 g/d arm ($P<0.05$). Serum α- and *trans*-beta carotene levels were reduced in the 9.0 g/d group vs controls ($P<0.05$), but all carotenoid values were within normal ranges
Ntanios et al (2002) (66)	N=53 subjects (TC=213 mg/dL[c]); subjects stratified into cohorts on the basis of TC (<198 mg/dL[c] or >198 mg/dL[c]); 3 wk	7.5 g spread at breakfast and 7.5 g at lunch or dinner were consumed. All subjects followed habitual Japanese diet (double-blind, controlled design)	TC and LDL cholesterol levels were 6% and 9% lower for all subjects, respectively, after consumption of free sterols ($P<0.001$). For the TC <198 mg/dL[c] group, TC and LDL cholesterol levels decreased 5% and 8%, respectively ($P<0.001$) and for the TC >198 mg/dL[c] group, they were 7% and 11% lower, respectively ($P<0.001$). The decreases were similar between the two cohorts. HDL cholesterol and TG levels did not change in any group. Plasma β-carotene was lower (21%) in subjects consuming plant sterols ($P<0.001$). Plasma vitamin A and E levels did not differ
Noakes (2002) (81)	n=20 men, n=26 women with hypercholesterolemia; 3 wk	25 g spreads per day, 3-way comparison study with 2.3 g sterol esters or 2.5 g stanol esters vs control. In addition, participants were advised to eat ≥5 servings of vegetables and fruit per day, of which ≥1 serving was from a high-carotenoid source. Subjects followed diets low in total and saturated fat (randomized double-blind, crossover design).	TC decreased 6.1% and 7.3% on sterol ester and stanol ester treatments, respectively ($P<0.001$), and LDL cholesterol level decreased 7.7% and 9.5%, respectively ($P<0.001$). The decreases on sterol vs stanol ester treatments were similar. HDL cholesterol and TG levels did not change. Consumption of 1 serving per day of high-carotenoid fruit or vegetable resulted in plasma carotenoid levels in the treatment groups that were similar to the control group.
Vanstone 2002 (79)	N=15 participants with primary familial hyperlipidemia; 3 wk	Four treatments: plant sterols (1.8 g/d); plant stanols (1.8 g/d); 50:50 mix of sterols and stanols (1.8 g/d); corn starch control. Subjects followed an average Canadian diet (randomized, crossover design)	TC level decreased 7.8%, 11.9%, 13.1% vs control, respectively ($P<0.01$). LDL cholesterol level decreased 11.3%, 13.4%, 16.0% vs control ($P<0.03$). HDL cholesterol and TG levels did not change.
Quilez (2003) (63)	N=57 patients with normocholesterolemia; 8 wk	3.2 g/d sterol esters in croissants and magdalenas; also enriched in α-tocopherol and beta carotene. Subjects followed an average Western diet (randomized double-blind, placebo-controlled design)	TC and LDL cholesterol levels decreased by 8.9% and 14.7%, respectively ($P<0.001$). HDL cholesterol and TG levels did not change nor did plasma tocopherol or carotenoid levels.

(continued)

Table 5. Blood lipid–lipoprotein level responses to sterols/stanol consumption and carotenoid/tocopherol concentrations across recent trials (continued)

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Hendriks (2003) (64)	N=185 participants with normo- or mild hypercholesterolemia participants; 39 wk	20 g spread with 1.6 g sterol esters per day. Subjects followed an average Dutch diet (randomized double-blind, placebo-controlled parallel arm design)	TC and LDL cholesterol levels decreased by 4% and 6%, respectively ($0.01<P<0.05$). β-Carotene concentrations decreased 15%-25% but carotenoid concentrations were not lower when expressed relative to LDL cholesterol.
Devaraj (2004) (75)	N=72 free-living adults with mild hypercholesterolemia; 8 wk	Orange juice fortified with plant sterols (2 g/d). Subjects followed an average American diet (randomized, placebo-controlled design)	TC and LDL cholesterol levels decreased 7.2% and 12.4%, respectively ($P<0.01$). HDL cholesterol and TG levels did not change.
Jauhiainen (2006) (68)	N=67 men and women with mild hypercholesterolemia; 5 wk	2 g plant stanols/d provided in 50 g low-fat cheese. Subject were instructed to follow their usual diet. (randomized, double-blind parallel arm design)	TC decreased 6% ($P<0.001$), LDL cholesterol level decreased 10% ($P<0.001$). HDL cholesterol and TG levels did not change.
Gylling (2006) (71)	N=38 women with mild hypercholesterolemia without heart disease; 12 mo	3 g stanol ester/d provided in 24 g margarine for up to 6 mo. For remaining 6 mo, subjects were randomized to 2 g or 3 g stanol ester/d (double-blind, randomized parallel arm design)	LDL cholesterol level decreased 10% ($P<0.05$) with 2 g/d and 17% with 3 g/d ($P<0.01$)
Goldberg (2006) (69)	N=26 patients with hypercholesterolemia on statin therapy; 6 wk	Stanol tablets (1.8 g/d) were given to subjects following an American Heart Association heart-healthy diet and on long- term statin therapy (double-blind, placebo-controlled parallel arm design)	LDL cholesterol level decreased 9.1% ($P=0.007$), TC decreased 12.9 mg/dL[c] ($P=0.03$). HDL cholesterol and TG levels did not change.
Castro Cabezas (2006) (70)	N=20 patients on lipid-lowering medications (11 treatment subjects); 6 wk	Stanol margarine (30-35 g/d); 3 g plant stanols given. Subjects followed a habitual diet (single-blind, randomized design).	LDL cholesterol level decreased 15.6% in the treatment group and 7.7% in the control group (no significant difference between groups). HDL cholesterol and TG levels did not change.

[a]TC=total cholesterol.
[b]LDL=low-density lipoprotein.
[c]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
[d]HDL=high-density lipoprotein.
[e]TG=triglycerides.
[f]To convert mg/dL triglycerides to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.6. Triglycerides of 159 mg/dL=1.80 mmol/L.

Table 6. Sterol/stanol content of selected food products

Product	Serving size	Amount of sterols or stanols per serving	Kilocalories per serving
Benecol Spread[a]	1 T	0.85 g plant stanol esters	70
Benecol Light Spread[a]	1 T	0.85 g plant stanol esters	50
Benecol Smart Chews[a]	1 chew	0.85 g plant stanol esters	20
Take Control Spread[b]	1 T	1.7 g plant sterol esters	80
Take Control Spread Light[b]	1 T	1.7 g plant sterol esters	45
Smart Balance OmegaPLUS Butter Spread[c]	1 T	0.45 g plant sterols	80
Minute Maid Heart Wise Orange Juice[d]	8 oz	1 g plant sterols	110
Nature Valley Heart Healthy Granola Bar[e]	1 bar	0.4 g plant sterols	160

[a]McNeil Nutritionals, Fort Washington PA.
[b]UnileverUSA, Inc, Englewood Cliffs, NJ. Take Control Spread is now known as Promise Active Buttery spread. Take Control Spread Light is now known as Promise Active Light Spread.
[c]Smart Balance, Inc, Paramus, NJ.
[d]The Coca-Cola Company, Atlanta, GA.
[e]General Mills, Inc, Minneapolis, MN.

trol design, reported plasma sitosterol levels in subjects who suffered a coronary event vs controls in the Prospective Cardiovascular Munster study (85) and the European Prospective Investigation into Cancer-Norfolk Population study (86). Another study (87) evaluated the association between plant sterols and CHD in a cohort of subjects participating in the Longitudinal Aging Study Amsterdam. In the Prospective Cardiovascular Munster study, plasma sitosterol concentrations were elevated in cases compared with controls. The upper quartile of sitosterol (>2.18 mg/L‡) was associated with a 1.8-fold increase in risk ($P<0.05$) compared with the lower three quartiles. In contrast, the European Prospective Investigation into Cancer-Norfolk study reported that among individuals in the highest tertile of sitosterol concentration, the unadjusted OR for future CAD was 0.75 (95% CI 0.56 to 1.01) and 0.79 (95% CI 0.56 to 1.13) after adjustment for traditional risk factors. In Longitudinal Aging Study Amsterdam, high plasma concentrations of plasma sitosterol were associated with reduced CHD risk (OR 0.78, 95% CI 0.62-0.98; $P<0.05$). Whereas one population study reported an adverse association between plasma sitosterol levels and coronary disease risk, two population studies reported no adverse association, of which one reported a beneficial association.

General Safety of Sterols and Stanols

Phytosterol esters are well tolerated. No adverse effects have been noted with up to 9 g/day for 8 weeks (67), or with lower doses given for a longer time period (64,73).

Because plant sterols and stanols interfere with the absorption of fat-soluble vitamins and carotenoids, in some studies (73,77,82), blood levels of α-tocopherol, α-carotene, and β-carotene were reduced following plant sterol consumption (65,88). When adjustments were made for reductions in total and individual lipoprotein cholesterol levels, vitamin concentrations were unaffected. Other studies showed lower levels of *trans*–β-carotene after correction for TC concentrations (80), lower levels of α-carotene after adjusting for LDL cholesterol levels (64), and lower plasma β-carotene after adjusting for plasma lipids (66). Another study reported that α-carotene and *trans*–β-carotene levels were reduced in a group receiving 9 g phytosterol esters per day; however, carotenoid values remained within normal ranges.

The possible decrease in carotenoid and fat soluble vitamin levels by sterols/stanols can be prevented with a diet rich in these nutrients. Daily consumption of one extra serving of a high-carotenoid fruit or vegetable increased plasma concentrations of carotenoids in subjects consuming 2.3 g/day sterol-enriched or 2.5g/day stanol-enriched spreads (81). Consumption of bakery products enriched with 3.2 g/day sterol esters and α-tocopherol and β-carotene prevented the decrease in plasma tocopherol and carotenoid concentrations (63). A diet rich in carotenoids and fat-soluble vitamins is recommended when consuming sterols/stanols.

Summary of Research-Based Dietary Recommendations for Consumption of Phytosterols

Plant sterols and stanols (2 to 3 g/day) decrease TC and LDL cholesterol levels by as much as 15% (36). Individuals with hypercholesterolemia can consume 2 to 3 g plant sterols or stanols as an adjunctive therapy to a diet low in SFA, TFA, and dietary cholesterol to further lower TC and LDL cholesterol levels. A variety of products contain plant sterols, including margarines, yogurt, orange juice, some cereals/cereal bars, and soft-gel capsules so personal preference can enhance adherence. These foods should be isocalorically substituted for other foods of equal or lower nutritional value to prevent excessive energy intake and weight gain. Table 6 summarizes the sterol/stanol content of various products available in the marketplace. Potential for reduced use of hypocholesterolemic agents should be considered if adherence is good and extra servings of foods rich in carotenes and beta carotenes are recommended.

‡To convert mg/L sitosterol to μmol/L, multiply mg/L by 2.41. Sitosterol of 2.18 mg/L=5.25 μmol/L.

Additional Research Needed

Research is needed to establish long-term safety of recommended doses of stanols and sterols and to evaluate their potential bioavailability of nutrients in foods, beverages, and supplements. Effect on the need for cholesterol-lowering medications also needs further research.

TOTAL AND SOLUBLE FIBER: EFFECT ON LDL CHOLESTEROL LEVEL LOWERING AND CVD PREVENTION

General Relationship

In population-based studies, diets high in total dietary fiber (>25 g/day) are associated with a decreased risk for CHD and CVD (89-95). Soluble fiber appears to have greater LDL cholesterol-level lowering potential than insoluble fiber but high total fiber remains inversely related to CHD (96).

Potential Mechanisms

β-Glucan (soluble fiber) increases bile acid production and decreases LDL cholesterol levels (95,97) and/or favorably affects LDL receptor status. High-fiber diets are associated with a lower body mass index (BMI), lower blood pressure, and lower TG levels (97).

Status of Current Research

Observational data and meta-analyses conclude that there are important benefits from high fiber intake on reduced all cause and CVD mortality. RCTs have documented benefits of dietary fiber on TC, LDL cholesterol, and TG levels (Table 7).

Observational Studies with Fiber. Two meta-analyses, five cohort studies, and other smaller RCTs have addressed the question of dietary fiber and CHD and CVD risk. Observational data (eg, Nurses' Health Study, Women's Health Study, Coronary Artery Risk Development in Young Adults Study study, Health Professional Follow-up Study, and the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study) (38,98,99) found that the highest intakes of total or soluble fiber were associated with reduced risk of CHD and CVD (38,98,99). The Nurses' Health Study cohort showed an inverse relationship between dietary fiber, especially wholegrain foods and fatal and nonfatal CHD ($P<0.001$) (89,100). One study of 49,032 men showed an inverse relationship between total fiber, cereal fiber, fruit fiber, and vegetable fiber and peripheral artery disease, but this was not evident after a multivariate adjustment (91). An observational study of 2,909 healthy adults reported a linear association from lowest to highest quintiles of dietary fiber intake with body weight, waist-to-hip ratio (WHR), fasting insulin adjusted for body mass index (BMI), and 2-hour post-glucose insulin adjusted for BMI (93).

The inverse relationship between fiber intake and CHD and CVD was further supported by a recent meta-analysis that pooled data from 10 prospective cohorts (94). For every 10 g/day increment in fiber there was a 12% reduction in coronary events and a 19% reduction in coronary deaths. For every 10 g/day increment in cereal fiber and fruit fiber intake there were decreases of 10% and 16% in coronary events and 25% and 30% in coronary deaths, respectively. An earlier meta-analysis reported 2 to 10 g/day soluble fiber was associated with significant decreases in TC (−1.5 mg/dL/g) and LDL cholesterol (−2.2 mg/dL/g) but no significant influence on TG or HDL cholesterol levels (95).

RCTs with Fiber. Four intervention studies reported that a higher fiber diet (approximately 30 g fiber per day increased in soluble fiber) reduced TC and/or LDL cholesterol levels (96,101-103). One study of 37 men and 31 postmenopausal women reported reductions in TC/HDL cholesterol levels ($P=0.001$) and LDL/HDL cholesterol ratio ($P=0.015$) and in apo B concentrations ($P<0.001$) with 30 g total and 13 g soluble fiber per day (96). One study of 20 male and 23 female healthy participants reported that 16 g total and 7 g soluble fiber, along with changes in SFA and dietary cholesterol, decreased systolic blood pressure (SBP) ($P=0.026$) (oats -6 ± 7 mm Hg, control -1 ± 10 mm Hg) (101). A different study of 36 overweight men fed 30 g total fiber with two large servings of high-fiber oat cereal (5.5 g beta-glucan) reported a 17% reduction in small LDL cholesterol ($P=0.01$); 6.2% reduction in LDL cholesterol particle number ($P=0.02$); and 5% decrease in LDL/HDL cholesterol ratio ($P=0.02$), whereas the control wheat group showed elevations in these lipid indexes (102). Also, a randomized controlled study of 127 free-living postmenopausal hypercholesterolemic women assessed whether or not there was a favorable synergistic lipid lowering benefit of adding soy to an oat fiber-rich National Cholesterol Education Program-type diet. Results showed that two servings of oats with added soy did not yield greater reduction in TC or LDL cholesterol level compared to an oats only group (103).

Published Research on Fiber and CVD Since Completion of the ADA Evidence Analysis Library

Controlled clinical studies on dietary fiber conducted since completion of the ADA Evidence Analysis Library on hyperlipidemia have evaluated water soluble fiber from oat bran (104), β-glucan (105), and psyllium (106). Results consistently demonstrate a TC and LDL cholesterol level lowering effect of water soluble fiber from oat bran incorporated into muffins and an oatmeal cereal product (8 g/day for 3 months) (104), β-glucan (5 g β-glucan from oats) (105), psyllium fiber as Metamucil (Procter & Gamble, Cincinnati, OH) (15 g psyllium for 12 weeks) (106) incorporated in a fruit drink for 5 weeks. The studies reported a 2.4 mg/dL and 1.96 mg/dL decrease in TC and LDL cholesterol levels with water soluble fiber from oats, respectively (104), and a 4.8% and 7.7% decrease in TC and LDL cholesterol levels, respectively, with β-glucan (105). Moreyra and colleagues (106) reported LDL cholesterol level decreased 63 mg/dL (1.63 mmol/L) in subjects taking 15 g psyllium plus 10 mg simvastatin per day, a cholesterol lowering response similar to that of 20 mg simvastatin plus placebo. Naumann and colleagues (105) reported decreased serum concentrations of lathosterol (−13%) and sitosterol (−11%), both markers of cholesterol absorption, illustrating that β-glucan lowers LDL cholesterol levels through reduced cholesterol absorption.

A prospective cohort study with 229 women reported that higher intakes of cereal fiber (>3 g/1,000 kcal) or >6 servings of whole grains per week were associated with a

Table 7. Blood lipid–lipoprotein level responses to dietary fiber across recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Jenkins (2002) (96)	n=37 men, n=31 postmenopausal women; 1 mo each	30 g total and 13 g soluble fiber diet (RCT[a], crossover design, high-fiber foods provided)	↓ 2.1% TC[b] (P=0.03), ↓ 5.2% TG[c] (P=0.037), ↓ 2.4% TC/HDL[d] cholesterol (P=0.001), ↓ 2.4% LDL[e]/HDL cholesterol (P=0.015), ↓ 2.9% apo B[f] concentrations (P<0.001)
Saltzman (2001) (101)	n=20 male, n=23 female healthy participants; 8 wk	16 g total and 7 g soluble fiber; changes in SFA[g] and dietary cholesterol (RCT, partial feeding study)	↓ SBP[h] (oats −6±7 mm Hg, control −1±10 mm Hg) (P<0.05), ↓ TC (oats −0.87± 0.47 mmol/L[i], control −0.34±0.5 mmol/L[i]) (P<0.05), ↓ LDL cholesterol (oats −0.6±0.41, control −0.2±0.41) (P<0.05)
Davy (2002) (102)	N=36 overweight men; 12 wk	30 g total fiber with 2 large servings of high-fiber oat cereal (5.5 g beta-glucan) (RCT, cereal provided)	17% ↓ small LDL cholesterol (P=0.01), 6.2% ↓ LDL cholesterol particle number (P=0.02), 5% ↓ LDL/HDL cholesterol (P=0.02). Control wheat group ↑ in lipid indexes
Van Horn (2001) (103)	n=127; free-living postmenopausal women with hypercholesterolemia; 9 wk	2 servings of oats with either milk or soy vs wheat with soy or milk group (RCT)	Addition of oats reduced TC and LDL cholesterol levels by 3% and 6.5%, respectively, beyond what was achieved by Step I diet alone. No additional benefits with soy in either group.
Erkkila (2005) (107)	N=229 postmenopausal women with established coronary h heart disease in a hypertension trial; cohort study	Assessed total and soluble fiber intake, via cereal and complex carbohydrate	Higher cereal fiber and whole-grain intake significantly, directly associated with reduced progression of coronary artery disease
Lairon (2005) (108)	n=2,532 men, n=3,429 women, cross-sectional study, French	24-hour recalls from 4 weekdays and 2 weekend days assessed for total fiber	Highest fiber intakes associated with lower body mass index, TC and LDL cholesterol levels
Naumann (2006) (105)	N=47 healthy participants; 3-wk run in; 5-wk intervention, double blind	Beta-glucan enriched fruit juice vs rice starch-based placebo	Significant reductions in TC and LDL cholesterol levels by 0.060 mmol/L[i] and 0.062 mmol/L[i], respectively
Chen (2006) (104)	N=110 participants from the community with baseline TC <240 mg/dL[i]; 12 wk	High-fiber intervention with 60 g oat bran concentrate and 84 g oatmeal squares vs wheat cereal and corn flakes control	No significant differences in reduction of TC, LDL cholesterol, or TG levels
Moreyra (2005) (106)	N=68 adults with hyperlipidemia eligible for statin prescription, ATP III-TLC[j] criteria; 12-wk randomized, blinded	Low-dose simvastatin (10 mg) plus psyllium (5 g) 3 times daily vs 20 g simvastatin	Simvastatin plus psyllium yielded same LDL cholesterol and apo B cholesterol level lowering results as higher-dose simvastatin alone

[a]RCT=randomized controlled trial.
[b]TC=total cholesterol.
[c]TG=triglycerides.
[d]HDL=High-density lipoprotein.
[e]LDL=low-density lipoprotein.
[f]apo B=apolipoprotein B.
[g]SFA=saturated fatty acid.
[h]SBP=systolic blood pressure.
[i]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
[j]ATP III-TLC=National Cholesterol Education Program Adult Treatment Panel III-therapeutic lifestyle changes.

smaller decline in minimum coronary diameter after 3.2±0.6 years of follow-up (cereal fiber: −0.09±0.02 vs −0.04±0.02 mm, P=0.03; whole grains: −0.10±0.02 vs −0.06±0.02 mm, P=0.04) (107).

A cross-sectional study of 2,532 men and 3,429 women in France reported the highest total dietary fiber and insoluble dietary fiber intakes were associated with significantly (P<0.05) lower risk of overweight and elevated WHR, blood pressure, plasma apo B, apo B:apolipoprotein A1 ratio, TC, TG, and homocysteine (Hcy) levels (108). A 5-g increase in total dietary fiber resulted in a 10.6% decrease in overweight risk, a 14.7% decrease in risk of high WHR, an 11.6% decrease in high blood pressure risk, a 9.2% decrease in risk of high apo B, and a 15.4% decrease in risk of high Hcy.

Summary of Research-Based Dietary Recommendations and Consumption of Fiber

A fat-modified diet that provides 25 to 30 g total dietary fiber including at least 7 to 13 g soluble fiber is well tolerated, effective, and recommended for lipid lowering and CVD risk reduction.

Additional Research Needed

The potential relationships between total fiber and soluble fiber, sources of fiber and additional CHD risk factors such as lipoprotein subclasses and particle sizes, particle density, clotting factors, blood pressure, metabolic syndrome, and fasting and postprandial insulin warrants further research.

N-3 FATTY ACIDS AND CVD PREVENTION

General Relationship

Evidence from epidemiologic and RCTs report that n-3 fatty acids decrease CVD risk, and notably the risk of sudden death and other cardiac events. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain n-3 fatty acids found in cold water fish, such as mackerel, salmon, herring, trout, sardines, and tuna. ALA is a shorter chain n-3 fatty acid found in various plant sources, including flaxseed, walnuts, canola oil, and soybeans. ALA can be converted to EPA but only in small (2% to 5%) amounts in humans (109). Even less is converted to DHA (<1% conversion) (110,111) (Table 8).

Potential Mechanisms

The potential mechanisms by which n-3 fatty acids from fish oil appear to exert a cardioprotective effect include reducing TG levels, decreasing platelet adhesion, favorably affecting endothelial function, decreasing vasoconstriction, reducing inflammation, and decreasing ventricular arrhythmias by modulating cardiac ion channels (112). ALA may protect against CVD by interfering with the production of proinflammatory eicosanoids produced via the n-6 PUFA pathway that converts LA to arachidonic acid and its eicosanoid derivatives (113).

Status of Current Research

Primary Prevention Data. Cohort and population-based studies have shown an inverse association between n-3 fatty acid consumption and risk of CHD death. The Chicago Western Electric Study (1,822 men; P<0.04), Physicians Health Study (22,071 men; P<0.04), and the Seven Countries Study (1,088 Finnish, 1,097 Italian, and 553 Dutch men; no linear trend) found that fish consumption ranging from 4 oz/week to 1.5 oz/day reduced risk of death from sudden and nonsudden cardiac events in men by 34% to 52% (114-116). A recent study reported a 40% reduced risk of CAD (P for trend=0.25) and 53% reduced risk for MI (P=0.03) in men and women (n= 41,578) with a median fish intake of 6 oz/day (117).

The relationship between fish consumption and n-3 fatty acid intake on the reduced risk of CHD mortality was reinforced in two meta-analyses that included 27 cohort and five case-controlled studies (118,119). A third meta-analysis (120) found no evidence of reduced mortality or combined CVD events in participants taking additional n-3 fatty acids. The latter study has been criticized for many methodologic problems (121).

More recently, prospective data from Finland on fish intake of n-3 fatty acids calculated from diet history intake data and risk of coronary heart mortality reported no significant relationships (122). Likewise, there was no consistent relationship between fish intake and stroke among a British population in the European Prospective Investigation into Cancer Norfolk prospective population study (123).

Plant Consumption and CHD Risk Reduction. Three large observational studies examined ALA intake in both men and women (38,109,124,125). ALA intakes between 1.36 g and 1.5 g/day reportedly reduced risk of IHD or acute MI by 45% to 59% (Nurses' Health Study, n=76,283; P for trend=0.01, Health Professionals Study, n=43,757; P for trend=0.01) (124,125). In the National Heart, Lung, and Blood Institute Family Heart Study (N=4,584), ALA intake was inversely associated with CAD. In the highest three quintiles of ALA intake, the prevalence OR of CAD was reduced by approximately 50% to 70% for women (P for trend=0.014) and about 40% for men (P for trend=0.012). The mean ALA intake was 0.81 g/day for men and 0.68 g/day for women (125). Table 8 describes recent n-3 fatty acid cohort and RCT studies in primary prevention.

Plasma and Adipose Tissue Levels of n-3 Fatty Acids and CHD Risk Reduction. Four case-controlled studies evaluated blood or adipose tissue levels of EPA, DHA, and ALA as biomarkers of cardiac events and disease progression (30,126-128). Two studies (126,127) reported lower baseline plasma phospholipid concentrations of DHA and EPA in subjects who experienced sudden death from cardiac causes or fatal IHD vs controls (P=0.007 and P=0.02). For every one standard deviation increase in plasma phospholipid ALA, and combined DHA and EPA, there was a 50% and 70% lower risk of fatal IHD (P=0.04, P=0.01), respectively (127). In another study investigating adipose tissue levels of ALA, subjects in the top quintiles (0.72% of fatty acids) had a reduced risk of nonfatal MI (P<0.0001) (30). Higher plasma DHA levels were associated with a reduced progression of coronary atherosclerosis (128). Postmenopausal women with plasma phospholipid DHA levels above the median had less atherosclerosis progression as measured by coronary angiography (P=0.007) (128).

Secondary Prevention Data: Fish Consumption and n-3 Supplementation. In patients with CHD, a meta-analysis and two RCTs found that marine-derived n-3 fatty acids obtained

Table 8. Blood lipid–lipoprotein level responses to n-3 fatty acids: Recent studies in healthy patients or those with mild hyperlipidemia

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Geppert (2006) (135)	N=106 healthy vegetarians with normal lipid levels; 8 wk	Microalgae oil (0.94 g DHA[a]/d) or olive oil (placebo) (RCT[b])	DHA supplementation ↑ TC[c], LDL[d] cholesterol ($P \leq 0.001$), and HDL[e] cholesterol ($P=0.002$). TG[f] ↓ by 23% ($P<0.001$)
Sanders (2006) (136)	n=40 women, n=39 men healthy participants; 4 wk	4 g oil/d (1.5 g DHA, 0.6 g EPA[g]) or olive oil (placebo) (RCT)	DHA supplementation ↑ TC, LDL cholesterol, and HDL cholesterol by 7.7%, 10.4%, and 9.0%, respectively ($P \leq 0.001$). TG ↓ not significant
Goyens (2006) (137)	n=23 women, n=14 men aged 68-78 y with mild hypercholesterolemia; 9 wk	↑ oleic acid control diet, ALA[h]-rich diet (6.8 g/d), and EPA/DHA-rich diet (1.05 g/d) (RCT)	EPA/DHA diet ↑ LDL cholesterol 0.39 mmol/L[i] ($P=0.0323$), ↑ apolipoprotein B concentrations 14 mg/dL[i] ($P=0.0031$)
Harper (2006) (138)	n=49 women, n=7 men without coronary heart disease; 26 wk	Flaxseed oil (3 g ALA/d) or olive oil (placebo) (RCT)	ALA ↑ TC 0.45 mmol/L[i] ($P=0.026$) and ↑ less atherogenic LDL particle size LDL-1 ($P=0.058$) and LDL-2 ($P=0.083$)
Iso (2006) (117)	n=27,435 women, n=27,063 men without cardiovascular disease; 11-y follow-up	Highest quintile of fish intake (median 180 g/d); lowest (median 23 g/d) (population-based cohort)	Participants in highest quintile of fish intake had ~40% reduced risk for coronary heart disease ($P=0.25$ for trend)
Jarvinen (2006) (122)	n=2,445 women, n=2,775 men aged 30-79 y without coronary heart disease/mean follow-up 21.5 y	Health examination survey data included dietary interview (population-based cohort)	Among women, higher fish consumption was associated with a 41% reduced risk for coronary heart disease ($P=0.02$ for trend)
Myint (2006) (123)	N=24,312 women and men with no previous stroke history; mean follow-up 8.5 y	Fish consumption assessed using food frequency questionnaire (population-based cohort)	↑ Stroke incidence in women who consumed less oily fish ($P=0.02$). No significant association between total fish intake and risk of stroke in men and women

[a]DHA=docosahexaenoic acid.
[b]RCT=randomized controlled trial.
[c]TC=total cholesterol.
[d]LDL=low-density lipoprotein.
[e]HDL=high-density lipoprotein.
[f]TG=triglycerides.
[g]EPA=eicosapentaenoic acid.
[h]ALA=α-linolenic acid.
[i]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.

either through diet or supplements decreased all-cause and MI mortality and sudden death (109,129-131). See Table 9 for descriptions and major findings.

One RCT failed to demonstrate a protective effect of supplemental EPA and DHA in 2,114 free-living men with angina (132). Subjects who took 3 g/day supplemental EPA and DHA (n=462) experienced higher cardiac mortality ($P=0.04$) and sudden death ($P=0.025$). However, subjects who consumed at least two portions of oily fish per week (n=1,109) experienced neither a significant increase nor decrease in risk of cardiac mortality (132).

One proposed mechanism by which n-3 fatty acids is thought to be protective is by reducing cardiac arrhythmias leading to sudden death. In patients with implantable cardioverter defibrillators (ICDs); however, one RCT (n=200) reported that fish oil supplementation (1.8 g/day EPA plus DHA) did not significantly reduce episodes of cardiac arrhythmias. An increase in both the incidence and rate of repeated ventricular tachycardia and ventricular fibrillation episodes were observed in the treatment group, suggesting that fish oil supplementation may be proarrhythmic in this population (133). In contrast, another RCT (n=402) reported that fish oil supplementation (2.6 g/d of EPA, plus DHA) resulted in a trend toward a prolonged time to the first ICD event (ventricular fibrillation or ventricular tachycardia) and a 28% reduction in all-cause mortality ($P=0.057$) in patients with ICDs. Moreover, additional antiarrhythmic benefit of fish oil supplementation continued for those on the protocol for at least 11 months (38% risk reduction; $P=0.034$) (134).

n-3 Supplementation and Effects on Serum Lipid Concentrations. It is well established that marine-derived n-3 fatty acids lower TG concentrations in a dose-dependent manner (124). Two studies reported a 20% to 23% reduction in TG levels with EPA and DHA combined or DHA alone in

Table 9. Blood lipid–lipoprotein level responses to n-3 fatty acids: Secondary prevention studies

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Bucher (2002) (129)	Meta-analysis; n=7,951 patients in the intervention n=7,855 control group with previous MI[a]/mean follow-up; 20 mo	2 dietary and 9 supplementation trials; EPA[b] range 0.3-6.0 g/d, DHA[c] range 0.6-3.7 g/d (RCT[d])	30% ↓ in fatal MI ($P<0.001$), 20% ↓ in overall mortality ($P<0.001$), 20% ↓ in TG[e] levels in active treatment group with little effect on LDL[f] and HDL[g] cholesterol level
Burr (1989) (130)	N=2,033 male post-MI patients; follow-up 2 y	Fatty fish twice/wk or 1.5 g fish oil capsule providing additional 500-800 mg/d n-3 fatty acids (RCT)	29% ↓ in all-cause mortality ($P<0.05$)
Burr (2003) (132)	N=3,114 men <70 y with angina; follow-up 3-9 y	Fatty fish twice/wk or 3 g fish oil/d (RCT)	↑ Risk of cardiac mortality ($P=0.047$) and sudden death ($P=0.025$) among subjects advised to consume fish. Subgroup analysis showed ↑ cardiac mortality in subjects taking fish-oil capsules ($P=0.024$).
GISSI-Prevenzione Investigators (1999) (131)	N=11,324 post-MI patients; follow-up 3.5 y	850 mg EPA and DHA/d (RCT)	20% ↓ in all-cause mortality ($P<0.05$), 45% ↓ in sudden death ($P=0.01$), 15% reduction in nonfatal MI and stroke ($P=0.02$)
Erikkila (2006) (128)	N=228 postmenopausal women with coronary artery disease participating in the Estrogen Replacement and Atherosclerosis Trial; follow-up 3.2 y	Measurement of plasma n-3 fatty acid levels in women with self-reported habitual fish intake and no supplements (prospective cohort)	Women with plasma DHA levels above the median had less of a ↓ in coronary artery diameter ($P=0.007$), smaller ↑ in % stenosis ($P=0.006$), and fewer new lesions ($P=0.009$)

[a]MI=myocardial infarction.
[b]EPA=eicosapentaenoic acid.
[c]DHA=docosahexaenoic acid.
[d]RCT=randomized controlled trial.
[e]TG=triglycerides.
[f]LDL=low-density lipoprotein.
[g]HDL=high-density lipoprotein.

patients with and without a previous history of CHD (129,135). Several RCTs reported significant increases in total, LDL cholesterol, HDL cholesterol, and apo B concentrations with DHA alone (0.94 g to 1.5 g/day), ALA alone (3 g/day), and EPA and DHA combined (1.05 g/day) (135-138). Table 9 reviews recent trial data regarding n-3 supplementation and effects on serum lipid levels.

Summary of Research-Based Dietary Recommendations and Consumption of n-3 Fatty Acids

The American Heart Association recommends 1 g EPA plus DHA per day for patients with CHD under a physician's care. Table 10 lists dietary sources. For primary prevention, the American Heart Association recommends at least two or more servings (approximately 4 oz per serving) of oily fish per week and inclusion of foods and oils rich in ALA, such as walnuts and soy or other vegetable oils (109). The FDA has allowed a qualified health claim for up to 3 g per day n-3 fatty acids to reduce the risk of CHD. This claim states, "Supportive but not conclusive research shows that consumption of EPA and DHA n-3 fatty acids may reduce the risk of CHD" (139). Until further research is available, fish oil supplementation should not be recommended in patients with angina or those with ICDs, even if they have documented CHD.

Additional Research Needed

There are limited intervention studies evaluating the relationship between ALA and risk of CHD. The literature is often confounded by numerous other factors, including fish vs supplement-based studies. In addition, information is needed about the efficacy of marine- and plant-derived n-3 fatty acids in women and in high-risk populations. The effect of plant-based and marine-based n-3 fatty acids on primary prevention of CHD in all population groups is needed. Research to determine the optimal dietary intake of n-3 fatty acids (ie, EPA, DHA, and ALA) and the ratio of n-6:n-3 fatty acids is warranted.

Hcy AND B VITAMINS AND CVD PREVENTION

General Relationship

Elevated serum Hcy levels, independent of other cardiac risk factors, are associated with increased risk for CHD.

Table 10. Selected food sources of n-3 fatty acids

Food	EPA[a] + DHA[b] content (g) per 100 g serving[c]	Energy per serving (kcal)
Herring, Atlantic, cooked	2.01	203
Salmon, Atlantic, farmed, cooked	2.15	206
Salmon, Atlantic, wild, cooked	1.84	182
Salmon, sockeye, cooked	1.23	216
Mackerel, Atlantic, cooked	1.20	262
Sardines, Pacific, cooked in tomato sauce, drained solids with bone	1.35	186
Trout, rainbow, farmed, cooked	1.15	169
Trout, rainbow, wild, cooked	0.98	150
Halibut, Atlantic, cooked	0.47	140
Shrimp, mixed species, cooked	0.32	99
Tuna, white, cooked in water, drained	0.86	128
Tuna, light, cooked in water, drained	0.27	116
Tuna, yellowfin, fresh, cooked	0.28	139
Cod, Atlantic, cooked	0.16	105

[a]EPA=eicosapentaenoic acid.
[b]DHA=docosahexaenoic acid.
[c]Sources: http://www.nal.usda.gov/fnic/foodcomp/search and http://www.nutritiondata.com.

Potential Mechanisms

Hyperhomocysteinemia and the associated metabolic defects are due to genetic mutations or vitamin B-6, B-12, or folate deficiencies (140). The effects of Hcy are independent of established risk factors such as hyperlipidemia and hypertension. Folate may have protective effects independent of Hcy lowering due to enhanced vascular nitric oxide activity (141,142) and could prevent endothelial dysfunction associated with a fat load or an oral dose of methionine.

Status of Current Research

Observational Studies. Several observational studies have shown that elevated plasma Hcy levels are associated with increased CVD risk (143-146). In addition, there is an inverse relationship between folate status (ie, dietary folate and/or serum folate) and serum total Hcy and CHD risk (143,145). Many trials have examined the influence of supplemental B vitamins on CHD outcomes. Data consistently show that supplementing with folic acid with or without other B vitamins, lowers Hcy levels (147-151); however, this is not accompanied by lower heart disease risk.

RCTs. Despite a reduction in plasma Hcy from B-vitamin supplementation, six RCTs (148-153) and one meta-analysis (154) failed to find CVD risk reduction (149,152,153), reduction in recurrence of cardiovascular events (148), and death from CVD (148,149,151), although one study reported a reduction in stroke (150) (Table 11). One study (151) reported an increased risk of CVD with a combined supplementation of vitamin B-12, folic acid, and vitamin B-6. In a recent meta-analysis (154), studying the effects of folic acid supplementation over 6 months to 5 years, data were pooled from 12 RCTs, including 16,958 men and women with pre-existing vascular disease. Hcy was decreased by 13.4% to 51.7%; however, no statistically significant relationship was noted between net change in Hcy and risk reduction for CVD (HR 0.95), CAD (HR 1.04), stroke (HR 0.86), and all cause mortality (HR 0.96), suggesting folic acid supplementation was ineffective in secondary prevention of CHD (154). One study (155) reported a 21% decrease in combined risk for ischemic stroke, CHD, or death with high dose vs low dose supplementation of vitamin B-6, vitamin B-12, and folate ($P<0.040$).

Restenosis and Supplementation with Folate, Vitamin B-12, and Vitamin B-6. One RCT with a combination of 1 mg folic acid, 400 μg vitamin B-12, and 10 mg vitamin B-6 per day or placebo administered to 205 patients for 6 months after successful coronary angioplasty, demonstrated that B vitamins significantly reduced Hcy levels and decreased the rate of restenosis and the need for revascularization of the target region (152). Further analysis showed that Hcy-lowering therapy with folic acid, vitamin B-12, and vitamin B-6 was effective for controlling restenosis 1 year after coronary angioplasty ($P<0.001$) (147). One RCT (153) did not find a relationship with serum Hcy, folate, and vitamin B-12 levels and the rate of in-stent restenosis after 6 months.

Dietary Patterns, Homocysetine, and Risk Reduction of CHD. One study (156) used validated self-administered food frequency questionnaires with 357 men and women, and found that a combined high intake of whole-grain bread, fresh fruit, olive oil, wine, mushrooms, cruciferous vegetables, and nuts as well as a low intake of fried potatoes affected biomarkers of Hcy metabolism. This was associated with a decreased CHD risk in two independent German study populations.

Summary of Research-Based Dietary Recommendations and Effect of B Vitamins on Hcy Levels

In 1998, the FDA implemented a Final Rule for fortifying specified grain products with folic acid (0.43 to 1.4 mg folic acid/1 lb specified grain) for the prevention of neural

Table 11. B vitamin intake and cardiovascular outcomes: Findings from recent trials

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Schnyder (2002) (152)	N=553 postangioplasty patients; 6 mo	1 mg folic acid, 400 μg B-12, 10 mg B-6 vs placebo (RCT[a])	↓ Hcy[b] (1.01 vs 1.36 mg/dL[c], $P<0.001$). No difference in non-fatal MI[d], cardiac deaths and overall deaths 38% ↓ repeat target lesion revascularization vs placebo $P=0.03$.
Genser (2002) (153)	N=292 postangioplasty and stent patients; 6 mo	Investigated the relation of Hcy, folate, and B-12 to the rate on in-stent restenosis (prospective cohort study)	No difference between patients with or without restenosis in regards to Hcy, folate, and B-12 ($P=0.581$, 0.166, and 0.163, respectively)
Liem (2003) (148)	N=593 participants with coronary heart disease; 2 y	0.5 mg folic acid vs placebo (RCT)	18% ↓ Hcy (12 to 9.4 μmol/L[c], $P<0.001$) vs baseline. No difference in any death or any other vascular events ($P=0.85$).
Toole (2004) (149)	N=3,680 poststroke participants; 2 y	High-dose: 25 mg B-6, 400 μg B-12, 2.5 mg folic acid vs low-dose: 2 mg B-6, 6 μg B-12, 0.2 mg folic acid (RCT)	17% ↓ Hcy (13.4 to 11.1 μmol/L[c]) vs baseline (no P value). No difference in stroke, coronary event, or death ($P=0.8$, 0.57, and 0.25, respectively).
Lonn (2006) (150)	N=5,522 with diabetes and cardiovascular disease; 5 y	2.5 mg folic acid, 50 mg B-6 and 1 mg B-12/d vs placebo (RCT)	19% ↓ Hcy vs baseline (no P value), no risk of the primary endpoint of a composite of death from cardiovascular disease causes, MI, or stroke ($P=0.41$), each endpoint analyze separately: ↓ stroke ($P=0.03$)
Bonaa (2006) (151)	N=3,749 post-MI men and women	Combined daily treatment of 0.8 mg folic acid, 0.4 mg B-12 (combination therapy), and 40 mg B-6 vs folic acid and B-12 (same doses) vs B-6 (same dose) alone vs placebo (RCT)	27% ↓ Hcy in combination therapy group and folic acid and B-12 group vs baseline levels, no impact on primary endpoint for folic acid and B-12 group ($P=0.31$) or B-6 group ($P=0.09$); 22% ↑ risk of cardiovascular disease in combination therapy vs placebo (95% CI[e] 1.00-1.5, $P=0.05$)
Bazzano (2006) (154)	Meta-analysis with N=16,958 men and women with pre-existing vascular disease from 12 RCTs; 16 mo to 5 y	Dosage of folic acid 0.5 mg/d to 15 mg/d (7 trials had placebo and 5 trials had a usual care group)	↓ Hcy 13.4% to 51.7%, no statistically significant relationship was noted between net change in Hcy and relative risk for cardiovascular disease (0.95), coronary heart disease (1.04), stroke (0.86), and all cause mortality (0.96). No significant harm nor benefit was noted of folic acid supplementation.
Spence (2005) (155)	N=2,155 men and women; efficacy analysis of 2 sub-groups of VISP study	High-dose group 2.5 mg folate, 25 mg B-6, 400 μg B-12 vs low-dose group 20 μg folate, 200 μg B-6, 6 μg B-12 (RCT)	High-dose group had 21% ↓ in combined risk for ischemic stroke, coronary disease, or death vs low-dose group ($P=0.049$). Also noted plasma Hcy ↑ significantly as serum B-12 fell in subjects who had B-12 levels above median suggesting this group was more sensitive.
Weikert (2005) (156)	n=357; case group vs n=26,893 control group (combined data from 2 German populations studies CORA (200 cases of MI; 255 controls) and PIC-C Potsdam (157 cases of MI among 26,795 participants)	Collected dietary intake data by validated self-administered questionnaires to identify a food pattern related to high folate and B-12 and low Hcy concentrations and to examine its association with coronary heart disease risk (one case-controlled and one prospective study group)	A dietary pattern with a combined high intake of whole-grain bread, fresh fruit, olive oil, wine, mushrooms, vegetables, and nuts was most positively associated and fried potatoes the most negatively to a dietary pattern that was in direct association with both plasma folate and B-12 levels, but inversely with plasma Hcy (P for trend=0.05 in the case control study sample and P for trend=0.041 in the prospective study sample) and was also associated with reduced risk of coronary heart disease

[a]RCT=randomized controlled trial.
[b]Hcy=homocysteine.
[c]To convert mg/dL homocysteine to mmol/L, multiply mg/dL by 7.397.
[d]MI=myocardial infarction.
[e]95% CI=95% confidence interval.

tube birth defects (157). It also has been shown that current fortification dose raised folate levels in 75 women and men with CAD (158). Moreover, the benefits of folic acid fortification were demonstrated in a Framingham Offspring cohort in which the prevalence of hyperhomocysteinemia was decreased from 18.7% to 9.8% (159). At this time, research does not warrant B-vitamin supplementation; however, a diet rich in B-vitamin foods and whole-grain bread, olive oil, mushrooms, cruciferous vegetables, and nuts (156) should be encouraged.

Additional Research Needed

Further research is needed to study the effects of dietary patterns on CHD incidence, recurrence of cardiovascular events, and revascularization events. No RCTs have been done to determine effects of folate supplementation on CHD incidence. There are ongoing secondary prevention studies in the United States, the United Kingdom, and Australia in patients with CAD to further evaluate the role of Hcy as a CVD risk factor. In addition, these studies will provide information about the effect of folate on CVD events.

ALCOHOL AND CVD PREVENTION

General Relationship

Population and cohort studies suggest an inverse relationship between daily consumption of 1 to 2 alcoholic beverages and CVD (160,161). Long-term clinical trials have not been conducted and results are often confounded. Adverse effects of consuming large amounts of alcohol include alcoholism, liver disease, cancer, and incapacitating and fatal accidents, thereby preventing health care professionals from encouraging alcohol consumption. For those who elect to consume alcohol, moderation is recommended.

Potential Mechanisms

Alcohol beneficially prolongs blood clot formation by lowering levels of fibrinogen and protein tissue-type plasminogen activator (162). In addition, moderate (30 g/day or 2 drinks/day) alcohol consumption increases HDL cholesterol levels but it also raises TG levels (163).

Status of Current Research

Retrospective and prospective observational studies in the United States and Europe, including a meta-analysis of 26 studies (164) indicate lower RR for those who regularly consume 1 to 2 alcoholic beverages daily compared with nondrinkers (Table 12). The benefit is reported for various endpoints, including total mortality, CVD death, CVD, MI, fatal MI, and CHD (165,166). The studies summarized in Table 12 report reduction of risk by about one third with consumption of 1 to 2 alcoholic beverages daily. Two other studies reported increased risk among specific groups. In a Danish cohort, consumption of 3 to 5 drinks/day increased CVD mortality by 35% (167); among young Swedish soldiers, consumption ≥15 g ethanol per day increased overall mortality by 37%, including an increase in strokes (168).

There are no clinical trial data assessing whether or not initiation of alcohol consumption in nondrinkers improves cardiovascular health. Data from 18,455 men in the Physicians Health Study reported that among men who initially consumed ≤1 drink per week who later consumed moderate amounts (>1 to <6 alcoholic drinks per week) had a 29% decreased CVD risk compared with men initially classified in the "low alcohol" intake group who did not increase intake ($P=0.05$) (169).

Although much of the epidemiologic data indicate a cardiovascular benefit of 1 to 2 drinks per day, the optimal amount of alcohol for an individual is not clear. The meta-analysis involving 10 studies and 176,042 persons assessed the dose response relationship of wine intake. The resulting J-shaped curve demonstrated a greater benefit up to a level of 150 mL/day (or one 5-oz glass). Maximum reduction in risk was predicted at 750 mL/day but this did not differ statistically from the 150 mL/day intake (164).

One clinical study assessed the effects of moderate alcohol consumption on CVD risk factors (170). Using a controlled feeding study design, postmenopausal women (n=51) consumed 0 g, 15g, and 30 g alcohol per day for 8 weeks. Compared to the control diet, LDL cholesterol decreased from 135.5 to 127.7 mg/dL ($P=0.04$) and TG decreased from 124 to 115.2 mg/dL ($P=0.05$) after 15 g/day of alcohol. There were no further changes at the higher alcohol dose. HDL cholesterol level increased significantly only after 30 g alcohol per day.

The available evidence suggests several caveats regarding the use of alcohol for cardiovascular benefit. No one type of alcoholic beverage (ie, beer, wine, or liquor) provides significantly greater benefit than another (163,164,171). Data from Italian men and women (172) suggest a greater benefit of consuming alcohol with meals, but an American study of men provides equivocal findings (163). Data from middle-aged and elderly Danish men without heart disease showed greater benefit in those with higher LDL cholesterol levels (173).

Published Research on Alcohol and CVD Events Since Completion of the ADA Evidence Analysis Library

Since the completion of the ADA EAL, numerous observational studies have been published in this area. In a defined cohort of men (n=8,867) in the Health Professionals Follow-up Study who reported four healthy lifestyle behaviors, including a BMI of <25, moderate to vigorous activity for at least 30 minutes per day, non-smoking, and a healthful diet score followed for 16 years, moderate alcohol consumption was associated with a lower risk for MI (174). Compared with men who did not drink alcohol, the HR for MI was 0.38 (95% CI 0.16 to 0.89) for an alcohol intake of 15 to 29.9 g/day. In another study conducted with middle-age men (n=25,052) and women (n=28,448) in Denmark, the amount of alcohol intake was inversely associated with CHD over a median follow-up period of 5.7 years (175). In women, drinking at least 1 day per week was associated with a lower CHD risk (0.64, 95% CI 0.51 to 0.81) vs drinking <1 day per week. Interestingly, there was no further reduction in CHD risk with greater alcohol consumption up to 7 days per week. In men, drinking frequency was inversely associated with risk of CHD over the entire range of drinking frequencies. For example, HRs were 0.93 (95% CI 0.75 to 1.16) for drinking on 1 day per week vs 0.59 (95% CI

Table 12. Relative risk (RR) for daily consumption of one to two alcoholic drinks compared to no alcohol intake

First author, (y), (reference)	Population/country	Endpoint	RR, odds ratio (OR), or hazard ratio (HR) and (95% confidence intervals)
Di Castelnuovo (2002) (164)	Meta-analysis of 26 studies, including 201,308 wine drinkers and 208,096 beer drinkers (US)	CVD[a]	RR=0.68 (0.59-0.77) for wine drinkers RR=0.78 (0.7-0.86) for beer drinkers
Rimm (1991) (160)	Health Professionals Study (N=51,529) (US)	CHD[b] events	RR=0.53 (0.35-0.79) (adjusted for cardiovascular risk factors)
Mukamal (2003) (161)	Health Professionals Follow-up Study (N=38,077) (US)	MI[c]	RR=0.68 (0.57-0.82) (multivariate adjustment)
Gronbaek (1995) (167)	n=6,051 men and n=7,234 women aged 30-70 y (Denmark)	CVD mortality	RR=0.47 (0.35-0.62) for wine drinkers RR=0.79 (0.68-0.91) for beer drinkers
Romelsjo (1999) (168)	n=50,465 young men conscripted into the army (Sweden)	Overall mortality	RR=1.37 (1.01-1.85) for those consuming ≥15 g ethanol/d (multivariate adjustment)
Mukamal (2006) (174)	n=8,867 from Health Professionals Study (US)	MI	RR=0.32 (0.13-0.75) for those consuming 15-29.9 g alcohol/d (multivariate adjustment)
Okamura (2006) (165)	N=250 men aged 40 to 49 (Japan)	CHD by CAC[d]	OR=3.75 (0.87-16.1) for those consuming ≥69 g alcohol/d (multivariate adjustment)
Ellison (2006) (166)	N=3,166 men and women (US)	CHD by CAC	Not significant
Tolstrup (2006) (175)	n=28,448 women and n=25,052 men	CHD events	For men, HR=0.63 (0.53-0.74) for those consuming ≥21 drinks over 5-7 d/wk compared to HR=1.47 (1.05-2.06) for abstainers; For women, HR=0.72 (0.57-0.92) for those consuming ≥14 drinks over 5-7 d/wk compared to HR=1.03 (0.68-1.56) for abstainers

[a]CVD=cardiovascular disease.
[b]CHD=coronary heart disease.
[c]MI=myocardial infarction.
[d]CAC=coronary artery calcification.

0.48 to 0.71) for drinking 7 days per week (P for trend <0.0001).

Summary of Research-Based Dietary Recommendations and Alcohol Use

Individuals who do not consume alcohol should not be encouraged to start drinking. Unless contraindicated, patients who currently drink alcohol should not exceed a maximum of one drink per day for women or up to two drinks per day for men as part of a cardioprotective dietary pattern within recommended energy levels. One serving of an alcoholic beverage is defined as 0.5 oz or 15 g pure grain alcohol. This is equivalent to 12 oz (355 mL) beer, 5 oz (148 mL) wine, or 1.5 oz (44 mL) 80-proof distilled spirits and contributes approximately 120 to 180 kcal/ serving. Alcoholic beverages provide energy but few essential nutrients. This recommendation is congruent with the Dietary Guidelines for Americans, 2005 (176) and the National Institute on Alcohol Abuse and Alcoholism's State of the Science Report (177).

Consumption of alcohol is not recommended for pregnant women, those at risk of alcoholism, or anyone engaging in activities that require attention, skill, or coordination such as driving a vehicle. Alcohol is not advised for use by those with cardiomyopathy, hypertension, or cardiac arrhythmias. Patients with high serum TG levels should avoid alcohol because it may contribute to the onset of pancreatitis. Overweight and/or diabetic patients should limit or avoid alcohol to reduce unnecessary energy intake (178).

Additional Research Needed

Randomized, double blind, long-term clinical trials evaluating effects of alcohol on CVD risk are unlikely to be conducted. Subjects cannot be blinded due to the inherent effects and risk for introducing alcoholism in susceptible individuals. Short-term studies to evaluate acute effects of alcohol on nonlipid factors such as inflammation and thrombosis would be useful. Future epidemiologic studies should clarify possible differences between genders, ethnic groups, or age groups, levels of BMI, physical activity, other risk factors, as well as differentiating between types of alcohol and alcohol consumed with and without meals.

ANTIOXIDANTS AND CVD PREVENTION

General Relationship

An estimated 40% of the US population takes vitamin supplements in various doses for purposes of disease prevention or treatment. Vitamins have significant health effects beyond preventing deficiency diseases, including antioxidant functions; evidence regarding benefits of supplement intake is inconclusive. The Institute of Medicine defines a dietary antioxidant as a "substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on normal physiological function in humans" (179).

Potential Mechanisms

Oxidative stress may play a significant role in CVD. Oxidation of LDL particles may be a key step in atherogenesis (180-182). That oxidatively modified LDL is atherogenic and exists in vivo is supported by a growing evidence base. In animal models, antioxidant supplementation inhibits atherosclerosis progression (183). Nutrients studied in these experiments have been ascorbic acid, α-tocopherol, and beta carotene.

Status of Current Research

Vitamin C. Prospective studies on ascorbic acid and CVD are inconsistent. A significant inverse relationship has been reported between plasma vitamin C and dietary vitamin C and CAD and CVD events in epidemiologic studies (184-186). Several confounding factors complicate the interpretation of these studies. Elevation of plasma ascorbic acid might reflect intake of foods that not only contribute vitamin C, but other nutrients such as potassium, folate, calcium, magnesium, and isoflavones that may confer cardiovascular benefits. Conflicting studies in large cohorts did not show an association between vitamin C intake and mortality (187,188).

An AHRQ (189) systematic review of four studies that used a placebo-controlled randomized design included at least 60 patients, with at least 6 months of follow-up (three studies were in combination with vitamin E or other antioxidants). The independent effects of vitamin C were only assessed in one study. The studies reviewed included: Multi-Vitamins and Probucol, Antioxidant Supplementation in Atherosclerosis Prevention Study, HDL-Atherosclerosis Treatment Study, and MRC/BHF Heart Protection Study. There is little evidence that vitamin C, in combination with vitamin E or other antioxidants, has any beneficial effect on cardiovascular health. The Antioxidant Supplementation in Atherosclerosis Prevention study assessed 250 mg vitamin C twice daily independent of other antioxidants and with vitamin E. The study concluded there was no effect on the degree of progression of carotid stenosis in the vitamin C alone group but in the group receiving vitamin C and E, there was a reduced rate of progression only in men, which was most pronounced in men who smoked, compared to men who did not (189).

Vitamin E. In prospective studies, α-tocopherol intake and/or supplementation appeared to reduce risk of coronary events in both men and women (190). Conversely, in a case control study, dietary or adipose tissue γ-tocopherol was not associated with decreased MI risk (954 participants). This study did not include vitamin E supplement users (191).

RCTs evaluating the effect of antioxidant intake on CAD have shown mixed results. In the Alpha-Tocopherol Beta-carotene (ATBC) Cancer Prevention Study (192,193) there was no benefit on CAD in subjects taking α-tocopherol or β-carotene. This trial was conducted in >29,000 Finnish male smokers. The dose, however, of α-tocopherol (50 mg/day) was below the protective range suggested by the Nurses' Health Study. Also, in the Heart Outcomes Prevention Evaluation study (194) with 2,545 women and 6,996 men there were no significant differences between vitamin E and placebo in MI, stroke or death from CVD. Similarly, in the GISSI-Prevention trial, there was no benefit on cardiovascular deaths and/or non-fatal MI in the group that took 300 mg vitamin E daily (131). The Cambridge Heart Antioxidant Study of 2,002 British men and women with angiographically proven CAD, showed a 77% reduction in nonfatal MI in subjects taking vitamin E vs placebo (195); however, there was an increase in cardiovascular and overall mortality. Recently, a 4-year extension of the Heart Outcomes Prevention Evaluation trial, found no effect on cancer, vascular events, and death; however, there was a 19% increased risk of heart failure (95% CI 1.05 to 1.35; P=0.007) (196).

The Heart Protection Study (197) published the findings of a UK trial with 20,536 adults with coronary disease, other occlusive arterial disease or diabetes. Subjects were randomized to receive antioxidant vitamin supplementation (600 mg vitamin E, 200 mg vitamin C, and 20 mg β-carotene daily) or matching placebo in a 5-year treatment period. There were no significant differences in all-cause mortality or deaths due to vascular and nonvascular causes, or nonfatal MI or coronary death, nonfatal or fatal stroke or coronary or noncoronary revascularization. Among these high-risk subjects, antioxidant vitamins appeared to be safe, but there was no beneficial effect. The Heart Protection Study results demonstrate that there is no benefit of antioxidant supplements on cardiovascular events among high-risk patients.

The AHRQ report found no evidence that vitamin E alone or in combination reduced cardiovascular mortality or all-cause mortality (189). The findings from the AHRQ are consistent with the results of a recent meta-analysis that vitamin E (n=81,788) did not beneficially affect mortality or significantly decrease risk of cardiovascular death (198). In addition, an RCT (199) found no effect of vitamin E on coronary outcomes. The AHRQ review also assessed the benefit of vitamin E on plasma lipids and found that supplementation with vitamin E alone or in combination with other antioxidants, in doses ranging from 100 IU to 1,200 IU, did not affect serum lipid levels.

β-Carotene. The Physicians Health Study did not demonstrate a benefit of 50 mg of β-carotene supplements on alternate days on CVD endpoints (200). The ATBC trial (192) showed β-carotene supplementation (20 mg daily) increased total mortality and lung cancer; there was a nonsignificant trend for an increase in CVD mortality after 6.5 years. The Beta-Carotene and Retinol Efficacy Trial was stopped 21 months early because the beta carotene group had 285 more lung cancer cases and 17% more deaths than the control group (201). Cardiovascular

mortality also was increased in the beta carotene group. Randomized studies assessing supplementation with beta carotene have shown no benefit and, in fact, there was an increased risk of lung cancer and overall mortality.

CoEnzyme Q10. The AHRQ report included five studies that used a placebo-controlled randomized design to assess the effect of coenzyme Q10 on clinical outcomes (189,202-205). The studies included at least 60 patients (or the equivalent of about 30 patients in both acute treatment and placebo group), and had at least 6 months of follow-up. These five studies, conducted mostly with heart failure patients, reported mixed results. A meta-analysis of eight studies that examined cardiac performance in cardiac patients also was included in the review (206). The authors of the meta-analysis stated, "indices of cardiac function were associated with a substantial improvement." However, subsequent studies have not confirmed these findings. Thus, the AHRQ report concluded that the effect of coenzyme Q10 on CVD remains an open question without convincing evidence to support its benefit or its harm.

Published Data on Antioxidants and CVD Since Completion of the ADA Evidence Analysis Library

The Vascular Basis for the Treatment of Myocardial Ischemia Study (207), a randomized, double-blind, placebo controlled trial with 300 patients with stable coronary disease was designed to assess whether antioxidant vitamins C and E can reduce myocardial ischemia in patients on a moderate LDL cholesterol intervention with diet and low-dose lovastatin or intensive LDL cholesterol lowering with atorvastatin. Although the intensive statin therapy lowered LDL cholesterol to about 80 mg/dL, there was no added benefit of supplemental vitamins C (1,000 mg/day) and E (800 mg/day) on any ischemia outcome.

In several recent epidemiologic studies (208-210), there has been a variable association reported between antioxidant vitamins/nutrients and coronary disease endpoints. For example, Hatzigeorgiou and colleagues (2006) reported no significant correlation between coronary artery calcification score and individual vitamin or total antioxidant vitamin intake. However, the highest quartile of vitamin E intake was positively associated with coronary calcification score (OR 1.77, 95% CI 1.02 to 3.06). In a nested case-control study (with 979 cases and 1,794 controls), Boekholdt and colleagues (209) reported that increasing plasma ascorbic acid quartiles was associated with a lower SBP and diastolic blood pressure (DBP) and higher HDL cholesterol levels. Individuals in the highest ascorbic acid quartile had a decreased OR for future coronary disease of 0.67 (95% CI 0.52 to 0.87). In this study, the authors note that higher plasma ascorbic acid levels are a marker for a higher intake of fruits and vegetables. Finally in the Physicians Health Study (210), plasma lycopene levels were not associated with risk of CVD in older men. Collectively, the supplement data to date do not justify recommending antioxidant vitamin supplements to reduce risk of CVD.

A Cochrane review and meta-analysis of 68 RCTs that included 232,606 participants found that supplementing with β-carotene, vitamin A, and vitamin E had no significant effect on mortality (211). When high-bias risk trials were omitted (high bias due to various reasons such as follow up and blinding), the results from the low-bias risk trials showed a positive association with mortality (RR 1.05, 95% CI 1.02 to 1.08). After excluding selenium trials, β-carotene (RR 1.07, 95% CI 1.02 to 1.11), vitamin A (RR 1.16, 95% CI 1.1 to 1.24), and vitamin E (RR 1.04, 95% CI 1.01 to 1.07), alone or combined with other antioxidants, all increased risk of mortality.

Summary of Research-Based Dietary Recommendations and Antioxidant Use

The current evidence does not support any recommendations for antioxidant supplementation. This is consistent with a recent statement that has been issued by a National Institutes of Health State-of-the-Science Conference on Multivitamin/Mineral Supplements and Chronic Disease Prevention (212), which concluded that the current evidence is insufficient to recommend either for or against the use of multivitamin/mineral supplements by the American public to prevent chronic disease. Meanwhile, the American population should be encouraged to increase fruit and vegetable consumption due to their unique nutrient profiles, including a vast array of antioxidants. Foods have hundreds of antioxidants and other nutrients that act in synergy to promote health. The bioactive components in foods that confer protection against CVD remain to be completely defined. A diet consisting of whole grains, legumes, a variety of fruits and vegetables, nuts, seeds, fatty fish such as salmon and mackerel, and nonfat or very-low-fat dairy foods is recommended along with physical activity daily and maintenance of a healthful body weight.

Additional Research Needed

Research is needed to determine the effect of a food-based approach that addresses the potential synergistic effects of antioxidants on CVD risk.

OBESITY AND CVD RISK

General Relationship

Obesity, defined as BMI $\geq$30, typically is accompanied by numerous CVD risk factors. A recent review has established that obesity is an independent risk factor for CHD based on data from the Framingham Heart Study, the Nurses' Health Study, the Buffalo Health Study, and the Cancer Prevention Study II (213). Waist circumference and WHR both measure abdominal adiposity and are each associated with CHD events and mortality. For those older than age 65 years, BMI does not correlate well with total and CVD mortality (225).

Potential Mechanisms

Obesity influences CHD risk factors, such as LDL cholesterol level, serum TG level, HDL cholesterol level, hypertension, and insulin resistance. In the second National Health and Nutrition Examination Survey, as BMIs of white males increased, TC, non-HDL cholesterol, LDL cholesterol, and serum TG levels increased (99). Likewise in China, higher BMI was associated with hypertension,

Table 13. Studies reporting a significant association between obesity measures and coronary heart disease (CHD)

	Measure of CHD		
Measure of obesity	**Population**	**CHD (risk factors)**	**Cardiovascular disease death (adjusted for risk factors)**
Body mass index	US white men in NHANES[a] II (n=4,834; $P<0.01$) (99); Chinese (n=14,000; significantly higher RR[b] (214); Australians (n=9,206; $P<0.0001$) (215)	Diabetic women in US Nurses' Health Study (n=5,897; $P<0.001$) (217); Women in US Nurses' Health Study (n=88,393; $P<0.001$) (226); Swedish men (N=20,099; age adjusted RR=1.72 (1.44-2.05) (216)	US men in Health Professionals Follow-up Study (n=39,766; P for trend <0.001) (98); US men and women in Cancer Prevention Study II (N=946,154; RR for 62,116 men 2.9 (2.37-3.56) (219); US women in Heart and Estrogen/Progestin Replacement Study (N=2,830; HR[c]=1.19 (1.06-1.35) (218); US white men and women in Cancer Prevention Study I (N=324,135; $P<01$ for women; $P<0.001$ for men) (234)
Waist circumference	US men and women in Baltimore Longitudinal Study of Aging (N=1,941, $P<0.001$) (231), Australians (n=9,206; $P<0.0001$) (215)	US women in Nurses' Health Study (n=44,702; P for trend <0.001) (232); US men in Physician's Health Study (n=16,164; P for trend = 0.0001) (233), Finnish men (N=2,682; $P=0.012$) (223)	US men in Health Professionals Follow-up Study (n=39,766; P for trend <0.001) (98); US women in HERS[d] (N=2,739; HR=1.32 (1.16-1.50) (218)
Waist-to-hip ratio	Australians (N=9,206; $P<0.0001$) (215)	US women in Nurses' Health Study (n=44,702; P for trend <0.001) (232); US men in Physician's Health Study (n=16,164; P for trend $=0.0001$) (233); Finnish men (N=2,682; $P=0.002$) (223)	Older women in Iowa Women's Health Study Cohort (n=41,188; P for trend <0.001) (235); Australians (N=9,206; $P<0.01$ for women; $P<0.0001$ for men) (215); UK men (n=5,811; $P=0.001$) and UK women (n=9,349; $P=0.005$) (227)

[a]NHANES=National Health and Nutrition Examination Survey.
[b]RR=relative risk.
[c]HR=hazard ratio.
[d]HERS=Heart and Estrogen/Progestin Replacement Study.

hypercholesterolemia, low HDL cholesterol level, and higher serum glucose levels (24,734 Chinese participants) (214). An Australian study reported BMI, waist circumference and WHR were strongly correlated with CHD risk factors (215).

In addition to the contribution of obesity to heart disease risk factors, evidence of an association sometimes remains after adjustment for CVD risk factors. After adjusting for age, heart rate, CVD risk factors, history of cancer, single status, socioeconomic status, and problematic drinking behavior, BMI continued to be associated with an increased incidence of MI in Swedish males (216). Likewise, in women with diabetes in the Nurses' Health Study, adjusting for hypertension and blood cholesterol did not diminish the inverse relationship between BMI and CHD (217). Adjusting for CHD risk factors eliminated the significant relationship between waist circumference and CHD mortality among 2,739 postmenopausal women with heart disease in the Heart and Estrogen/Progestin Replacement Study (218).

Conclusions regarding obesity and CHD risk regarding use of BMI, waist circumference, and WHR were based on 10 cohorts from the United States (98,99,217,219) and five international studies representing individuals residing in Sweden, Korea, Australia, and China (214-216,220,221). Although all three measures of obesity are associated with increased CHD risk (for people aged <65 years), waist, and WHR seem to give the best assessment of CHD risk status. Table 13 summarizes significant relationships of each measure with heart disease.

BMI

In all cohorts, higher BMIs were consistently associated with increased risk of CHD mortality among those younger than age 65 years (98,99,214-219,221-223). In some studies this relationship was no longer present when analyses were adjusted for other CHD risk factors (215,221,223,224). A linear relationship was observed between increasing BMI and CHD risk. In the Health Professionals Follow-Up Study, males with a BMI above 30 had a four times greater likelihood of CVD death than those with a BMI below 23 (98).

BMI was not significantly related to risk of CHD or CVD events in older individuals (>65 years of age) (222,225). Also, the Cancer Prevention Study II (219) found that association of BMI with CVD death was stron-

ger for whites than African Americans, especially among African-American men.

Published Research on BMI and CVD since Completion of the ADA Evidence Analysis Library

New research conducted since the completion of the ADA Evidence Analysis Library review supports previous studies showing that risk of CHD mortality is increased with a higher BMI (226). In the Nurses' Health Study, the relative risk of CHD was 3.44 (95% CI 2.81 to 4.21) for obese women (226). This study also reported a 27% (95% CI 12% to 45%) increased risk of CHD in women who gained weight during adulthood (4 to 10 kg) compared with women who maintained a stable body weight. Current studies present data showing the importance of body fatness and abdominal obesity over BMI in the relationship between overweight and obesity and CHD risk (227,228). Elevated BMI predicted stroke in a cohort followed for 16 to 21 years and 22 to 28 years, but not 0 to 15 years (229), which is consistent with the findings of Lawlor and colleagues (230) reporting no association between BMI measured in childhood and risk of IHD and stroke.

ABDOMINAL ADIPOSITY

Waist circumference was associated with overall or CVD mortality in five studies (98,218,231-233). The lowest CVD mortality risk in men (<65 years of age) was for a waist circumference of 36.3 to 37.9 in. In contrast, a study reported a 1.34 relative increased risk in men with a waist circumference >36.5 in (233). Among 44,702 women, a higher risk (3.06) was reported with waist circumferences >38 in compared to <30 in (232). Even after adjusting for age, diabetes mellitus, hypertension, and blood lipids, waist circumference was positively associated with CHD among 16,164 postmenopausal women with heart disease (218).

A higher WHR was associated with increased incidence of CHD (232,233), CHD events (223) and CVD mortality (215,224). Two US studies reported that women in the highest quintile for WHR were more than three times more likely to experience CHD (232) or CVD death (224) than those in the lowest quintile. Finnish males with a WHR near 1.0 or greater had almost three times the risk of CHD events vs those in the lowest quintile (<0.91 WHR) (223). US men with a WHR near 1.0 were at 50% greater risk for CHD than those in the lowest quintile (233).

Based on Health Professionals Follow-up Study data, waist circumference strongly predicted risk of CVD death among the younger and older men, whereas waist circumference only predicted risk of overall mortality in younger men (98). Data from the Iowa Women's Health Study found WHR to be a better marker than BMI for risk of death in older women (224).

Current Recommendations

For individuals irrespective of risk status, waist circumference, or WHR are better predictors of CHD and risk for CVD death than BMI, especially in those ≤65 years of age.

Additional Research Needed

Research is needed to determine the appropriate BMI, WHR, and waist circumference cutpoints for different sex, age, and ethnic groups.

PHYSICAL ACTIVITY AND EFFECT ON LIPID/LIPOPROTEIN LEVELS AND CVD PROTECTION

General Relationship

The relationship between physical activity and reduction in CVD risk factors and CHD events in both primary and secondary prevention has been consistently demonstrated in observational and randomized controlled clinical studies primarily in white individuals. Qualitative methods used to assess physical activity were a limiting factor in some of the cohort and case controlled trials that were reviewed.

Potential Mechanisms

The effects of physical activity on CVD risk reduction are due, in part, to favorable effects on blood pressure, TG levels, HDL cholesterol levels, insulin sensitivity, glucose tolerance, and body weight. Physical activity and weight loss decrease LDL cholesterol levels and lessen the reduction in HDL cholesterol that often occurs with a diet that is low in total fat and SFA (234).

Status of Current Research

Several observational cohort studies found that physical activity was associated with a reduction in CHD and CVD in healthy subjects (171,235-240). Both leisure time physical activity and exercise with increased intensity were protective (171,236). One study found that moderate fitness appeared to exert a protective effect against CVD risk factors (237).

The data supporting the relationship between physical activity and reduced risk from all-cause and cardiac mortality in secondary prevention is from a Cochrane review that included 32 RCTs of exercise only or comprehensive exercise-based cardiac rehabilitation (241). Another case-controlled study found that changing from a sedentary to a more active lifestyle later in life may strongly decrease CHD risk in patients with stable CHD (242). Table 14 summarizes the major findings in studies showing the association between physical activity and a reduced risk of CHD and CVD in both primary and secondary prevention.

The relationship between physical activity, diet, and lipoprotein levels was investigated using two studies, one of which contained data from a meta-analysis of 51 trials, including 28 RCTs of >12 weeks duration (243,244). Results from the meta-analysis showed that endurance training in all weight categories was associated with a mean increase in HDL cholesterol levels of 4.6% and reductions in TG and LDL cholesterol levels of 3.7% and 5.0%, respectively (243). The effect of physical activity on reducing LDL cholesterol levels was magnified when combined with diet. Compared to either lifestyle approach alone, the combination of a low-saturated-fat and low-cholesterol diet and physical activity significantly reduced LDL cholesterol levels from baseline in both men (−20 mg/dL) and women (−14.5 mg/dL) (244).

Table 14. Studies reporting an association between physical activity and reduced risk of coronary heart disease (CHD) and cardiovascular disease (CVD) in primary and secondary prevention

First author, (y), (reference)	Major finding
Manson (2002) (235)	Postmenopausal women (n=73,743) who either walked or exercised vigorously for at least 2.5 h/wk had a 30% ↓ in CVD risk ($P<0.001$).
Lakka (1994) (236)	Finnish men (n=1,453) who engaged in >2.2 h/wk of physical activity had a 69% ↓ in risk for acute MI[a] ($P=0.02$).
Blair (1996) (237)	Cardiorespiratory fit men (n=25,341) with any combination of CVD risk factors (smoking, ↑ blood pressure, ↑ total cholesterol) had lower adjusted death rates than low-fit men with no risk factors ($P=0.004$).
Tanasescu (2002) (171)	Increasing intensity of aerobic exercise combined with weight training appears to be effective in ↓ CHD risk in men (n=44,452; $P=0.03$ for trend).
Jolliffe (2000) (241)	Individuals with coronary artery disease who participated in exercise only (n=2,845) or comprehensive exercise-based rehabilitation programs (n=5,595) had a 27% ($P<0.05$) and 13% (P=NS[b]) ↓ in all-cause mortality respectively. Cardiac mortality ↓ by 31% ($P<0.05$) and 26% ($P<0.05$), respectively. (Cochrane Review)
Sundquist (2005) (240)	After adjusting for CHD risk factors in addition to socioeconomic status, men (n=2,645) and women (n=2,551) who performed physical activity at least 2 d/wk had a 41% lower risk of developing CHD (95% confidence interval 0.37-0.95, no *P* value).
Noda (2005) (238)	Japanese men (n=31,023) and women (n=42,242) aged 40-79 y had a 49% lower risk of CHD mortality ($P=0.005$) when participating in a sports activity ≥5 h/wk, and a 16% lower risk of total CVD mortality ($P=0.006$) when walking ≥1 h/d.
Janssen (2006) (245)	The relative risk of all-cause mortality in elderly patients (≥65 y) with coronary artery disease (n=1,045) decreased in a curvilinear dose-response manner with increasing levels of physical activity ($P<0.001$ for trend). The beneficial effect of physical activity on mortality risk was consistent within other CAD risk factors.
Rothenbacher (2006) (242)	Patients with stable CHD (n=518; 176 with CHD, 342 matched controls) who were physically active in both early (age 20-39 y) and later adulthood (age 40-49 y) had a 62% ↓ risk for CHD ($P=0.0002$). (case-control study).
Schnohr (2006) (239)	Men (n=2,136) and women (n=2,758) aged 20-79 y who performed long-term moderate (walking 2-4 h/wk) or high physical activity (walking >4 h/wk or vigorous activity 2-4 h/wk) had a 29% and 44% ↓ risk of death from CHD, respectively ($P=0.003$ for trend).

[a]MI=myocardial infarction.
[b]NS=not significant.

Published Research of Physical Activity and CVD Since Completion of ADA Evidence Analysis Library

Recent studies support earlier research and show an inverse graded relationship between physical activity and all-cause mortality in men and women with coronary disease (relative risk was decreased by 10% at 500 kcal/week; 19% at 1,000 kcal/week; 30% at 2,000 kcal/week; 38% at 3,000 kcal/week; 43% at 4,000 kcal/week; 46% at 5,000 kcal/week) (245). Increasing physical activity is associated with reduced coronary and stroke mortality (238,239). In the Noda and colleagues study (238), multivariate-adjusted HRs for the highest vs the second lowest categories of walking/participation in sports were 0.71 (95% CI 0.54 to 0.94) and 0.80 (95% CI 0.48 to 1.31), respectively, for ischemic stroke; 0.84 (95% CI 0.64 to 1.09) and 0.51 (95% CI 0.32 to 0.82), respectively, for CHD; and 0.84 (95% CI 0.75 to 0.95) and 0.73 (95% CI 0.60 to 0.90), respectively, for CVD. Moreover, with increased leisure time physical activity, incidence rates of CHD decreased in men and women by 41% if they were active at least twice a week vs those who performed no physical activity (240).

Physical Activity Recommendations

The American Heart Association, the Centers for Disease Control and Prevention, and the American College of Sports Medicine all support the recommendation that individuals should engage in at least 30 minutes per day of moderate-intensity physical activity on most (preferably all) days of the week. Accumulating shorter amounts of physical activity of 10-minute durations throughout the day has also been included in these recommendations. Moderate-intensity physical activity is defined as 40% to 60% of maximal heart rate or VO_{2max} (or 4 to 6 metabolic equivalents) (246).

Additional Research Needed

Behavioral strategies and tools to motivate individuals to become and remain physically active and the possible factors that influence the implementation of physical activity are areas that require further research (234). In addition, more studies are needed to examine the influence of sex, socioeconomic status, race, and ethnicity on the relationship of physical activity and CHD.

ATP III (1)[a]	WHO (282)[b]
• Abdominal obesity, measured by waist: Men >102 cm (>40 in) Women >88 cm (>35 in) • Plasma triglyceride level ≥150 mg/dL[c] • High-density lipoprotein cholesterol level: Men <40 mg/dL[d] Women <50 mg/dL[d] • Blood pressure ≥130/≥85 mm Hg • Fasting blood glucose level ≥100 mg/dL[e]	• Type 1 diabetes mellitus • Impaired fasting blood glucose • Impaired glucose tolerance or for those with normal fasting blood glucose levels (<110 mg/dL[e]), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions And two of the following: • Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) • Plasma triglyceride level ≥150 mg/dL[c] • High-density lipoprotein cholesterol level: Men <35 mg/dL[d] Women <39 mg/dL[d] • Body mass index: Men >30 and/or waist-to-hip ratio >0.9 Women >30 and/or waist-to-hip ratio >0.85 • Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

[a]Three of the five criteria must be met.
[b]Insulin resistance, identified by one of the listed criteria.
[c]To convert mg/dL triglycerides to mmol/L, multiply mg/dL by 0.0113. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.6. Triglycerides of 159 mg/dL=1.80 mmol/L.
[d]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
[e]To convert mg/dL glucose to mmol/L, multiply mg/dL by 0.0555. To convert mmol/L glucose to mg/dL, multiply μmol/L by 18.0. Glucose of 108 mg/dL=6.0 mmol/L.

Figure. Criteria for diagnosing metabolic syndrome, according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the World Health Organization (WHO).

DIETARY STRATEGIES TO PREVENT AND TREAT METABOLIC SYNDROME

General Relationship

Observational studies have shown that people with metabolic syndrome are three to four times more likely to die of CHD after adjusting for common risk factors (220). The age-adjusted prevalence of metabolic syndrome is approximately 24% of the population and about 44% of individuals between ages 60 and 69 years have metabolic syndrome (247). Thus, identifying and aggressively managing patients with the metabolic syndrome is warranted. Obesity plays a major role in metabolic syndrome and contributes to the other risk factors, including hypertension and dyslipidemia. Therefore, prevention of overweight and obesity remains the major goal.

Potential Mechanisms

The diagnosis of metabolic syndrome is based on criteria described by ATP III or the World Health Organization (Figure). Prevention of weight gain and obesity may be the single most effective means of preventing metabolic syndrome (248). Because insulin resistance is also considered an underlying feature of metabolic syndrome, dietary patterns that contribute to insulin resistance are likewise problematic (247). An eating pattern that is associated with reduced risk factors such as the Mediterranean diet would be preferred (249,250). The PREMIER Study involved a multicomponent intervention that included the Dietary Approaches to Stop Hypertension (DASH) diet (251). This eating pattern emphasizes fruits, vegetables, low-fat dairy products, and whole grains. The PREMIER study is noteworthy in that it provides evidence that this approach not only lowers blood pressure and blood lipid levels over 18 months, but also offers a healthful eating pattern that can be adopted and followed by free-living individuals.

Status of Current Research

Studies reviewed were limited to those that identified patients with the metabolic syndrome. Four observational studies found that physical inactivity was associated with increased risk; thus, engaging in some form of physical activity reduces risk or prevalence of the metabolic syndrome (249,252-254). This relationship has been established in African-American, Native-American, and white women (n=46) (252), Greek individuals (n=2,282 participants) (249), middle-aged white men (n=1,069) (253), and men and women ≥20 years of age residing in the United States (n=8,808) (254). Similarly, a case-controlled study reported that in individuals with metabolic syndrome, being physically active vs sedentary was associated with an 11% reduced risk of acute coronary syndrome (250).

Observational studies also provide evidence that dietary factors are associated with metabolic syndrome. A cross-sectional study of 8,808 US adults in the third National Health and Nutrition Examination Survey reported that individuals with metabolic syndrome consumed significantly fewer fruits and vegetables than those without metabolic syndrome (128±3.3 vs 136.9±1.7 servings/month; $P=0.024$) and had a lower intake of vitamin A ($P=0.023$). Those with metabolic syndrome also had lower serum concentrations of components associated with fruit and vegetable intake when compared to those without metabolic syndrome after controlling for a number of covariates ($P<0.001$ for all) (254). In a cross-

sectional study of 2,282 Greek men and women, a Mediterranean-type diet was associated with lower prevalence of metabolic syndrome compared to those not following this type of diet (OR 0.81, 95% CI 0.68 to 0.976; $P=0.014$) (249). Furthermore, in a case-controlled study of 1,926 Greek men and women, consuming a Mediterranean diet was associated with a 23% reduced risk of an acute coronary event in patients with metabolic syndrome (OR 0.77, 95% CI 0.645 to 0.918; *P* value not reported) (250).

The HERITAGE Family Study (HEalth, RIsk factors, exercise Training And GEnetics Family Study) (255), a 20-week aerobic exercise program that included three 30-minute sessions per week reduced the prevalence of metabolic syndrome by 30.5% (95% CI and *P* value not reported) and decreased CVD risk factors (ie, TG level, blood pressure, glucose, and waist circumference; low HDL cholesterol level was not improved). The overall prevalence of metabolic syndrome in the HERITAGE sample decreased from 16.9% before training to 11.8% after training and results similar in sex and ethnic subgroups (n=954). In addition, a retrospective cohort study found 125 metabolic syndrome patients enrolled in a rapid weight loss program (a very-low-energy diet with ad libitum physical activity and group education) for at least 4 weeks, improved weight (−39.3 lb, 15.1% weight loss; $P=0.002$), BMI (−6.1 units; $P=0.002$), SBP (−14.6 mm Hg; $P=0.002$) and DBP (−7.9 mm Hg; $P=0.061$), fasting blood glucose (−19 mg/dL§ $P=0.011$), TG (−104.2 mg/dL; $P=0.011$), and TC (−24.4 mg/dL; $P=0.002$) at the end of 16 weeks compared to 4 weeks into the program (256).

Summary of Research-Based Dietary and Physical Activity Recommendations for Metabolic Syndrome

Aerobic exercise and weight loss are effective for preventing and treating the metabolic syndrome. A diet containing ample amounts of fruits and vegetables is recommended, in part, to decrease energy density of the diet to facilitate weight loss. The American Heart Association, National Heart, Lung, and Blood Institute, and American Diabetes Association suggest that reducing body weight (by 7% to 10% over 6 months to 1 year) be done by combining a weight loss diet with a daily minimum of 30 minutes of moderate intensity activity.

Additional Research Needed

Further research is needed to determine whether or not physical activity at any level with or without accompanying weight loss reduces risk of metabolic syndrome. In addition, the optimal amount of energy from fat and carbohydrate, along with the quality of carbohydrate (refined vs complex and/or carbohydrates with low glycemic index) and type and amount of physical activity needed to prevent or treat metabolic syndrome remains unclear.

§To convert mg/dL fasting blood glucose to mmol/L, multiply mg/dL by 0.0555. To convert mmol/L fasting blood glucose to mg/dL, multiply mmol/L by 18.0. Fasting blood glucose of 108 mg/dL=6.0 mmol/L.

DIET AND LIFESTYLE STRATEGIES TO LOWER BLOOD PRESSURE

General Relationship

Hypertension is a major risk factor for CHD. Among CHD patients, 80% to 90% have one of the four major risk factors for CHD, one of which is hypertension (248,257). Approximately 50 million adults in the United States and about 1 billion worldwide have hypertension or prehypertension (258).

Potential Mechanisms

Elevated blood pressure damages the endothelial lining of the arteries, which allows LDL cholesterol to enter in increased amounts. It further stiffens the arteries and increases the risk of MI or stroke and can also affect the kidneys eventually leading to end-stage renal disease if not treated.

Status of Current Research

Studies examining the effect of diet on blood pressure are summarized in Table 15. Three RCTs assessed the benefit of a DASH diet on lowering blood pressure. The landmark study, Dietary Approaches to Stop Hypertension, was a carefully controlled feeding trial that recruited normotensive and hypertensive adults (N=459). This study found that a diet rich in fruits, vegetables, and low-fat dairy products but low in saturated and total fat reduced SBP by 5.5 mm Hg and DBP by 3.0 mm Hg more than the control diet ($P<0.001$). The blood pressure reduction in hypertensive adults (11.4 mm Hg SBP; 5.5 mm Hg DBP) is equivalent to drug therapy, but even among normotensive adults, blood pressure is reduced (6).

Subsequently, the DASH-Sodium Trial, another controlled feeding trial of normotensive and hypertensive adults (N=390) found that reducing sodium intake in addition to consuming a DASH diet was effective. Reducing the sodium intake from 150 mmol/day to 100 mmol/day reduced SBP by 2.1 mm Hg ($P<0.001$) during the control diet and by 1.3 mm Hg ($P=0.03$) during the DASH diet. Further reducing sodium intake to 50 mmol/day caused additional reductions of 4.6 mm Hg ($P<0.001$) during the control diet and 1.7 mm Hg ($P<0.01$) during the DASH diet. Compared to the high-sodium control diet, the low-sodium DASH diet produced a mean SBP that was 7.1 mm Hg lower in normotensive individuals and 11.5 mm Hg lower in hypertensive individuals (259).

The DASH diet also has been studied in dietary interventions of blood pressure in free-living individuals who were counseled on following the DASH diet. In the PREMIER trial of normotensive and hypertensive adults (n=810), the mean net reduction in SBP was 3.7 mm Hg ($P<0.001$) for subjects following established dietary advice to lose weight, increase physical activity, reduce sodium intake to <100 mEq sodium, and reduce alcohol intake, compared to 4.3 mm Hg ($P<0.001$) for those following a combination of DASH and the established dietary advice (260).

Clinically significant long-term reductions in blood pressure and reduced risk for hypertension can be achieved with modest weight loss and increased physical activity. In the Trials of Hypertension Prevention multi-

Table 15. Major findings of recent studies on the relationship between diet and blood pressure

First author, (y), (reference)	Population/duration	Intervention (type)	Major findings
Appel (1997) (6)	N=459 normotensive and hypertensive adults; 8 wk	DASH[a] diet, rich in fruits, vegetables, and low-fat dairy products but low in saturated and total fat vs control diet (controlled feeding trial)	↓ SBP[b] 5.5 mm Hg, ↓ DBP[c] by 3.0 mm Hg ($P<0.001$)
Sacks (2001) (259)	N=390 normotensive and hypertensive adults; 90 d	For DASH diet and control diet ↓ sodium intake from 150 mmol/d to 100 mmol/d and 50 mmol/d (controlled feeding trial)	100 mmol/d: control diet ↓ SBP 2.1 mm Hg ($P<0.001$), DASH diet ↓ SBP 1.3 mm Hg ($P=0.03$). 50 mmol/d: control diet ↓ SBP 4.6 mm Hg ($P<0.001$), DASH diet ↓ SBP 1.7 mm Hg ($P<0.01$) vs control, DASH diet mean SBP was ↓ 7.1 mm Hg for nornotensive and ↓ 11.5 mm Hg for hypertensive
Appel (2003) (260)	N=810 normotensive and hypertensive adults; 18 mo	DASH diet plus traditional dietary advice vs traditional dietary advise: lose weight, ↑ physical activity, ↓ sodium, ↓ alcohol (randomized clinical trial)	Mean SBP ↓ 3.7 mm Hg for traditional ($P<0.001$) and ↓4.3 mm Hg for DASH plus traditional ($P<0.001$). These data are the 6-mo outcome data.
Stevens (2001) (261)	N=1,191 free-living adults at 110%-165% of ideal body weight; 36 mo	Usual care control vs weight-loss intervention (randomized controlled trial)	Mean difference between control and intervention at 6 mo was −3.7 mm Hg for SBP and −2.7 mm Hg for DBP. Participants who matintained 4.5 g or more weight loss had sustained ↓ in DBP through follow-up. Decreased SBP and DBP was $P<0.001$. No P values specifically indicated for weight maintenance.
Miller (2002) (262)	N=43 adults with hypertension and overweight; 9 wk	Hypocaloric (500 kcal deficit/d) DASH diet with sodium at 100 mmol/d and supervised moderate-intensity physical activity 3 times/wk vs control diet (randomized controlled feeding trial)	↓ mean 24-hr SBP 9.5 mm Hg ($P<0.001$), ↓ DBP 5.3 mm Hg ($P<0.002$)
Appel (2001) (263)	N=681 free-living older people (aged 60-80 y) with hypertension; 36 mo	Reduced sodium intervention of 80 mmol/d vs control (randomized controlled trial)	↓ mean SBP 4.3 mm Hg ($P<0.0001$), ↓ DBP 2.0 mm Hg ($P=0.001$)
Behall (2006) (264)	N=25 middle-aged adults with normotension or slight hypertension and hypercholesterolemia; 17 wk	Comparison of whole grain types: whole wheat/brown rice vs barley vs half barley/half whole wheat-brown rice (controlled feeding trial)	Whole wheat/brown rice and half/half ↓ SBP 7.4 mm Hg, and 8.9 mm Hg, respectively and all grain diets ↓ DBP approximately 5 mm Hg over initial levels ($P<0.05$)
Djousse (2006) (267)	N=4,959 subjects (aged 25-94 y) from National Heart, Lung, and Blood Institute Family Heart Study; 2 phases over 2.5 y	Dairy product, saturated fat, and linolenic acid consumption effects on blood pressure (cross-sectional study)	Lowest to highest category of dairy intake, linear ↓ in SBP (P for linear trend = 0.003).
Elmer (2006) (251)	N=810 adults with normotension and hypertension; 18 mo	DASH diet plus traditional dietary advice vs traditional dietary advise: lose weight, ↑ physical activity, ↓ sodium, ↓ alcohol (randomized clinical trial)	Mean SBP ↓ −8.6 mm Hg for traditional and ↓11.1 mm Hg for DASH plus traditional; odds ratio or difference from baseline at 18 mo (95% CI[d]) = −1.0 (−2.8 to 0.8). These data are the 18-mo results.
Fu (2006) (265)	N=70 healthy postmenopausal women, aged 55 y; observational study (time/length not given)	Comparison of cardiovascular autonomic functions in vegetarians and age-matched omnivores (observational study)	Vegetarians had lower SBP −12 mm Hg and lower DBP −10 mm Hg compared to nonvegetarians ($P=0.001$)
Elliott (2006) (266)	N=4,680 men and women aged 40-59 y from population samples in Japan, China, the United Kingdom, and the United States; 2 consecutive day visits with same at follow-up 3-6 wk later	Association between protein intake and blood pressure studied (cross-sectional epidemiologic study)	Higher vegetable protein intake by 2.8% ±2% kcal were associated with −2.72 mm Hg SBP and −1.67 mm Hg DBP ($P<0.0001$). For animal protein intake, significant direct associations did not persist after adjustments for weight and height.
Rasmussen (2006) (312)	N=162 healthy male and female subjects aged 30-65 with normal or moderately increased body weight; 3 mo	Subjects randomized to either a diet rich in monounsaturated fatty acid or one rich in saturated fatty acid. Each group further randomized to either placebo or fish oil supplement (controlled, parallel, multicenter study; 5 sites)	SBP and DBP ↓ on monounsaturated fat diet -2.2% ($P=0.009$) and −3.8% ($P=0.0001$). No change on saturated fat diet. Addition of n-3 fatty acids had no significant effect on blood pressure.

[a]DASH=Dietary Approaches to Stop Hypertension.
[b]SBP=systolic blood pressure.
[c]DBP=diastolic blood pressure.
[d]95% CI=95% confidence interval.

center RCT conducted with elevated to mildly hypertensive free-living adults at 110% to 165% of ideal body weight, researchers reported that blood pressure was significantly lower in subjects (n=595) in the weight loss intervention group, than the subjects (n=596) in the usual care control group at 6, 18, and 36 months. At 6 months, the difference between the group means (usual care vs intervention) in SBP was −3.7 mm Hg and in DBP was −2.7 mm Hg. Subjects who successfully maintained a weight loss of 4.5 kg or more experienced a reduction in DBP that was sustained throughout the remainder of follow-up (261).

The randomized controlled Diet, Exercise, and Weight Loss Intervention Trial showed that provision of a hypocaloric (500 kcal deficit/day) DASH diet with sodium intake at 100 mmol/day and supervised moderate intensity physical activity three times per week in 20 hypertensive overweight adults resulted in a reduced mean 24-hour SBP by 9.5 mm Hg ($P<0.001$) and DBP by 5.3 mm Hg ($P<0.002$) compared to 23 subjects in the control group (262).

Special populations such as the elderly also have been studied. In the Trial of Nonpharmacological Interventions in the Elderly, a randomized controlled trial of 681 free-living hypertensive older people (aged 60 to 80 years), mean reductions in SBP were 4.3 mm Hg ($P<0.0001$) and DBP were 2.0 mm Hg ($P=0.001$) from the reduced sodium intervention of 80 mmol/day, net of controls (263).

Published Research on Diets to Lower Blood Pressure Since Completion of the ADA Evidence Analysis Library

Since the completion of the ADA Evidence Analysis Library, several trials have been published regarding diet and blood pressure changes. An 18-month follow-up of the PREMIER trial found consistent findings with the 6-month results, both behavior interventions significantly decreased body weight, energy, total fat, saturated fat, cholesterol level, and sodium intake (251). Intakes of calcium, magnesium, fiber, and folate were significantly greater in the established DASH group than in the advice and established groups. For both behavior intervention groups, the mean weight loss was significantly greater than for the advice group (mean difference of −2.2 kg for the established group and −2.7 kg for the established plus DASH group; $P<0.001$ for each). Compared with the advice group, the ORs for hypertension at 18 months were 0.83 (95% CI 0.67 to 1.04) for the established group and 0.77 (95% CI 0.62 to 0.97) for the established plus DASH group. Absolute reductions in blood pressure at 18 months tended to be greater for participants in the established and established plus DASH groups vs the advice group. The PREMIER Study shows that individuals can implement and maintain multiple lifestyle behavior changes.

In a small study (seven men, nine premenopausal women, and nine postmenopausal women) conducted by Behall and colleagues (264), subjects followed a Step I diet for 2 weeks and then replaced 20% of energy with whole wheat/brown rice, barley or half wheat-rice/half barley for an additional 5 weeks. Compared to baseline, the whole wheat/brown rice and half/half diets significantly decreased SBP (118, 110, and 109 mm Hg, respectively; $P<0.003$) and DBP was decreased in subjects on all-whole-grain diets (baseline 71 mm Hg; whole wheat/brown rice 65 mm Hg; half/half 66 mm Hg; barley 66 mg Hg, respectively; $P<0.003$) (264).

A recent study in China reported descriptive data on a small group of healthy postmenopausal women (n=70) who had practiced vegetarianism ≥2 years compared with omnivores (265). The vegetarians had significantly lower systolic (121 vs 133 mm Hg) and DBP (72 vs 82 mm Hg) ($P<0.001$ for both).

The International Study of Macro and Micro Nutrients and Blood Pressure study (266), a cross-sectional epidemiologic study of 4,680 persons aged 40 to 59 years in four countries reported a significant inverse relationship between vegetable protein intake and blood pressure. A vegetable protein intake of 2.8% of energy was associated with a decrease of 2.1 mm Hg systolic and a decrease of 1.4 mm Hg diastolic ($P<0.001$ for both).

In the National Heart, Lung, and Blood Institute Family Heart Study there was an inverse relationship reported between dairy product intake and the prevalence of hypertension (267). The ORs for the quartiles were 1.0 (reference), 0.82 (95% CI 0.64 to 1.05), 0.68 (95% CI 0.53 to 0.89), and 0.62 (95% CI 0.45 to 0.84). In this study, dairy consumption was inversely associated systolic (P for trend=0.003) but not diastolic (P for trend=0.09) blood pressure.

Summary of Research-Based Dietary Recommendations to Lower Blood Pressure

Studies clearly demonstrate that implementing lifestyle recommendations for the reduction of blood pressure and following the DASH diet pattern improve hypertensive status. Consuming a Mediterranean-type diet rich in fruits, vegetables, and low-fat dairy products and reduced in sodium and saturated fat represents an ideal eating pattern. Weight loss and increased physical activity contribute to ideal lifestyle conditions.

Additional Research Needed

More research is needed to identify strategies that enable individuals to maintain weight loss and improve diet patterns in a lifestyle that enables optimum blood pressure status to be achieved and regulated on a consistent basis.

EFFECTIVENESS OF MEDICAL NUTRITION THERAPY (MNT) FOR HYPERLIPIDEMIA

Space does not permit a thorough review of the current MNT literature (268-281), but patients with hypercholesterolemia needing dietary counseling should be referred to a registered dietitian (RD) for MNT. To influence dietary changes, as well as cholesterol lowering, individuals need a minimum of two to six visits with an RD over a 6-week to 6-month period. Initial visits should last 45 to 90 minutes and subsequent visits between 30 and 60 minutes. Greater benefit may occur with increased time spent with an RD. A detailed review of the existing data appear in the ADA Evidence Analysis Library (270).

Table 16. Graded conclusion statements and number of primary and secondary papers supporting findings presented in the American Dietetic Association Evidence Analysis Library

Topic	No. of primary articles (reference numbers)	No. of meta-analyses or review articles (reference numbers)	Summary statement	Grade
Total fat, SFA[a], and cholesterol	4 (15,16,19,283)	1 (21)	A diet consisting of 25%-35% total fat, <7% SFA and TFA[b], and <200 mg dietary cholesterol ↓ serum total and LDL[c] cholesterol 9%-16% and ↓ the risk of CHD[d]	I
	2 (22,144)	3 (9,20,23)	Isocalorically replacing SFA with MUFA[e] and PUFA[f] is associated with ↓ in LDL cholesterol level	I
TFA	5 (11,22,26,283,284)	2 (23,24)	TFA ↑ TC[g] and LDL cholesterol. Unlike SFAs, TFAs do not ↑ and may ↓ HDL[h] cholesterol level. TFA ↑ TC/HDL cholesterol ratio in a dose-dependent manner	I
	3 (30-32)	0	Population and cohort studies show high TFA intake ↑ risk of CHD events	II
Fish	3 (114-116)	2 (44,129)	Epidemiologic studies indicate that regular consumption of an average of two servings of fatty fish per week (about 3.5 oz per serving) high in long-chain n-3 fatty acids, such as EPA[i] and DHA[j] is associated with a 30%-40% ↓ risk of death from cardiac events in subjects without prior disease	II
n-3 Fatty acids	2 (126,127)	0	Randomized clinical trials have shown that approximately 1 g/d EPA and DHA from a supplement or fish decreases the risk of death from cardiac events in patients with heart disease	II
	1 (132)	0	One recent study of moderate quality has shown no protective effect of fish in patients with angina (n=1,109). However, the fish oil supplemented group with angina in this study (3 g/wk, n=462) showed significantly higher cardiac death and sudden death ($P<.05$). There is insufficient research to indicate if the harm associated with fish oil supplement intake by angina patients is a result of the difference between fish and supplement intervention or special population characteristics	III
	1	1 (124)	Plant-derived Epidemiologic studies indicate that inclusion of vegetable oils and food sources high in ALA[k], resulting in a total intake of more than 1.5 g/d, is associated with a 40%-65% ↓ risk of death from cardiac events	III
	1 (30)	0	↑ Plasma levels, adipose tissue, and cholesterol ester concentrations of ALA, EPA and DHA have been associated with reduced risk of mortality	II
Dietary fiber	5 (89-92,100)	2 (94,285)	Consuming diets high in total dietary fiber (>25 g/d) is associated with ↓ risk for CHD and CVD[l]	II
	5 (93,96,101-103)	1 (95)	Consuming diets high in total fiber (17-30 g/d) and soluble fiber (7-13 g/d) as part of a diet low in SFA and cholesterol can further ↓ TC by 2%-3% and LDL cholesterol up to 7%	I
	Same	Same	Limited research indicates that other risk factors for CHD may be modified by a diet low in SFA and cholesterol and high in total and soluble fiber. These risk factors include blood pressure, lipoprotein subclasses and particle sizes, and fasting and postprandial insulin levels	III
Plant stanols and sterols	11 (23,63-67,73,77,80-82)	0	Plant sterols and stanols are potent hypocholesterolemic agents and a daily consumption of 2-3 g (through margarine, low-fat yogurt, orange juice, breads, and cereals) lowers TC concentrations in a dose-dependent manner by 4%-11% and LDL cholesterol concentrations by 7%-15% without changing HDL cholesterol levels or triacylglycerol concentrations	I
	3 (80-82)	0	The TC and LDL cholesterol- lowering effects of stanols and sterols are evident even when sterols and stanols are consumed as part of a cholesterol-lowering diet	I
	11 (23,63-67,73,77,80-82)	0	The cholesterol-lowering effects are similarly caused by sterols and stanols. Sterols lowered TC by 6%-11% and LDL cholesterol by 7%-15%. Stanols lowered TC by 4%-10% and LDL cholesterol by 7%-14%. Although the reduction in TC and LDL cholesterol levels are similar, two high-quality randomized controlled trials in adults with hypercholesterolemia report slightly greater though nonsignificant effects with consumption of stanols compared to sterols	II
	Same	0	Nonesterified and esterified forms of sterols and stanols are equally effective. Consumption of 2-3 g nonesterified sterols and stanols reduce TC by 4%-11% and LDL cholesterol by 8%-15% and esterified sterols and stanols reduce TC by 6%-10% and LDL cholesterol by 7%-15%	III
	2 (83, 84)	0	For patients receiving statin therapy, plant stanols further reduce LDL cholesterol and TC levels	I

(continued)

Table 16. Graded conclusion statements and number of primary and secondary papers supporting findings presented in the American Dietetic Association Evidence Analysis Library (continued)

Topic	No. of primary articles (reference numbers)	No. of meta-analyses or review articles (reference numbers)	Summary statement	Grade
	Same	0	Data regarding whether or not the dose of statins can be reduced by the use of stanols and sterols are needed	V
	11 (23,63-67,73,77,80-82)	0	An intake of 2-3 g/d plant sterols and stanols generally appears safe	II
	6 (64,65,73,77,80,82)	0	It is unclear if there are unintended adverse effects when consuming stanols and sterols. Some studies have observed no significant differences in plasma carotenoid concentrations, including α-carotene and lycopene, and vitamins A, D, and E but other studies have found that α-tocopherol, α-carotene, and β- carotene plasma concentrations decrease after consumption of sterols and stanols, even after adjusting for changes in plasma lipid levels	V
	2 (63,81)	0	Preliminary research suggests that consuming one extra carotenoid rich fruit or vegetable per day has been shown to maintain plasma carotenoid levels when also consuming sterol-enriched spreads	V
Soy protein	7 (14,51-55,286)	2 (49,50)	Studies varied greatly in their estimation of the effect of diets low in saturated fat and cholesterol containing ~26-50 g soy protein either as food or as a soy supplement, with 0-165 mg isoflavones. Studies of individuals with normal and elevated cholesterol (TC >200 mg/dL[m]) and individuals with diabetes varied showing no effect on TC up to 20% lower serum TC, no effect on TG[n] up to 22% lower, small effect (4%) up to 24% lower LDL cholesterol	II
	Same	Same	Effect of soy protein and/or isoflavones may vary based on initial cholesterol levels	III
	1 (54)	1 (50)	A significant dose-response relationship has not been established between level of soy protein and/or isoflavones in the diet needed to achieve significant decreases in TC and LDL cholesterol levels	III
	Same	0	Diets containing up to 30 g/d soy protein (as supplements) were well tolerated	II
	1 (286)	1 (50)	There is insufficient evidence supporting the benefit of added isoflavones on improving TC and LDL cholesterol levels	III
Nuts	5 (39-43)	1 (44)	Consumption of 50-113 g/d (1/2 to 1 c) nuts with a diet low in SFA and cholesterol decreased TC by 4%-21% and LDL cholesterol level 6%-29% when weight was not gained	II
	1 (38)	3 (21,44,287)	Consumption of 5 oz/wk nuts is associated with reduced risk of CHD	II
Alcohol	7 (163,167-169,172,173, 288)	1 (164)	Population and cohort studies, primarily of men, suggest 1-2 beverages containing alcohol per day are associated with reduced risk of CVD. Excessive intakes are associated with increased all-cause mortality.	II
	Same	Same	Most data do not support an association between type of alcoholic beverage (wine, beer, and liquor) and protection against CVD	II
	Same	Same	The CVD benefits of alcohol may be realized when alcohol is consumed with meals	III
Obesity measures	15 (98,214-219,221,223, 225,232,233, 289-291)	0	Data from several countries indicate BMI[o] correlates with CHD events and mortality	II
	Same	0	The relationship btw BMI and CHD events and mortality is attenuated, eliminated or not changed after adjusting for CHD risk	III
	Same	0	BMI does not correlate well with total and CVD mortality in those aged ≥65 y	III
	Same	0	Studies from Western countries indicate waist circumference and waist-to-hip ratio correlate with CHD events and mortality	II
	Same	0	It is unclear if abdominal adiposity remains an independent predictor of CHD after adjustment for BMI	III
	Same	0	WHR may be an independent predictor of CVD and CHD mortality and acute coronary events after adjusting for other risk factors	II

(continued)

Table 16. Graded conclusion statements and number of primary and secondary papers supporting findings presented in the American Dietetic Association Evidence Analysis Library (continued)

Topic	No. of primary articles (reference numbers)	No. of meta-analyses or review articles (reference numbers)	Summary statement	Grade
Antioxidants-vitamin E	9 (131,187,188, 190,191,195,199,292-294)	6 (183,189,198, 295,296)	Supplemental vitamin E (100 IU to 1,200 IU/d) alone, or in combination with other antioxidants, has not been shown to have a favorable or unfavorable effect on serum lipids	II
	Same	Same	Supplemental vitamin E, given in both natural and synthetic forms, in doses between 30 and 600 mg/d or 400-800 IU/d, alone or in combination with other antioxidants, has not been shown to ↓ the risk for all cause mortality, cardiovascular death, fatal or nonfatal myocardial infarction. Doses at this level have not been shown to cause harm	II
Antioxidants—β-carotene	0	4 (189,198,295)	Supplemental β-carotene (60-200 mg/d) does not ↓ the risk for cardiovascular death or nonfatal myocardial infarction in primary and secondary prevention patients	I
	Same	Same	Supplemental β-carotene (60-120 mg/d) is associated with ↑ in all-cause mortality and cardiovascular death in patients at ↑ risk for lung cancer	II
Antioxidants—vitamin C	0	3 (189,295)	Supplemental vitamin C (50-1,000 mg/d) in combination with other antioxidants (vitamin E, β-carotene, selenium) has not been shown to have any effect on all cause mortality, cardiovascular death, or fatal or nonfatal myocardial infarction	II
	0	1 (189)	Supplemental vitamin C and E, β-carotene, and selenium should not be taken with simvastatin-niacin drug combination because the combination of these antioxidants may lower HDL_2, a beneficial subfraction of HDL cholesterol	II
Antioxidants-food-based	0	2 (295)	Epidemiologic data suggest that intake of foods rich in vitamins E, C, and β-carotene (dietary antioxidants) as part of a cardioprotective dietary pattern have been associated with ↓ risk for CHD	III
Antioxidants-coenzyme Q10	0	1 (189)	Not enough evidence exists to demonstrate the benefits or harm of supplemental coenzyme Q10 and its use in CVD	III
Homocysteine and B vitamins	7 (143,145,297-301)	2 (144,146)	A high level of serum homocysteine independent of other cardiac risk factors, has been associated with ↑ risk for CHD. Conversely, low homocysteine levels have been associated with ↓ risk	II
	8 (143,145,147-149,302) (48,303)	1 (304)	Supplemental folate (0.5-2.5 mg) given alone or in combination with vitamin B-6 (10-25 mg) and vitamin B-12 (0.4 mg) ↓ homocysteine levels by 17%-34% but did not ↓ the risk for coronary events after 6 mo-2 y in stable coronary artery disease patients, poststroke patients, or postangioplasty patients who had normal baseline homocysteine and TC concentrations	II
Physical activity	9 (169,171,235-237,305-307)	1 (234)	Observational studies have shown that physical activity ↓ the risk of CVD and CHD events	II
	3 (244,255,308)	Same	Data suggest that the most commonly observed lipid change in relation to endurance training is a significant ↑ in HDL cholesterol level (mean 4.6% ↑, range 5.8% ↓ to a 25% ↑); however, ↓ in LDL cholesterol level (mean 5% ↓) and TG level (mean 3.7% ↓) may also occur	II
	0	1 (309)	Exercise has shown to ↓ all-cause mortality and cardiac mortality in secondary prevention patients	II

(continued)

Table 16. Graded conclusion statements and number of primary and secondary papers supporting findings presented in the American Dietetic Association Evidence Analysis Library (continued)

Topic	No. of primary articles (reference numbers)	No. of meta-analyses or review articles (reference numbers)	Summary statement	Grade
Metabolic syndrome	5 (249,250,252-254)	3 (1,310,311)	↑ BMI and waist circumference are associated with ↑ risk of metabolic syndrome	II
	Same	Same	Evidence shows that physical activity at any level, light, moderate or vigorous, is associated with ↓ incidence of metabolic syndrome	II
	Same	Same	Food patterns emphasizing a diet high in fruits and vegetables and whole grains is associated with ↓ incidence of metabolic syndrome	II
	2 (255,256)	3 (1,310,311)	Lifestyle modification resulting in weight ↓ and ↑ physical activity has been shown to improve risk factors associated with metabolic syndrome. Energy restriction combined with daily activity of at least 30 min at moderate intensity resulted in weight loss of at least 7% and improved components of metabolic syndrome	II
	Same	Same	A cardioprotective dietary pattern (low in SFA, TFA, and cholesterol, limited in simple sugar intake and increased in consumption of fruits, vegetables, and whole grains) provides the background for modifying the energy balance to achieve weight loss. Extremes in intakes of carbohydrate or fats should be avoided	IV
Dietary strategies to lower blood pressure	7 (6,7,15,259-262,263)	0	Consuming a diet rich in fruits and vegetables and low-fat dairy products and low in sodium and SFA will ↓ blood pressure. Decreases have been 4-12 mm Hg systolic and 1-3 mm Hg diastolic. This dietary pattern enhanced by weight loss and increased physical activity will also have beneficial effects (4-10 mm Hg systolic and 3-5 mm Hg diastolic)	I

[a]SFA=saturated fatty acid.
[b]TFA=*trans*-fatty acid.
[c]LDL=low-density lipoprotein.
[d]CHD=coronary heart disease.
[e]MUFA=monounsaturated fatty acid.
[f]PUFA=polyunsaturated fatty acid.
[g]TC=total cholesterol.
[h]HDL=high-density lipoprotein.
[i]EPA=eicosapentanoic acid.
[j]DHA= docosahexaenoic acid.
[k]ALA=α-linolenic acid.
[l]CVD=cardiovascular disease.
[m]To convert mg/dL cholesterol to mmol/L, multiply mg/dL by 0.0259. To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.7. Cholesterol of 193 mg/dL=5.00 mmol/L.
[n]TG=triglycerides.
[o]BMI=body mass index.

Glossary of Acronyms and Selected Definitions

ACSM: American College of Sports Medicine
ADA: American Dietetic Association
AHA: American Heart Association
AHRQ: Agency for Healthcare Research and Quality
ALA: α-linolenic acid
apoAI: apolipoprotein AI
apoB: apolipoprotein B
ASAP: Antioxidant Supplementation in Atherosclerosis Prevention Study
ATBC: Alpha-Tocopherol, Beta carotene Cancer Prevention Study
ATP III: Adult Treatment Panel of the National Cholesterol Education Program
BMI: body mass index
CAC: coronary artery calcification
CAD: coronary artery disease (type of atherosclerosis that causes narrowing of the coronary arteries)
CARDIA: coronary Artery Risk Development in Young Adults Study
CARET: Beta-Carotene and Retinol Efficacy Trial
CDC: Center for Disease Control and Prevention
CHAOS: Cambridge Heart Antioxidant Study
CHD: coronary heart disease (condition caused by atherosclerosis that can produce chest pain or heart attack)
CLA: conjugated linoleic acid
CSFII: Continuing Survey of Food Intakes by Individuals
CVD: cardiovascular disease (umbrella term used to describe diseases that affect the heart or blood vessels)
DARE: Database of Abstracts of Reviews of Effects
DART: Diet and Reinfarction Trial
DASH: Dietary Approaches to Stop Hypertension
DBP: diastolic blood pressure
DEW-IT: Diet, Exercise and Weight Loss Intervention Trial
DHA: docosahexaenoic acid
DM: diet modification
EAL: Evidence Analysis Library http://adaevidencelibrary.com
EPA: eicosapentaenoic acid
FBG: fasting blood glucose
FDA: Food and Drug Administration
GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
HATS: HDL-Atherosclerosis Treatment Study
Hcy: homocysteine
HDL-C: high-density lipoprotein cholesterol
HERS: Heart and Estrogen/Progestin Replacement Study
HOPE: Heart Outcomes Prevention Evaluation
HPS: Heart Protection Study
HR: hazard ratio
IBW: ideal body weight
ICD: implantable cardioverter defibrillator
IHD: ischemic heart disease
INTERMAP: International Study of Macro and Micro Nutrients and Blood Pressure
LA: linoleic acid
LASA: Longitudinal Aging Study Amsterdam
LDL-C: low-density lipoprotein-cholesterol
LMP: lauric, myristic, and palmitic fatty acids
MI: myocardial infarction
MNT: medical nutrition therapy
MUFA: monounsaturated fatty acids
MVP: multi-vitamins and probucol
n-3: omega-3 fatty acid
NCEP: National Cholesterol Education Program
NHANES: National Health and Nutrition Examination Survey
NHLBI: National Heart, Lung and Blood Institute
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIH: National Institutes of Health
NORVIT: Norwegian Vitamin Trial
PAD: peripheral artery disease
PHSO: partially hydrogenated soybean oil
PROCRAM: Prospective Cardiovascular Munster Study
PUFA: polyunsaturated fatty acids
RCT: randomized controlled trial
RD: registered dietitian
SBP: systolic blood pressure
SFA: saturated fatty acids
TC: total cholesterol
TFA: *trans*-fatty acids
TG: triglycerides
TLC: Therapeutic Lifestyle Changes Diet
TOHP II: Trials of Hypertension Prevention
TONE: Trial of Nonpharmacological Interventions in the Elderly
UFA: unsaturated fatty acids
VF: ventricular fibrillation
VT: ventricular tachycardia
WHI: Women's Health Initiative
WHO: World Health Organization
WHR: Waist-to-hip ratio

Additional Research Needed

Further research is recommended to determine the optimal number, duration, frequency, and time interval of RD visits for attainment as well as maintenance of normalized lipid levels. RCTs should investigate if MNT could obviate or reduce the need for antihyperlipidemia medications. Furthermore, RCTs should investigate if MNT and antihyperlipidemia medications when used concomitantly could lower the dose of these medications, and the subsequent cost savings of MNT vs antihyperlipidemia medications should also be examined. Cost savings from MNT that consist of a reduction in years of medication use and in the number of hospitalizations avoided from MI, unstable angina, or revascularization procedures also should be studied. Further research should be conducted on lipid reduction outcomes of MNT in patients previ-

ously identified as "dietary failures" or "poor dietary responders" assuming these patients have not received individualized MNT from an RD.

CONCLUSIONS

Lifestyle interventions are essential for the prevention of CVD. Reducing dyslipidemia (elevated TC, LDL cholesterol, TG, and low HDL cholesterol levels), overweight/obesity, hypertension, and increasing physical activity have beneficial affects on these risk factors. This article has reviewed the current evidence showing the importance of diet and physical activity for reducing risk of CVD via major risk factor modifications. Table 16 provides a summary of all of the graded conclusion statements developed for the ADA Evidence Analysis Library on diet and hyperlipidemia. The ADA Evidence Analyis Library itself provides a full detailed description of all of these data.

Numerous dietary factors/nutrients have been identified that affect CVD risk factors. Because most patients present with multiple risk factors, including the diagnosis of metabolic syndrome, an individualized dietary pattern is recommended to optimize CVD risk factor reduction while meeting nutrient needs. RDs are uniquely skilled in this process.

Dietary considerations to help achieve these goals include a diet:

- low in SFA (<7%), TFA (<1% calories), and dietary cholesterol (<200 mg);
- rich in n-3 fatty acids, EPA, and DHA (500 mg/day for primary prevention; 1 g/day for secondary prevention; and 2 to 4 g/day for TG lowering; physician supervision is indicated for patients); consume fish at least twice a week;
- ample in total dietary fiber (30 g/day) with emphasis on soluble fiber;
- that includes unsalted nuts (1 oz) as tolerated and limited by energy needs; consider other vegetable protein sources such as soy and legumes;
- that includes skim/low-fat dairy foods and/or other calcium/vitamin D-rich sources;
- rich in vitamins, minerals, phytochemicals, and antioxidants from multiple servings of fruits and vegetables and low in sodium (<2,300 mg/day);
- rich in B vitamins and fiber from food sources such as whole grains and vegetables;
- that may include plant sterols and stanols in high risk individuals; and
- that achieves a healthful body weight and energy balance with the recommended dietary intervention by increasing physical activity and maintaining an adequate energy intake. MNT represents the ideal approach to treating these patients.

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