Why it Works: Selected References

If you search the medical literature you will find a vast amount of consistent data regarding optimal eating patterns for improving cardiovascular health. You will also find many studies evaluating the effects of diet on cholesterol levels. At Step One we took all this data and translated it into a practical – and delicious – line of foods.

Our products are all based on published research, and made with whole food ingredients chosen specifically for their documented health benefits and cholesterol lowering potential. There are no artificial additives or wasted calories.

On the pages that follow you will find a small sampling of the studies that inspired the creation of Step One Foods, as well as some of the research that guided our ingredient selection and food formulation:

1. Jenkins DJ, Kendall CW, Marchie A, et al. The Garden of Eden--plant based diets, the genetic drive to conserve cholesterol and its implications for heart disease in the 21st century. Comp Biochem Physiol A Mol Integr Physiol. 2003;136(1):141-151.

It is likely that plant food consumption throughout much of human evolution shaped the dietary requirements of contemporary humans. Diets would have been high in dietary fiber, vegetable protein, plant sterols and associated phytochemicals, and low in saturated and trans-fatty acids and other substrates for cholesterol biosynthesis. To meet the body's needs for cholesterol, we believe genetic differences and polymorphisms were conserved by evolution, which tended to raise serum cholesterol levels. As a result modern man, with a radically different diet and lifestyle, especially in middle age, is now recommended to take medications to lower cholesterol and reduce the risk of cardiovascular disease. Experimental introduction of high intakes of viscous fibers, vegetable proteins and plant sterols in the form of a possible Myocene diet of leafy vegetables, fruit and nuts, lowered serum LDL-cholesterol in healthy volunteers by over 30%, equivalent to first generation statins, the standard cholesterol-lowering medications. Furthermore, supplementation of a modern therapeutic diet in hyperlipidemic subjects with the same components taken as oat, barley and psyllium for viscous fibers, soy and almonds for vegetable proteins and plant sterol-enriched margarine produced similar reductions in LDL-cholesterol as the Myocene-like diet and reduced the majority of subjects' blood lipids concentrations into the normal range. We conclude that reintroduction of plant food components, which would have been present in large quantities in the plant based diets eaten throughout most of human evolution into modern diets can correct the lipid abnormalities associated with contemporary eating patterns and reduce the need for pharmacological interventions.

2. **Van Horn L, McCoin M, Kris-Etherton PM, et al. The evidence for dietary prevention and treatment of cardiovascular disease. J Am Diet Assoc. 2008;108(2):287-331.**

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.

3. **de Lorgeril M, et al. 1999. Mediterranean alpha linoleic acid rich diet in secondary prevention of heart disease; The Lyon Diet Heart Study. Circulation; 99:779-85.**

The Lyon Diet Heart Study is a randomized secondary prevention trial aimed at testing whether a Mediterranean-type diet may reduce the rate of recurrence after a first myocardial infarction. An intermediate analysis showed a striking protective effect after 27 months of follow-up. This report presents results of an extended follow-up (with a mean of 46 months per patient) and deals with the relationships of dietary patterns and traditional risk factors with recurrence.

Three composite outcomes (COs) combining either cardiac death and nonfatal myocardial infarction (CO 1), or the preceding plus major secondary end points (unstable angina, stroke, heart failure, pulmonary or peripheral embolism) (CO 2), or the preceding plus minor events requiring hospital admission (CO 3) were studied. In the Mediterranean diet group, CO 1 was reduced (14 events versus 44 in the prudent Western-type diet group, P=0.0001), as were CO 2 (27 events versus 90, P=0.0001) and CO 3 (95 events versus 180, P=0. 0002). Adjusted risk ratios ranged from 0.28 to 0.53. Among the traditional risk factors, total cholesterol (1 mmol/L being associated with an increased risk of 18% to 28%), systolic blood pressure (1 mm Hg being associated with an increased risk of 1% to 2%), leukocyte count (adjusted risk ratios ranging from 1.64 to 2.86 with count >9x10(9)/L), female sex (adjusted risk ratios, 0.27 to 0. 46), and aspirin use (adjusted risk ratios, 0.59 to 0.82) were each significantly and independently associated with recurrence.

The protective effect of the Mediterranean dietary pattern was maintained up to 4 years after the first infarction, confirming previous intermediate analyses. Major traditional risk factors, such as high blood cholesterol and blood pressure, were shown to be independent and joint predictors of recurrence, indicating that the Mediterranean dietary pattern did not alter, at least qualitatively, the usual relationships between major risk factors and recurrence. Thus, a comprehensive strategy to decrease cardiovascular morbidity and mortality should include primarily a cardioprotective diet. It should be associated with other (pharmacological?) means aimed at reducing modifiable risk factors. Further trials combining the 2 approaches are warranted.

4. **Harper CR , Jacobson TA. 2001. The fats of life; The role of Omega-3 fatty acids in the prevention of coronary heart disease. Arch of Int Med; 161:2185-2192.**

Epidemiological and clinical trial evidence suggests that omega-3 polyunsaturated fatty acids (PUFAs) might have a significant role in the prevention of coronary heart disease. Dietary sources of omega-3 PUFA include fish oils rich in eicosapentaenoic acid and docosahexaenoic acid along with plants rich in alpha-linolenic acid. Randomized clinical trials with fish oils (eicosapentaenoic acid and docosahexaenoic acid) and alpha-linolenic acid have demonstrated reductions in risk that compare favorably with those seen in landmark secondary prevention trials with lipid-lowering drugs. Several mechanisms explaining the cardioprotective effect of omega-3 PUFAs have been suggested, including antiarrhythmic, hypolipidemic, and antithrombotic roles. Although official US guidelines for the dietary intake of omega-3 PUFAs are not available, several international guidelines have been published. Fish is an important source of omega-3 PUFAs in the US diet; however, vegetable sources, including grains and oils, offer an alternative source for those who are unable to regularly consume fish.

5. **Hu FB, et al. 1997. Dietary fat intake and the risk of coronary heart disease in women. NEJM; 337:1491-1499.**

The relation between dietary intake of specific types of fat, particularly trans unsaturated fat and the risk of coronary disease remains unclear. We therefore studied this relation in women enrolled in the Nurses' Health Study.
We prospectively studied 80,082 women who were 34 to 59 years of age and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes in 1980. Information on diet was obtained at base line and updated during follow-up by means of validated questionnaires. During 14 years of follow-up, we documented 939 cases of nonfatal myocardial infarction or death from coronary heart disease. Mutivariate analyses included age, smoking status, total energy intake, dietary cholesterol intake, percentages of energy obtained from protein and specific types of fat, and other risk factors.

Each increase of 5 percent of energy intake from saturated fat, as compared with equivalent energy intake from carbohydrates, was associated with a 17 percent increase in the risk of coronary disease (relative risk, 1.17; 95 percent confidence interval, 0.97 to 1.41; P=0.10). As compared with equivalent energy from carbohydrates, the relative risk for a 2 percent increment in energy intake from trans unsaturated fat was 1.93 (95 percent confidence interval, 1.43 to 2.61; P<0.001); that for a 5 percent increment in energy from monounsaturated fat was 0.81 (95 percent confidence interval, 0.65 to 1.00; P=0.05); and that for a 5 percent increment in energy from polyunsaturated fat was 0.62 (95 percent confidence interval, 0.46 to 0.85; P= 0.003). Total fat intake was not signficantly related to the risk of coronary disease (for a 5 percent increase in energy from fat, the relative risk was 1.02; 95 percent confidence interval, 0.97 to 1.07; P=0.55). We estimated that the replacement of 5 percent of energy from saturated fat with energy from unsaturated fats would reduce risk by 42 percent (95 percent confidence interval, 23 to 56; P<0.001) and that the replacement of 2 percent of energy from trans fat with energy from unhydrogenated, unsaturated fats would reduce risk by 53 percent (95 percent confidence interval, 34 to 67; P<.001).

Our findings suggest that replacing saturated and trans unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease in women than reducing overall fat intake.

6. Ornish D, et al. 1990. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet; 336:129-33.

In a prospective, randomised, controlled trial to determine whether comprehensive lifestyle changes affect coronary atherosclerosis after 1 year, 28 patients were assigned to an experimental group (low-fat vegetarian diet, stopping smoking, stress management training, and moderate exercise) and 20 to a usual-care control group. 195 coronary artery lesions were analysed by quantitative coronary angiography. The average percentage diameter stenosis regressed from 40.0 (SD 16.9)% to 37.8 (16.5)% in the experimental group yet progressed from 42.7 (15.5)% to 46.1 (18.5)% in the control group. When only lesions greater than 50% stenosed were analysed, the average percentage diameter stenosis regressed from 61.1 (8.8)% to 55.8 (11.0)% in the experimental group and progressed from 61.7 (9.5)% to 64.4 (16.3)% in the control group. Overall, 82% of experimental-group patients had an average change towards regression. Comprehensive lifestyle changes may be able to bring about regression of even severe coronary atherosclerosis after only 1 year, without use of lipid-lowering drugs.

7. Ascherio, A. 2002. Epidemiological Studies on Dietary Fats and Coronary Heart Disease. Am J Med; 113(9B):9S–12S.

The results of large prospective epidemiologic investigations support the hypothesis that coronary disease risk depends on the quality rather than quantity of dietary fat. Whereas saturated fat and cholesterol appear to increase the risk of coronary heart disease (CHD) as predicted by their effects on blood lipids, strong evidence has emerged that the deleterious effects of trans unsaturated fatty acids (trans fatty acids) extend beyond those predicted by their well-known adverse influence on the ratio of low-density lipoprotein to high-density lipoprotein cholesterol. On the other hand, increased consumption of the polyunsaturated fats, linoleic acid and linolenic acid, appears to reduce the risk of CHD.

8. Bazzano LA, et al. 2003. Dietary fiber intake and reduced risk of coronary heart disease US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Intern Med; 163(16):1897-1904.

Prospective studies suggest that dietary fiber intake, especially water-soluble fiber, may be inversely associated with the risk of coronary heart disease (CHD).

We examined the relationship between total and soluble dietary fiber intake and the risk of CHD and cardiovascular disease (CVD) in 9776 adults who participated in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study and were free of CVD at baseline. A 24-hour dietary recall was conducted at the baseline examination, and nutrient intakes were calculated using Food Processor software. Incidence and mortality data for CHD and CVD were obtained from medical records and death certificates during follow-up.

During an average of 19 years of follow-up, 1843 incident cases of CHD and 3762 incident cases of CVD were documented. Compared with the lowest quartile of dietary fiber intake (median, 5.9 g/d), participants in the highest quartile (median, 20.7 g/d) had an adjusted relative risk of 0.88 (95% confidence interval [CI], 0.74-1.04; P =.05 for trend) for CHD events and of 0.89 (95% CI, 0.80-0.99; P =.01 for trend) for CVD events. The relative risks for those in the highest (median, 5.9 g/d) compared with those in the lowest (median, 0.9 g/d) quartile of water-soluble dietary fiber intake were 0.85 (95% CI, 0.74-0.98; P =.004 for trend) for CHD events and 0.90 (95% CI, 0.82-0.99; P =.01 for trend) for CVD events.

A higher intake of dietary fiber, particularly water-soluble fiber, reduces the risk of CHD.

9. Jacobs DR, Jr, et al. 1998. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Healthy Study. Am J Clin Nutr; 68(2):248-257.

A recent review of epidemiologic literature found consistently reduced cancer and heart disease rates in persons with high compared with low whole-grain intakes. We hypothesized that whole-grain intake was associated with a reduced risk of ischemic heart disease (IHD) death. We studied 34,492 postmenopausal women aged 55-69 y and free of IHD at baseline in 1986. There were 438 IHD deaths between baseline and 1995. Usual dietary intake was determined with use of a 127-item food-frequency questionnaire. Whole-grain intake in median servings/d was 0.2, 0.9, 1.2, 1.9, and 3.2 for quintiles of intake. The unadjusted rate of IHD death was 2.0/1 x 10(3) person-years in quintile 1 and was 1.7, 1.2, 1.0, and 1.4 IHD deaths/1 x 10(3) person-years in succeeding quintiles (P for trend < 0.001). Adjusted for demographic, physiologic, behavioral, and dietary variables, relative hazards were 1.0, 0.96, 0.71, 0.64, and 0.70 in ascending quintiles (P for trend = 0.02). The lower risk with higher whole-grain intake was not explained by intake of fiber or several other constituents of whole grains.

A clear inverse association between whole-grain intake and risk of IHD death existed. A causal association is plausible because whole-grain foods contain many phytochemicals, including fiber and antioxidants, that may reduce chronic disease risk. Whole-grain intake should be studied further for its potential to prevent IHD and cancer.

10. Ludwig DA, et al. 1999. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. JAMA; 282(16):1539-1546.

Dietary composition may affect insulin secretion, and high insulin levels, in turn, may increase the risk for cardiovascular disease (CVD). To examine the role of fiber consumption and its association with insulin levels, weight gain, and other CVD risk factors compared with other major dietary components utilizing the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a multicenter population-based cohort study of the change in CVD risk factors over 10 years (1985-1986 to 1995-1996) in Birmingham, Ala; Chicago, III; Minneapolis, Minn; and Oakland, Calif. A total of 2909 healthy black and white adults, 18 to 30 years of age at enrollment participated. Body weight, insulin levels, and other CVD risk factors at year 10, adjusted for baseline values were main outcome measures.

After adjustment for potential confounding factors, dietary fiber showed linear associations from lowest to highest quintiles of intake with the following: body weight (whites: 174.8-166.7 lb [78.3-75.0 kg], P<.001; blacks: 185.6-177.6 lb [83.5-79.9 kg], P = .001), waist-to-hip ratio (whites: 0.813-0.801, P = .004; blacks: 0.809-0.799, P = .05), fasting insulin adjusted for body mass index (whites: 77.8-72.2 pmol/L [11.2-10.4 microU/mL], P = .007; blacks: 92.4-82.6 pmol/L [13.3-11.9 microU/mL], P = .01) and 2-hour postglucose insulin adjusted for body mass index (whites: 261.1-234.7 pmol/L [37.6-33.8 microU/mL], P = .03; blacks: 370.2-259.7 pmol/L [53.3-37.4 microU/mL], P<.001). Fiber was also associated with blood pressure and levels of triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fibrinogen; these associations were substantially attenuated by adjustment for fasting insulin level. In comparison with fiber, intake of fat, carbohydrate, and protein had inconsistent or weak associations with all CVD risk factors.

Fiber consumption predicted insulin levels, weight gain, and other CVD risk factors more strongly than did total or saturated fat consumption. High-fiber diets may protect against obesity and CVD by lowering insulin levels.

11. Mozaffarian D et al. 2004. Dietary intake of trans fatty acids and systemic inflammation in women. American Journal of Clinical Nutrition. Vol. 79 No. 4.

Trans Fatty acid (TFA) intake predicts risks of coronary artery disease and diabetes. Systemic inflammation may be involved in the pathogenesis of such conditions; however, relations between TFA intake and systemic inflammation are not well established. We investigated the relations between TFA intake and inflammatory markers. In 823 generally healthy women in the Nurses' Health Study I and II, concentrations of soluble tumor necrosis factor alpha receptors 1 and 2 (sTNF-R1, sTNF-R2), interleukin 6 (IL-6), and C-reactive protein (CRP) were measured. Usual dietary intakes assessed from 2 semiquantitative food-frequency questionnaires were averaged for each subject.

In age-adjusted analyses, TFA intake was positively associated with sTNF-R1 and sTNF-R2 (P for trend < 0.001 for each): sTNF-R1 and sTNF-R2 concentrations were 10% (+108 pg/mL; 95% CI: 50, 167 pg/mL) and 12% (+258 pg/mL; 138, 377 pg/mL) higher, respectively, in the highest intake quintile than in the lowest. These associations were not appreciably altered by adjustment for body mass index, smoking, physical activity, aspirin and nonsteroidal antiinflammatory drug use, alcohol consumption, and intakes of saturated fat, protein, n-6 and n-3 fatty acids, fiber, and total energy. Adjustment for serum lipid concentrations partly attenuated these associations, which suggests that they may be partly mediated by effects of TFAs on serum lipids. TFA intake was not associated with IL-6 or CRP concentrations overall but was positively associated with IL-6 and CRP in women with higher body mass index (P for interaction = 0.03 for each).

TFA intake is positively associated with markers of systemic inflammation in women. Further investigation of the influences of TFAs on inflammation and of implications for coronary disease, diabetes, and other conditions is warranted.

12. Pereira MA, Liu S. 2003. Types of carbohydrates and risk of cardiovascular disease. J Womens Health; 12(2):115-122.

The purpose of this review is to provide an overview of the role of dietary carbohydrates in the etiology of cardiovascular disease (CVD) among women. Many factors are thought to affect insulin resistance, and little is known about the role of diet. Through effects on postprandial glucose and insulin, dietary glycemic load may have an important role in the insulin resistance syndrome (IRS). Dietary fiber, through its influence on the glycemic load or through other pathways, may also have important effects on this syndrome. Many short-term experimental studies have supported these hypotheses. Interestingly, associations may be stronger among overweight individuals than among nonoverweight individuals. Similar to findings for fruits and vegetables, whole grain intake has been found to be consistently associated with a reduction in risk of coronary heart disease (CHD) among both men and women. Several large randomized trials of primary and secondary prevention to date have demonstrated the efficacy of diets based on an abundance of plant foods and, therefore, high carbohydrate quality. The recommendations to follow a diet including an abundance of fiber-rich foods in order to prevent CVD and diabetes are based on a wealth of consistent scientific evidence. More long-term controlled trials are needed to improve our understanding of efficacy and mechanisms. Women and a variety of racial/ethnic groups should be represented in these studies whenever possible.

13. Rimm EB, et al.1996. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. JAMA; 275(6):447-451.

To examine prospectively the relationship between dietary fiber and risk of coronary heart disease. In 1986, a total of 43,757 US male health professionals 40 to 75 years of age and free from diagnosed cardiovascular disease and diabetes completed a detailed 131-item dietary questionnaire used to measure usual intake of total dietary fiber and specific food sources of fiber. Fatal and nonfatal myocardial infarction (MI) were main outcome measures.

During 6 years of follow-up, we documented 734 cases of MI (229 were fatal coronary heart disease). The age-adjusted relative risk (RR) for total MI was 0.59 (95% confidence interval [CI], 0.46 to 0.76) among men in the highest quintile of total dietary fiber intake (median, 28.9 g/d) compared with men in the lowest quartile (median, 12.4 g/d). The inverse association was strongest for fatal coronary disease (RR, 0.45; 95% CI, 0.28 to 0.72). After controlling for smoking, physical activity and other known nondietary cardiovascular risk factors, dietary saturated fat, vitamin E, total energy intake, and alcohol intake, the RRs were only modestly attenuated. A 10-g increase in total dietary fiber corresponded to an RR for total MI of 0.81 (95% CI, 0.70 to 0.93). Within the three main food contributors to total fiber intake (vegetable, fruit, and cereal), cereal fiber was most strongly associated with a reduced risk of total MI (RR, 0.71; 95% CI, 0.55 to 0.91 for each 10-g increase in cereal fiber per day).

Our results suggest an inverse association between fiber intake and MI. These results support current national dietary guidelines to increase dietary fiber intake and suggest that fiber, independent of fat intake, is an important dietary component for the prevention of coronary disease.

14. Steffen LM, et al. 2003. Associations of whole-grain, refined grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr; 78(3):383-390.

Recent epidemiologic study results showed that subjects who had high intakes of whole-grain foods had lower risks of death and heart disease than did subjects who had low intakes. However, the findings were inconsistent for fruit and vegetable intake. The relations of whole-grain, refined-grain, and fruit and vegetable intakes with the risk of total mortality and the incidence of coronary artery disease (CAD) and ischemic stroke were studied in the Atherosclerosis Risk in Communities (ARIC) cohort (baseline: age 45-64 y, n = 15,792). Proportional hazards regression analyses were used to assess the relations of whole-grain, refined-grain, and fruit and vegetable intakes with the risk of death and the incidence of CAD and ischemic stroke, with adjustment for age, sex, ethnicity, energy intake, and cardiovascular disease risk factors. Dietary intakes were assessed by using a food-frequency questionnaire.

Over an 11-y follow-up period, whole-grain intake was inversely associated with total mortality and incident CAD. The relative hazards of death for quintiles 2-5 of fruit and vegetable intake were 1.08 (95% CI: 0.88, 1.33), 0.94 (0.75, 1.17), 0.87 (0.68, 1.10), and 0.78 (0.61, 1.01), respectively; P for trend = 0.02. An inverse association between fruit and vegetable intake and CAD was observed among African Americans but not among whites (P for interaction = 0.01). The risk of ischemic stroke was not significantly related to whole-grain, refined-grain, or fruit and vegetable consumption.

These observational findings suggest a beneficial effect of whole-grain and fruit and vegetable consumption on the risks of total mortality and incident CAD but not on the risk of ischemic stroke.

15. Grundy S. 1999. The optimal ratio of fat-to-carbohydrate in the diet. Annu Rev Nutr;19:325-341.

A major issue in human nutrition is the optimal relation of carbohydrate-to-fat in the diet. According to some investigators, a high proportion of fat energy to total energy favors the development of several chronic diseases. Among these are obesity, coronary heart disease, diabetes, and cancer. The theory that a high proportion of fat relative to other nutrients promotes the development of obesity is founded on research with experimental animals and in human population surveys. This theory has been difficult to prove in prospective feeding studies in humans; therefore it remains a contentious issue. Regarding coronary heart disease, little evidence supports a claim that a high proportion of dietary fat predisposes to disease. On the other hand, strong evidence bolsters the claim that certain fatty acids raise the risk for coronary heart disease. These include saturated fatty acids and trans fatty acids, both of which raise serum cholesterol levels. In contrast, neither monounsaturated nor polyunsaturated fatty acids raise serum cholesterol levels and seemingly pose little risk for coronary disease. The relationship between dietary fat and type 2 diabetes is tied largely to the issue of obesity, because obesity is a major cause of diabetes. Although animal studies and epidemiological studies have implicated dietary fat as a factor in cancer, recent prospective epidemiological data in humans have cast doubt on the possibility of a strong relationship. In summary, clear evidence points to the need to reduce intakes of saturated and trans fatty acids in the diet. Beyond this change, a balanced ratio of unsaturated fatty acids to carbohydrate leading to fat intake of approximately 30% of total energy seems appropriate for the American public.

16. Perez-Jimenez F, et al. 1999. Circulating levels of endothelial function are modulated by dietary monounsaturated fat. Atheroscler; 145(2):351-358.

For the most part, the benefits of monounsaturated-rich diets (MUFA-diet) have been related to their action on plasma lipid levels. However other non-lipidic effects could also be involved in their protective effects. One of these involves the decrease in plasma levels of plasminogen activator inhibitor type 1 (PAI-1), the main inhibitor of fibrinolysis. Given that the PAI-1 is of endothelial origin, one hypothesis is that the MUFA-diet could protect against CHD by modulating some endothelial components.

Healthy male subjects (n = 25) received three different consecutive diets, each lasting 28 days: a low fat NCEP-I-diet, with 28% calories as fat, 10% saturated fat (SAT), 12% monounsaturated (MUFA) and 6% polyunsaturated (PUFA); a MUFA-diet, with 38% calories as fat, 10% SAT, 22% MUFA and 6% PUFA; and a SAT rich-diet (SAT-diet), with 38% calories as fat, 20% SAT, 12% MUFA and 6% PUFA. After each dietary period, the plasma lipid profile was determined, including total cholesterol, HDL cholesterol, LDL cholesterol, total triglyceride, apo A1, apo B plasma levels and conjugated diene formation, after incubation of LDL particles with Cu 5 microM/l. Endothelial products measured in plasma were von Willebrand factor (vWF), E-selectin, Thrombomodulin and Tissue Factor Pathway Inhibitor (TFPI) levels. We observed a decrease in vWF, PAI-1 and TFPI plasma levels and an increase in lag time of conjugated diene formation after the MUFA-diet. There was a positive correlation between the decreases in TFPI and vWF and the changes in total cholesterol, LDL-C, apo B plasma levels. The decrease in TFPI was negatively correlated with the increase in lag time of conjugated diene formation. PAI-1 plasma levels were positively correlated with total cholesterol, LDL-C and triglycerides and negatively correlated with HDL-C.

Consumption of a Mediterranean-type MUFA-diet produces a decrease in plasma levels of vWF, TFPI and PAI-1 plasma levels in young healthy males. Given that these substances are of endothelial origin, one could suggest that the MUFA of the diet has a beneficial effect on endothelial function resulting in protective changes against thrombogenesis.

17. Zhao G, Etherton TD, Martin KR et al. 2004. Dietary -Linolenic Acid Reduces Inflammatory and Lipid Cardiovascular Risk Factors in Hypercholesterolemic Men and Women. J. Nutr. 134:2991-2997.

Alpha-linolenic acid (ALA) reduces cardiovascular disease (CVD) risk, possibly by favorably changing vascular inflammation and endothelial dysfunction. Inflammatory markers and lipids and lipoproteins were assessed in hypercholesterolemic subjects (n = 23) fed 2 diets low in saturated fat and cholesterol, and high in PUFA varying in ALA (ALA Diet) and linoleic acid (LA Diet) compared with an average American diet (AAD). The ALA Diet provided 17% energy from PUFA (10.5% LA; 6.5% ALA); the LA Diet provided 16.4% energy from PUFA (12.6% LA; 3.6% ALA); and the AAD provided 8.7% energy from PUFA (7.7% LA; 0.8% ALA). The ALA Diet decreased C-reactive protein (CRP, P < 0.01), whereas the LA Diet tended to decrease CRP (P = 0.08). Although the 2 high-PUFA diets similarly decreased intercellular cell adhesion molecule-1 vs. AAD (-19.1% by the ALA Diet, P < 0.01; -11.0% by the LA Diet, P < 0.01), the ALA Diet decreased vascular cell adhesion molecule-1 (VCAM-1, -15.6% vs. -3.1%, P < 0.01) and E-selectin (-14.6% vs. -8.1%, P < 0.01) more than the LA Diet. Changes in CRP and VCAM-1 were inversely associated with changes in serum eicosapentaenoic acid (EPA) (r = -0.496, P = 0.016; r = -0.418, P = 0.047), or EPA plus docosapentaenoic acid (r = -0.409, P = 0.053; r = -0.357, P = 0.091) after subjects consumed the ALA Diet. The 2 high-PUFA diets decreased serum total cholesterol, LDL cholesterol and triglycerides similarly (P < 0.05); the ALA Diet decreased HDL cholesterol and apolipoprotein AI compared with the AAD (P < 0.05). ALA appears to decrease CVD risk by inhibiting vascular inflammation and endothelial activation beyond its lipid-lowering effects.

18. Anderson JW, et al. 1992. Prospective Randomized controlled comparison of the effects of low-fat and low-fat plus high fiber diets on serum lipid concentrations. Am J of Clin Nut. 56:887-894.

Previous studies examining the hypocholesterolemic effects of high-soluble-fiber diets have not been designed to control for dietary fat intake. Serum cholesterol reductions may therefore be accounted for by differences in consumption of fat. Moderately hypercholesterolemic, nonobese, Caucasian men and women, 30-50 y old were randomly assigned to low-fat, low-fat plus high-fiber, or usual-diet groups and followed for 12 mo. At 12 mo the high-fiber group consumed significantly more soluble fiber than both the low-fat and usual-diet groups (P = 0.0063 and P = 0.0001); the high-fiber group did not differ from the low-fat group in quantity of dietary fat consumed. The high-fiber group experienced a greater average reduction (13%) in serum cholesterol than did the low-fat (9%) and usual-diet (7%) groups. After adjustment for relevant covariates, the reduction in the high-fiber group was significantly greater than that in the low-fat group (P = 0.0482). Supplementation with soluble fiber reduces serum cholesterol beyond the reduction observed with low-fat diet alone.

19. Mattson F, Grundy SM. 1985. Comparison of effects of dietary saturated, monounsaturated and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. Journal of Lipid Research; 26:194-202.

Twenty patients consumed a liquid diet in which the predominant fatty acids were either saturated (Sat), monounsaturated (Mono), or polyunsaturated (Poly). The fats in these three diets comprised 40% of total calories and consisted of palm oil, high-oleic safflower oil, and high-linoleic safflower oil, respectively. During the third and fourth week of each dietary period, multiple samples of blood were taken and were analyzed for plasma total cholesterol (TC), triglycerides (TG), and cholesterol in lipoprotein fractions (VLDL-C, LDL-C, and HDL-C). Twelve of the patients had normal TG levels; in these patients, both Mono and Poly diets caused statistically significant and equal lowerings of plasma LDL-C, but the Poly diet lowered HDL-C levels more frequently than did the Mono diet. Neither diet changed the level of plasma TG. The proportions of total protein and the various lipid components in isolated fractions (VLDL, IDL, LDL, HDL) were not altered by the two diets. Eight patients had hypertriglyceridemia; these individuals showed considerable variability in response to Mono and Poly diets. Although there was a trend towards reductions in TC and LDL-C levels by both types of unsaturated fats, the changes were inconsistent; furthermore, HDL-C concentrations were low on the Sat diet and were unaffected by either the Mono or the Poly diet. The results of this study show that oleic acid is as effective as linoleic acid in lowering LDL-C levels in normo-triglyceridemic patients, and oleic acid seemingly reduces HDL-C levels less frequently than does linoleic acid. Neither type of unsaturated fat had striking effects on lipoprotein levels of hypertriglyceridemic patients.

20. Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. 1997. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr 65:1747-64.

Quantitative relations between dietary fat and cholesterol and plasma lipid concentrations have been the subject of much study and some controversy during the past 40 y. Previous meta-analyses have focused on the most tightly controlled, highest-quality experiments. To test whether the findings of these investigations are generalizable to broader experimental settings and to the design of practical dietary education interventions, data from 224 published studies on 8143 subjects in 366 independent groups including 878 diet-blood lipid comparisons were subjected to weighted multiple-regression analysis. Inclusion criteria specified intervention studies published in English between 1966 and 1994 reporting quantitative data on changes in dietary cholesterol and fat and corresponding changes in serum cholesterol, triacylglycerol, and lipoprotein cholesterol concentrations. Regression models are reported for serum total cholesterol, triacylglycerol, and low-density-high-density-, and very-low-density-lipoprotein cholesterol, with multiple correlations of 0.74, 0.65, 0.41, 0.14, and 0.34, respectively. Interactions of dietary factors, initial dietary intakes and serum concentrations, and study and subject characteristics had little effect on these models. Predictions indicated that compliance with current dietary recommendations (30% of energy from fat, < 10% from saturated fat, and < 300 mg cholesterol/d) will reduce plasma total and low-density-lipoprotein-cholesterol concentrations by approximately 5% compared with amounts associated with the average American diet.

21. Robinson F, Hackett AF, Billington D, Stratton G. 2002. Changing from a mixed to self-selected vegetarian diet - influence on blood lipids. J Hum Nutr Diet 15: 323-329.

To observe any changes in serum concentrations of lipids, when UK meat-eaters switch to a self selected vegetarian diet for 6 months. Observational study using capillary blood samples and 3-day estimated dietary diary. Twelve male and 31 female adult volunteers aged between 18 and 42 years. Serum lipids; nutrient intake and anthropometric measurements at baseline and 6 months after switching to a self-selected vegetarian diet.

Total energy intake and amount of energy derived from saturated fatty acids decreased significantly after changing to a vegetarian diet (P < 0.05) whereas energy derived from carbohydrate, and intakes of nonstarch polysaccharide intake increased. On switching to a vegetarian diet, total cholesterol and triacylglycerol concentrations were not significantly changed, but HDL-C was 21% higher than at baseline (1.21 mmol L(-1) vs. 1.47 mmol L(-1); P = 0.001).

These results suggest that beneficial changes to diet occurred on changing to a self-selected vegetarian diet. Changing to a self-selected vegetarian diet appears to be one way of achieving a better blood lipid profile.

22. Anderson JW, Hanna TJ. 1999. Impact of nondigestible carbohydrates on serum lipoproteins and risk for cardiovascular disease. J Nutr;129(S):1457S-1466S.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the U.S. and in most developed countries. Many nutritional factors contribute to risk for ASCVD including total and saturated fat consumption, fruits and vegetables in the diet and dietary fiber intake. This review will focus on the relationship of dietary fiber intake to risk for coronary heart disease (CHD) and ASCVD (which includes, principally, CHD, cerebral vascular disease and peripheral vascular disease). Fiber-rich foods such as vegetables, fruits, whole-grain cereals and legumes are rich sources of nutrients, phytochemicals and antioxidants. For example, most high fiber foods contain soluble and insoluble fiber, minerals, vitamins, other micronutrients and phytochemicals. Cereals and legumes also contain complex carbohydrates and unsaturated fatty acids. Some high fiber foods are rich in monounsaturated fatty acids, whereas others provide (n-3) fatty acids. Legumes and certain vegetables provide oligosaccharides. When assessing the health benefits of dietary fiber, one should consider the potential effects of associated nutrients, micronutrients and phytochemicals. These interactions will be reviewed as we discuss relationships of dietary fiber to ASCVD.

23. Harsha DW, Lin PH, Obarzanek E, Karanja NM, Moore TJ, Caballero B. 1999. Dietary Approaches to Stop Hypertension: a summary of study results. DASH Collaborative Research Group. J Am Diet Assoc 99:S35-9.

The Dietary Approaches to Stop Hypertension multicenter trial examined the impact of dietary patterns on blood pressure in 459 adults with blood pressure < 160 mm Hg systolic and 80 to 95 mm Hg diastolic. After a 3-week run-in period on a control diet low in fruits, vegetables, and dairy products, and with a fat content typical for Americans, participants were randomized for 8 weeks to either the control diet, a diet rich in fruits and vegetables, or a combination diet that emphasized fruits, vegetables, and low-fat dairy products. Body weight and sodium intake were held constant, and physical activity did not change during the intervention. Baseline mean +/- standard deviation systolic and diastolic blood pressures were 131.3 +/- 10.8 mm Hg and 84.7 +/- 4.7 mm Hg, respectively. Relative to the control diet, the combination diet reduced blood pressure by 5.5 mm Hg and diastolic blood pressure by 3.0 mm Hg (P < .001). For those on the fruits and vegetables diet, blood pressure reductions relative to control were 2.8 mm Hg systolic (P < .001) and 1.1 mm Hg diastolic (P < .07). In 133 participants with hypertension, the combination diet produced a net blood pressure reduction of 11.4 and 5.5 mm Hg systolic and diastolic, respectively (P < .001). In participants without hypertension (n = 326), the corresponding blood pressure reductions were 3.5 mm Hg systolic (P < .001) and 2.1 mm Hg diastolic (P < .003). In other subgroup analyses, minorities showed relatively larger reductions in blood pressure than nonminorities (P < .001). We conclude that the dietary pattern reflected in the combination diet can substantially reduce blood pressure, and, accordingly, provides an additional lifestyle approach to preventing and treating hypertension.

24. Plaisted CS, Lin PH, Ard JD, McClure ML, Svetkey LP. 1999. The effects of dietary patterns on quality of life: a substudy of the Dietary Approaches to Stop Hypertension trial. J Am Diet Assoc 99:S84-9.

Few studies have examined the effects of dietary changes, particularly modifications of whole dietary patterns, on quality of life. The Dietary Approaches to Stop Hypertension (DASH) trial compared the effects of 3 dietary patterns on blood pressure. In this substudy, we examined the effect of these diets on health-related quality of life. All DASH participants ate a control diet for 3 weeks and then were randomly assigned to continue the control diet, to a fruits and vegetables diet or to a combination diet for 8 weeks. The combination diet emphasized fruits, vegetables, and low-fat dairy products. It included whole grains, poultry, fish, and nuts, and was reduced in fats, red meat, sweets, and sugar-containing beverages. The control diet was similar to typical American intake; the fruits and vegetables diet was rich in fruits and vegetables but was otherwise similar to the control diet. Both the fruits and vegetables diet (P < .001) and the combination diet (P < .001) significantly lowered blood pressure. At the Duke University Medical Center, Durham, NC, site, participants completed the Medical Outcomes Study Short Form-36 questionnaire to assess their health-related quality of life at baseline and at the end of the dietary intervention. Eighty-three participants completed the questionnaires at both time points. In general, health-related quality of life improved in all treatment groups except for the control group in perceptions of change in health, which diminished. In the combination diet group all the subscales were improved or unchanged compared with baseline values. However, only the change in health score improved significantly (P < .05) as compared with that of the control diet group. When all the subscales were summed into a total score, the control diet was associated with mean improvement of 4.0%, the fruits and vegetables diet with 5.0%, and the combination diet with 5.9% from baseline. These data suggest that the fruits and vegetables diet and particularly the combination diet cannot only lower blood pressure, but may also improve the perception of health-related quality of life.

25. Appell LJ, et al. 1997. A clinical trial of the effects of dietary patterns on blood pressure. N Eng J Med;336(13):1117-1124.

It is known that obesity, sodium intake, and alcohol consumption factors influence blood pressure. In this clinical trial, Dietary Approaches to Stop Hypertension, we assessed the effects of dietary patterns on blood pressure.
We enrolled 459 adults with systolic blood pressures of less than 160 mm Hg and diastolic blood pressures of 80 to 95 mm Hg. For three weeks, the subjects were fed a control diet that was low in fruits, vegetables, and dairy products, with a fat content typical of the average diet in the United States. They were then randomly assigned to receive for eight weeks the control diet, a diet rich in fruits and vegetables, or a "combination" diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat. Sodium intake and body weight were maintained at constant levels.

At base line, the mean (+/-SD) systolic and diastolic blood pressures were 131.3+/-10.8 mm Hg and 84.7+/-4.7 mm Hg, respectively. The combination diet reduced systolic and diastolic blood pressure by 5.5 and 3.0 mm Hg more, respectively, than the control diet (P<0.001 for each); the fruits-and-vegetables diet reduced systolic blood pressure by 2.8 mm Hg more (P<0.001) and diastolic blood pressure by 1.1 mm Hg more than the control diet (P=0.07). Among the 133 subjects with hypertension (systolic pressure, > or =140 mm Hg; diastolic pressure, > or =90 mm Hg; or both), the combination diet reduced systolic and diastolic blood pressure by 11.4 and

5.5 mm Hg more, respectively, than the control diet (P<0.001 for each); among the 326 subjects without hypertension, the corresponding reductions were 3.5 mm Hg (P<0.001) and 2.1 mm Hg (P=0.003).

A diet rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat can substantially lower blood pressure. This diet offers an additional nutritional approach to preventing and treating hypertension.

26. Gardner CD. 2001. The role of plant-based diets in the treatment and prevention of coronary artery disease. Coronary Artery Disease; 12(7):553-559.

We have studied the effects of moderate dietary fat restriction on plasma triglyceride, cholesterol, glucose, and insulin response in 27 subjects. Compared with a control diet (45% fat, 40% carbohydrate [CHO], 15% protein) the low fat (higher CHO) diet (30% fat, 55% CHO, 15% protein) produced a 41% increase in fasting triglyceride level (155 +/- 17 to 219 +/- 23 mg%) with no change in fasting plasma cholesterol level. Furthermore, this increase in triglyceride levels; induced by the higher CHO content of the low fat diet, was seen in 26 out of 27 subjects. Postprandial triglyceride, glucose, and insulin levels were also higher on the low fat (higher CHO) diet. Since hypertriglyceridemia is a significant risk factor for the development of coronary heart disease, and since our data indicate that the moderate increase in dietary CHO associated with a low fat diet will elevate plasma triglyceride levels, we believe that more caution is necessary before recommending the wide-spread use of low fat diets for heart disease prevention.

27. Liu S, et al. 2003. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. Am J Clin Nutr; 78(5):920-927.

Although increased consumption of dietary fiber and grain products is widely recommended to maintain healthy body weight, little is known about the relation of whole grains to body weight and long-term weight changes. We examined the associations between the intakes of dietary fiber and whole- or refined-grain products and weight gain over time. In a prospective cohort study, 74,091 US female nurses, aged 38-63 y in 1984 and free of known cardiovascular disease, cancer, and diabetes at baseline, were followed from 1984 to 1996; their dietary habits were assessed in 1984, 1986, 1990, and 1994 with validated food-frequency questionnaires. Using multiple models to adjust for covariates, we calculated average weight, body mass index (BMI; in kg/m(2)), long-term weight changes, and the odds ratio of developing obesity (BMI > or = 30) according to change in dietary intake.

Women who consumed more whole grains consistently weighed less than did women who consumed less whole grains (P for trend < 0.0001). Over 12 y, those with the greatest increase in intake of dietary fiber gained an average of 1.52 kg less than did those with the smallest increase in intake of dietary fiber (P for trend < 0.0001) independent of body weight at baseline, age, and changes in covariate status. Women in the highest quintile of dietary fiber intake had a 49% lower risk of major weight gain than did women in the highest quintile (OR = 0.51; 95% CI: 0.39, 0.67; P < 0.0001 for trend).

Weight gain was inversely associated with the intake of high-fiber, whole-grain foods but positively related to the intake of refined-grain foods, which indicated the importance of distinguishing whole-grain products from refined-grain products to aid in weight control.

28. Streppel MT, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study. Am J Clin Nutr. 2008 Oct;88(4):1119-25.

Little is known about the effects of dietary fiber intake on long-term mortality. We aimed to study recent and long-term dietary fiber intake in relation to coronary heart disease and all-cause mortality. The effects of recent and long-term dietary fiber intakes on mortality were investigated in the Zutphen Study, a cohort of 1,373 men born between 1900 and 1920 and examined repeatedly between 1960 and 2000. During that period, 1,130 men died, 348 as a result of coronary heart disease. Hazard ratios were obtained from time-dependent Cox regression models.

Every additional 10 g of recent dietary fiber intake per day reduced coronary heart disease mortality by 17% (95% CI: 2%, 30%) and all-cause mortality by 9% (0%, 18%). The strength of the association between long-term dietary fiber intake and all-cause mortality decreased from age 50 y (hazard ratio: 0.71; 95% CI: 0.55, 0.93) until age 80 y (0.99; 0.87, 1.12). We observed no clear associations for different types of dietary fiber.

A higher recent dietary fiber intake was associated with a lower risk of both coronary heart disease and all-cause mortality. For long-term intake, the strength of the association between dietary fiber and all-cause mortality decreased with increasing age.

29. Wolk A, et al. 1999. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. JAMA; 281:1998-2004.

Epidemiological studies of men suggest that dietary fiber intake protects against coronary heart disease (CHD), but data on this association in women are sparse. To examine the association between long-term intake of total dietary fiber as well as fiber from different sources and risk of CHD in women, the Nurses' Health Study, a large, prospective cohort study of US women followed up for 10 years from 1984 was used. Dietary data were collected in 1984, 1986, and 1990, using a validated semiquantitative food frequency questionnaire. A total of 68782 women aged 37 to 64 years without previously diagnosed angina, myocardial infarction (MI), stroke, cancer, hypercholesterolemia, or diabetes at baseline were included. Incidence of acute MI or death due to CHD by amount of fiber intake was the main outcome measure.

Response rate averaged 80% to 90% during the 10-year follow-up. We documented 591 major CHD events (429 nonfatal MIs and 162 CHD deaths). The age-adjusted relative risk (RR) for major CHD events was 0.53 (95% confidence interval [CI], 0.40-0.69) for women in the highest quintile of total dietary fiber intake (median, 22.9 g/d) compared with women in the lowest quintile (median, 11.5 g/d). After controlling for age, cardiovascular risk factors, dietary factors, and multivitamin supplement use, the RR was 0.77 (95% CI, 0.57-1.04). For a 10-g/d increase in total fiber intake (the difference between the lowest and highest quintiles), the multivariate RR of total CHD events was 0.81 (95% CI, 0.66-0.99). Among different sources of dietary fiber (eg, cereal, vegetables, fruit), only cereal fiber was strongly associated with a reduced risk of CHD (multivariate RR, 0.63; 95% CI, 0.49-0.81 for each 5-g/d increase in cereal fiber).

Our findings in women support the hypothesis that higher fiber intake, particularly from cereal sources, reduces the risk of CHD.

30. Pelletier X, Belbraouet S, Mirabel D, et al. A diet moderately enriched in phytosterols lowers plasma cholesterol concentrations in normocholesterolemic humans. Ann Nutr Metab. 1995;39(5):291-295.

Twelve normolipidic healthy human subjects were fed a diet with or without additional soybean phytosterols for 4 weeks in a crossover design. The order of the treatments was randomized. Phytosterols were added to the diet blended in butter. The dietary ratio cholesterol:phytosterols was 0.7 during the control period (436 mg cholesterol/day and 29 mg phytosterols/day) and 1.88 during the phytosterols period (410 mg cholesterol/day and 740 mg phytosterols/day). Blood cholesterol was 10% lower after subjects consumed the phytosterol-enriched diet than when they consumed the control diet ($p < 0.001$), which was due to a 15% LDL cholesterol decrease ($p < 0.001$). The HDL cholesterol:LDL cholesterol ratio was markedly enhanced (+25%) ($p < 0.01$). These findings suggest that a significant lowering of plasma total and LDL cholesterol can be effected by a modest dietary intake of soybean phytosterols.

31. Berger A, Jones PJ, Abumweis SS. Plant sterols: factors affecting their efficacy and safety as functional food ingredients. Lipids Health Dis. 2004;3(1):5.

Plant sterols are naturally occurring molecules that humanity has evolved with. Herein, we have critically evaluated recent literature pertaining to the myriad of factors affecting efficacy and safety of plant sterols in free and esterified forms. We conclude that properly solubilized 4-desmetyl plant sterols, in ester or free form, in reasonable doses (0.8-1.0 g of equivalents per day) and in various vehicles including natural sources, and as part of a healthy diet and lifestyle, are important dietary components for lowering low density lipoprotein (LDL) cholesterol and maintaining good heart health. In addition to their cholesterol lowering properties, plant sterols possess anti-cancer, anti-inflammatory, anti-atherogenicity, and anti-oxidation activities, and should thus be of clinical importance, even for those individuals without elevated LDL cholesterol. The carotenoid lowering effect of plant sterols should be corrected by increasing intake of food that is rich in carotenoids. In pregnant and lactating women and children, further study is needed to verify the dose required to decrease blood cholesterol without affecting fat-soluble vitamins and carotenoid status.

32. AbuMweis SS, Barake R, Jones P. Plant sterols/stanols as cholesterol lowering agents: A meta-analysis of randomized controlled trials. Food & Nutrition Research. 2008; DOI: 10.3402/fnr.v52i0.1811.

Consumption of plant sterols has been reported to reduce low density lipoprotein (LDL) cholesterol concentrations by 5-15%. Factors that affect plant sterol efficacy are still to be determined. To more precisely quantify the effect of plant sterol enriched products on LDL cholesterol concentrations than what is reported previously, and to identify and quantify the effects of subjects' characteristics, food carrier, frequency and time of intake on efficacy of plant sterols as cholesterol lowering agents. Fifty-nine eligible randomized clinical trials published from 1992 to 2006 were identified from five databases. Weighted mean effect sizes were calculated for net differences in LDL levels using a random effect model.

Plant sterol containing products decreased LDL levels by 0.31 mmol/L (95% CI, -0.35 to -0.27, P= < 0.0001) compared with placebo. Between trial heterogeneity was evident (Chi-square test, P = <0.0001) indicating that the observed differences between trial results were unlikely to have been caused by chance. Reductions in LDL levels were greater in individuals with high baseline LDL levels compared with those with normal to borderline baseline LDL levels. Reductions in LDL were greater when plant sterols were incorporated into fat spreads, mayonnaise and salad dressing, milk and yoghurt comparing with other food products such as croissants and muffins, orange juice, non-fat beverages, cereal bars, and chocolate. Plant sterols consumed as a single morning dose did not have a significant effect on LDL cholesterol levels.

Plant sterol containing products reduced LDL concentrations but the reduction was related to individuals' baseline LDL levels, food carrier, and frequency and time of intake.

33. Hendriks HF, Weststrate JA, van Vliet T, Meijer GW. Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects. Eur J Clin Nutr. 1999;53(4):319-327.

To investigate the dose-response relationship between cholesterol lowering and three different, relatively low intake levels of plant sterols (0.83, 1.61, 3.24 g/d) from spreads. To investigate the effects on lipid-soluble (pro)vitamins. A randomized double-blind placebo controlled balanced incomplete Latin square design using five spreads and four periods. The five study spreads included butter, a commercially available spread and three experimental spreads fortified with three different concentrations of plant sterols. One hundred apparently healthy normocholesterolaemic and mildly hypercholesterolaemic volunteers participated. Each subject consumed four spreads, each for a period of 3.5 week.

Compared to the control spread, total cholesterol decreased by 0.26 (CI: 0.15-0.36), 0.31 (CI: 0.20-0.41) and 0.35 (CI: 0.25-0.46) mmol/L, for daily consumption of 0.83, 1.61 and 3.24 g plant sterols, respectively. For LDL-cholesterol these decreases were 0.20 (CI: 0.10-0.31), 0.26 (CI: 0.15-0.36) and 0.30 (CI: 0.20-0.41). Decreases in the LDL/HDL ratio were 0.13 (CI: 0.04-0.22), 0.16 (CI: 0.07-0.24) and 0.16 (CI: 0.07-0.24) units, respectively. Differences in cholesterol reductions between the plant sterol doses consumed were not statistically significant. Plasma vitamin K1 and 25-OH-vitamin D and lipid standardized plasma lycopene and alpha-tocopherol were not affected by consumption of plant sterol enriched spreads, but lipid standardized plasma (alpha + beta)-carotene concentrations were decreased by about 11 and 19% by daily consumption of 0.83 and 3.24 g plant sterols in spread, respectively.

The three relatively low dosages of plant sterols had a significant cholesterol lowering effect ranging from 4.9-6.8%, 6.7-9.9% and 6.5-7.9%, for total, LDL-cholesterol and the LDL/HDL cholesterol ratio, respectively, without substantially affecting lipid soluble (pro)vitamins. No significant differences in cholesterol lowering effect between the three dosages of plant sterols could be detected. This study would support that consumption of about 1.6 g of plant sterols per day will beneficially affect plasma cholesterol concentrations without seriously affecting plasma carotenoid concentrations.

34. Miettinen TA, Gylling H. Plant stanol and sterol esters in prevention of cardiovascular diseases. Ann Med. 2004;36(2):126-134.

Statin trials have indicated that effective reduction of serum cholesterol should last up to one year before reduced risk of cardiovascular diseases can be detected. This observation can be applied most probably also to the use of plant stanol/sterol ester spreads for the treatment of hypercholesterolemia. However, despite the fact that the two spreads lower serum cholesterol similarly in short term studies, a comparison of one year results reveals an inconsistent effect of plant sterol spread as compared with that of plant stanol spread on cholesterol concentration in both men and women. This favors the use of plant stanol ester spread for long-term lowering of serum cholesterol. Doses of about 2 g/day of plant stanols as fatty acid ester spread enhances fecal elimination of cholesterol, but not of bile acids, through inhibition of cholesterol absorption by about 40%. This lowers serum total and low density lipoprotein (LDL) cholesterol despite enhanced compensatory increase in cholesterol synthesis by about 10% and 15% as compared with control spread, respectively, and by up to 20% as compared with the baseline diet. About one-third of mildly hypercholesterolemic subjects reach an accepted cholesterol level. A small dose of statin should be added to treatment in individuals resistant to monotherapy with plant stanol ester spread. A life-long consumption of plant stanol ester spread has been predicted to lower coronary events by about 20%.

35. Jenkins DJ, Kendall CW, Marchie A, et al. Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. Am J Clin Nutr. 2005;81(2):380-387.

3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors reduce serum cholesterol and are increasingly advocated in primary prevention to achieve reductions in LDL cholesterol. Newer dietary approaches combining cholesterol-lowering foods may offer another option, but these approaches have not been compared directly with statins in the same persons. The objective was to compare, in the same subjects, the cholesterol-lowering potential of a dietary portfolio with that of a statin. Thirty-four hyperlipidemic participants underwent all three 1-mo treatments in random order as outpatients: a very-low-saturated-fat diet (control diet), the same diet plus 20 mg lovastatin (statin diet), and a diet high in plant sterols (1.0 g/1000 kcal), soy-protein foods (including soy milks and soy burgers, 21.4 g/1000 kcal), almonds (14 g/1000 kcal), and viscous fibers from oats, barley, psyllium, and the vegetables okra and eggplant (10 g/1000 kcal) (portfolio diets). Fasting blood samples were obtained at 0, 2, and 4 wk.

LDL-cholesterol concentrations decreased by 8.5+/-1.9%, 33.3+/-1.9%, and 29.6+/-1.3% after 4 wk of the control, statin, and portfolio diets, respectively. Although the absolute difference between the statin and the portfolio treatments was significant at 4 wk (P=0.013), 9 participants (26%) achieved their lowest LDL-cholesterol concentrations with the portfolio diet. Moreover, the statin (n=27) and the portfolio (n=24) diets did not differ significantly (P=0.288) in their ability to reduce LDL cholesterol below the 3.4-mmol/L primary prevention cutoff.

Dietary combinations may not differ in potency from first-generation statins in achieving current lipid goals for primary prevention. They may, therefore, bridge the treatment gap between current therapeutic diets and newer statins.

36. Jenkins DJ, Kendall CW, Faulkner DA, et al. Assessment of the longer-term effects of a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. Am J Clin Nutr. 2006;83(3):582-591.

Cholesterol-lowering foods may be more effective when consumed as combinations rather than as single foods. Our aims were to determine the effectiveness of consuming a combination of cholesterol-lowering foods (dietary portfolio) under real-world conditions and to compare these results with published data from the same participants who had undergone 4-wk metabolic studies to compare the same dietary portfolio with the effects of a statin. For 12 mo, 66 hyperlipidemic participants were prescribed diets high in plant sterols (1.0 g/1000 kcal), soy protein (22.5 g/1000 kcal), viscous fibers (10 g/1000 kcal), and almonds (23 g/1000 kcal). Fifty-five participants completed the 1-y study. The 1-y data were also compared with published results on 29 of the participants who had also undergone separate 1-mo metabolic trials of a diet and a statin.

At 3 mo and 1 y, mean (+/-SE) LDL-cholesterol reductions appeared stable at 14.0 +/- 1.6% ($P < 0.001$) and 12.8 +/- 2.0% ($P < 0.001$), respectively ($n = 66$). These reductions were less than those observed after the 1-mo metabolic diet and statin trials. Nevertheless, 31.8% of the participants (n = 21 of 66) had LDL-cholesterol reductions of >20% at 1 y (x +/- SE: -29.7 +/- 1.6%). The LDL-cholesterol reductions in this group were not significantly different from those seen after their respective metabolically controlled portfolio or statin treatments. A correlation was found between total dietary adherence and LDL-cholesterol change ($r = -0.42$, $P < 0.001$). Only 2 of the 26 participants with <55% compliance achieved LDL-cholesterol reductions >20% at 1 y.

More than 30% of motivated participants who ate the dietary portfolio of cholesterol-lowering foods under real-world conditions were able to lower LDL-cholesterol concentrations >20%, which was not significantly different from their response to a first-generation statin taken under metabolically controlled conditions.

37. Andersson SW, Skinner J, Ellegard L, et al. Intake of dietary plant sterols is inversely related to serum cholesterol concentration in men and women in the EPIC Norfolk population: a cross-sectional study. Eur J Clin Nutr. 2004;58(10):1378-1385.

We examined the relation between intake of natural dietary plant sterols and serum lipid concentrations in a free-living population. Cross-sectional population-based study of 22,256 men and women aged 39-79 y resident in Norfolk, UK, participating in the European Prospective Investigation into Cancer (EPIC-Norfolk). MAIN EXPOSURE AND OUTCOME MEASURES: Plant sterol intake from foods and concentrations of blood lipids.

Mean concentrations of total cholesterol and low-density lipoprotein cholesterol, adjusted for age, body mass index and total energy intake, decreased with increasing plant sterol intake in men and women. Mean total serum cholesterol concentration for men in the highest fifth of plant sterol intake (mean intake 463 mg daily) was 0.25 mmol/l lower and for low-density lipoprotein cholesterol 0.14 mmol/l lower than those in the lowest fifth of plant sterol consumption (mean intake 178 mg daily); the corresponding figures in women were 0.15 and 0.13 mmol/l. After adjusting for saturated fat and fibre intakes, the results for total cholesterol and low-density lipoprotein cholesterol were similar, although the strength of the association was slightly reduced.

In a free-living population, a high intake of plant sterols is inversely associated with lower concentrations of total and low-density lipoprotein serum cholesterol. The plant sterol content of foods may partly explain diet-related effects on serum cholesterol concentration.

38. Bassett CM, Rodriguez-Leyva D, Pierce GN. Experimental and clinical research findings on the cardiovascular benefits of consuming flaxseed. Appl Physiol Nutr Metab. 2009 Oct;34(5):965-74.

Functional foods and nutraceuticals are becoming popular alternatives to pharmacological treatments by providing health benefits and (or) reducing the risk of chronic diseases. Flaxseed is a rich source of 3 components with demonstrated cardioprotective effects: the omega-3 fatty acid alpha-linolenic acid (ALA), dietary fibre, and phytoestrogen lignans. Multiple clinical dietary intervention trials report that consuming flaxseed daily can modestly reduce circulating total cholesterol (TC) by 6%-11% and low-density lipoprotein (LDL) cholesterol by 9%-18% in normolipemic humans and by 5%-17% for TC and 4%-10% for LDL cholesterol in hypercholesterolemic patients, as well as lower various markers associated with atherosclerotic cardiovascular disease in humans. Evidence to date suggests that the dietary fibre and (or) lignan content of flaxseed provides the hypocholesterolemic action. The omega-3 ALA found in the flaxseed oil fraction also contributes to the antiatherogenic effects of flaxseed via anti-inflammatory and antiproliferative mechanisms. Dietary flaxseed may also protect against ischemic heart disease by improving vascular relaxation responses and by inhibiting the incidence of ventricular fibrillation.

39. Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. Am J Clin Nutr. 2009 Aug;90(2):288-97. Epub 2009 Jun 10.

Several clinical trials have investigated the effects of flaxseed and flaxseed-derived products (flaxseed oil or lignans) on blood lipids; however, the findings have been inconsistent. We aimed to identify and quantify the effectiveness of flaxseed and its derivatives on blood lipid profiles. A comprehensive literature search was performed on the basis of English reports of randomized controlled trials of flaxseed or its derivatives on lipid profiles in adults, which were published from January 1990 to October 2008. Attempts also were made to access unpublished data. Study quality was assessed by using the Jadad score, and a meta-analysis was conducted.

Twenty-eight studies were included. Flaxseed interventions reduced total and LDL cholesterol by 0.10 mmol/L (95% CI: -0.20, 0.00 mmol/L) and 0.08 mmol/L (95% CI: -0.16, 0.00 mmol/L), respectively; significant reductions were observed with whole flaxseed (-0.21 and -0.16 mmol/L, respectively) and lignan (-0.28 and -0.16 mmol/L, respectively) supplements but not with flaxseed oil. The cholesterol-lowering effects were more apparent in females (particularly postmenopausal women), individuals with high initial cholesterol concentrations, and studies with higher Jadad scores. No significant changes were found in the concentrations of HDL cholesterol and triglycerides.

Flaxseed significantly reduced circulating total and LDL-cholesterol concentrations, but the changes were dependent on the type of intervention, sex, and initial lipid profiles of the subjects. Further studies are needed to determine the efficiency of flaxseed on lipid profiles in men and premenopausal women and to explore its potential benefits on other cardiometabolic risk factors and prevention of cardiovascular disease.

40. Mandaşescu S, Mocanu V, Dăscaliţa AM, Haliga R, Nestian I, Stitt PA, Luca V. Flaxseed supplementation in hyperlipidemic patients. Rev Med Chir Soc Med Nat Iasi. 2005 Jul-Sep;109(3):502-6.

The aim of this study was to investigate the effect of daily consumption of dietary flaxseed (as a source of linolenic acid, LNA) on plasma lipid concentrations in mildly hyperlipidemic patients. 40 hyperlipidemic patients with plasma total cholesterol greater than 240 mg/dL were distributed in 3 groups: 10 patients who received hypo-lipidic diet (diet group), 10 patients who received hypo-lipidic diet plus statins (diet+HL group), 20 patients who received hypo-lipidic diet plus 20 g ground flax-seeds/day (diet+flax group). Body mass index (BMI), serum total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG) and cholesterol/HDL-cholesterol ratio were measured at the beginning and after 60 days of treatment.

Flaxseed supplementation was associated with significant reductions in TC (-17.2%), LDL-C (-3.9%), TG (-36.3%) and TC/HDL-C ratio (-33.5%). There were no significant differences in absolute change in BMI nor in percentage change in TC, HDL-C, LDL-C, TC/HDL-C ratio between flaxseed and statin groups.

Dietary flaxseed significantly improves lipid profile in hyperlipidemic patients and may favorably modify cardiovascular risk factors.

41. Patade A, Devareddy L, Lucas EA, Korlagunta K, Daggy BP, Arjmandi BH. Flaxseed reduces total and LDL cholesterol concentrations in Native American postmenopausal women. J Womens Health (Larchmt). 2008 Apr;17(3):355-66.

The objective of the study was to investigate the extent to which the daily incorporation of approximately 30 g of flaxseed, a rich source of lignans, omega-3 fatty acids, and fiber, for a period of 3 months into the diet of Native American postmenopausal women positively affects their lipid profiles. Fifty-five mild to moderately hypercholesterolemic (> or =5.1 to < or =9.8 mmol/L) Native American postmenopausal women were randomly assigned to control (A), flaxseed (B) or flaxseed + additional oat bran fiber (C) groups. Overnight fasting venous blood was collected at baseline and at the end of the treatment period to analyze lipid parameters.

Dietary flaxseed supplementation lowered total cholesterol and low-density lipoprotein cholesterol (LDL-C) by approximately 7% and 10%, respectively. However, the levels of high-density lipoprotein (HDL) and triglyceride remained unaltered. No changes were observed in other clinical and hematological parameters.

The results of the present study indicate that Native American postmenopausal women benefit from regular consumption of flaxseed by reducing their risk of cardiovascular disease as seen from lowered LDL-C and total cholesterol levels.

42. Bierenbaum ML, Reichstein R, Watkins TR. Reducing atherogenic risk in hyperlipemic humans with flax seed supplementation: a preliminary report. J Am Coll Nutr. 1993 Oct;12(5):501-4.

The effect on serum lipids of a flax seed supplement consisting of three slices of flax seed-containing bread and 15 g of ground flax seed was studied in 15 hyperlipemic subjects on long-term intake (800 IU/day) of vitamin E. The flax seed, which was high in alpha-linolenic acid and fiber, and which has been reported to lower serum cholesterol in elderly subjects, was provided in a 3-month feeding trial. Serum total and low-density lipoprotein cholesterol levels were reduced significantly; high-density lipoprotein cholesterol did not change during flax seed consumption. Thrombin-stimulated platelet aggregation decreased with the supplement. Serum lipid oxidation products decreased significantly during the washout period.

43. Djoussé L, Arnett DK, Carr JJ, Eckfeldt JH, Hopkins PN, Province MA, Ellison RC; Investigators of the NHLBI FHS. Dietary linolenic acid is inversely associated with calcified atherosclerotic plaque in the

coronary arteries: the National Heart, Lung, and Blood Institute Family Heart Study. Circulation. 2005 Jun 7;111(22):2921-6. Epub 2005 May 31.

High dietary intake of linolenic acid is associated with a lower risk of cardiovascular disease mortality. However, little is known about the association between linolenic acid and subclinical atherosclerosis. To examine the association between dietary linolenic acid measured by food frequency questionnaire and calcified atherosclerotic plaque in the coronary arteries (CAC) measured by cardiac CT, we studied 2004 white participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study aged 32 to 93 years. The presence of CAC was defined on the basis of total CAC score of > or =100. We used generalized estimating equations to estimate odds ratios for the presence of CAC across quintiles of linolenic acid. The average consumption of dietary linolenic acid was 0.82+/-0.36 g/d for men and 0.69+/-0.29 g/d for women. From the lowest to the highest quintile of linolenic acid, adjusted odds ratios (95% CI) for the presence of CAC were 1.0 (reference), 0.61 (0.42 to 0.88), 0.55 (0.35 to 0.84), 0.57 (0.37 to 0.88), and 0.35 (0.22 to 0.55), respectively (P for trend <0.0001), after we controlled for age, gender, education, family risk group, smoking, fruit and vegetable intake, history of coronary artery disease, hypertension, diabetes mellitus, and statin use. When linolenic acid was used as a continuous variable, the multivariate adjusted odds ratio was 0.38 (95% CI, 0.24 to 0.46) per gram of linolenic acid intake. Use of different cut points for CAC score yielded similar results.

Consumption of dietary linolenic acid is associated with a lower prevalence of CAC in a dose-response fashion in white men and women.

44. Kahlon TS, Smith GE. In vitro binding of bile acids by blueberries (Vaccinium spp.), plums (Prunus spp.), prunes (Prunus spp.) strawberries (Fragaria X ananassa), cherries (Malpighia punicifolia), cranberries (Vaccinium macrocarpon) and apples (Malus spp.)

The in vitro binding of bile acids by blueberries (Vaccinium spp.), plums (Prunus spp.), prunes (Prunus spp.), strawberries (Fragaria X ananassa), cherries (Malpighia punicifolia) cranberries (Vaccinium macrocarpon) and apples (Malus sylvestris) was determined using a mixture of bile acids secreted in human bile at a duodenal physiological pH of 6.3. Six treatments and two blank incubations were conducted to testing various fresh raw fruits on an equal dry matter basis. Considering cholestyramine (bile acid binding, cholesterol lowering drug) as 100% bound, the relative in vitro bile acid binding on dry matter (DM), total dietary fiber (TDF) and total polysaccharides (PCH) basis was for blueberries 7%, 47% and 25%; plums 6%, 53% and 50%; prunes 5%, 50% and 14%; strawberries 5%, 23% and 15%; cherries 5%, 37% and 5%; cranberries 4%, 12% and 7%; and apple 1%, 7% and 5%, respectively. Bile acid binding on DM basis for blueberries was significantly (P <or= 0.05) higher than all the fruits tested. The bile acid binding for plums was similar to that for prunes and strawberries and significantly higher than cherries, cranberries and apples. Binding values for cherries and cranberries were significantly higher than those for apples. These results point to the relative health promoting potential of blueberries > plums = prunes = strawberries = cherries = cranberries > apples as indicated by their bile acid binding on DM basis. The variability in bile acid binding between the fruits tested maybe related to their phytonutrients (antioxidants, polyphenols, hydroxycinnamic acids, flavonoids, anthocyanins, flavonols, proanthocyanidins, catechins), structure, hydrophobicity of undigested fractions, anionic or cationic nature of the metabolites produced during digestion or their interaction with active binding sites. Inclusion of blueberries, plums, prunes, strawberries, cherries and cranberries in our daily diet as health promoting fruits should be encouraged. Animal studies are planned to validate in vitro bile acid binding of fruits observed herein to their potential of atherosclerosis amelioration (lipid and lipoprotein lowering) and cancer prevention (excretion of toxic metabolites).

45. Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. Am J Clin Nutr. 1999;70(3 Suppl):504S-511S.

Because nuts have favorable fatty acid and nutrient profiles, there is growing interest in evaluating their role in a heart-healthy diet. Nuts are low in saturated fatty acids and high in monounsaturated and polyunsaturated fatty acids. In addition, emerging evidence indicates that there are other bioactive molecules in nuts that elicit cardioprotective effects. These include plant protein, dietary fiber, micronutrients such as copper and magnesium, plant sterols, and phytochemicals. Few feeding studies have been conducted that have incorporated different nuts into the test diets to determine the effects on plasma lipids and lipoproteins. The total- and lipoprotein-cholesterol responses to these diets are summarized in this article. In addition, the actual cholesterol response was compared with the predicted response derived from the most current predictive equations for blood cholesterol. Results from this comparison showed that when subjects consumed test diets including nuts, there was an approximately 25% greater cholesterol-lowering response than that predicted by the equations. These results suggest that there are non-fatty acid constituents in nuts that have additional cholesterol-lowering effects. Further studies are needed to identify these constituents and establish their relative cholesterol-lowering potency.

46. Jenkins DJ, Kendall CW, Marchie A, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. Circulation. 2002;106(11):1327-1332.

Although recent studies have indicated that nut consumption may improve levels of blood lipids, nuts are not generally recommended as snacks for hyperlipidemic subjects because of their high fat content. Furthermore, the effective dose is still unknown.

The dose-response effects of whole almonds, taken as snacks, were compared with low-saturated fat (<5% energy) whole-wheat muffins (control) in the therapeutic diets of hyperlipidemic subjects. In a randomized crossover study, 27 hyperlipidemic men and women consumed 3 isoenergetic (mean 423 kcal/d) supplements each for 1 month.

Supplements provided 22.2% of energy and consisted of full-dose almonds (73+/-3 g/d), half-dose almonds plus half-dose muffins, and full-dose muffins. Fasting blood, expired air, blood pressure, and body weight measurements were obtained at weeks 0, 2, and 4. Mean body weights differed <300 g between treatments. The full-dose almonds produced the greatest reduction in levels of blood lipids. Significant reductions from baseline were seen on both half- and full-dose almonds for LDL cholesterol (4.4+/-1.7%, P=0.018, and 9.4+/-1.9%, P<0.001, respectively) and LDL:HDL cholesterol (7.8+/-2.2%, P=0.001, and 12.0+/-2.1%, P<0.001, respectively) and on full-dose almonds alone for lipoprotein(a) (7.8+/-3.5%, P=0.034) and oxidized LDL concentrations (14.0+/-3.8%, P<0.001), with no significant reductions on the control diet. No difference was seen in pulmonary nitric oxide between treatments.

Almonds used as snacks in the diets of hyperlipidemic subjects significantly reduce coronary heart disease risk factors, probably in part because of the nonfat (protein and fiber) and monounsaturated fatty acid components of the nut.

47. Sabate J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. Am J Clin Nutr. 2003;77(6):1379-1384.

Frequent consumption of nuts may lower the risk of cardiovascular disease by favorably altering serum lipid and lipoprotein concentrations. We compared the effects of 2 amounts of almond intake with those of a National Cholesterol Education Program Step I diet on serum lipids, lipoproteins, apolipoproteins, and glucose in healthy and mildly hypercholesterolemic adults. In a randomized crossover design, 25 healthy subjects (14 men, 11 women) with a mean (+/- SD) age of 41 +/- 13 y were fed 3 isoenergetic diets for 4 wk each after being fed a 2-wk run-in diet (containing 34% of energy from fat). The experimental diets included a Step I diet, a low-almond diet, and a high-almond diet, in which almonds contributed 0%, 10%, and 20% of total energy, respectively.

Inverse relations were observed between the percentage of energy in the diet from almonds and the subject's total cholesterol (P value for trend < 0.001), LDL-cholesterol (P < 0.001), and apolipoprotein B (P < 0.001) concentrations and the ratios of LDL to HDL cholesterol (P < 0.001) and of apolipoprotein B to apolipoprotein A (P < 0.001). Compared with the Step I diet, the high-almond diet reduced total cholesterol (0.24 mmol/L or 4.4%; P = 0.001), LDL cholesterol (0.26 mmol/L or 7.0%; P < 0.001), and apolipoprotein B (6.6 mg/dL or 6.6%; P < 0.001); increased HDL cholesterol (0.02 mmol/L or 1.7%; P = 0.08); and decreased the ratio of LDL to HDL cholesterol (8.8%; P < 0.001).

Isoenergetic incorporation of approximately 68 g of almonds (20% of energy) into an 8368-kJ (2000-kcal) Step I diet markedly improved the serum lipid profile of healthy and mildly hypercholesterolemic adults. Total and LDL-cholesterol concentrations declined with progressively higher intakes of almonds, which suggests a dose-response relation.

48. Spiller GA, Jenkins DA, Bosello O, Gates JE, Cragen LN, Bruce B. Nuts and plasma lipids: an almond-based diet lowers LDL-C while preserving HDL-C. J Am Coll Nutr. 1998;17(3):285-290.

The aim of this study was to compare lipid-altering effects of an almond-based diet with an olive oil-based diet, against a cheese and butter-based control diet. Forty-five free-living hyperlipidemic men (n = 12) and women (n = 33) with a mean plasma total cholesterol (TC) of 251 +/- 30 mg/dL followed one of three diets; almond-based, olive oil-based, or dairy-based for 4 weeks. Total fat in each diet was matched, and the study-provided sources of fat comprised the major portion of fat intake.

Reductions in TC and low-density lipoprotein-cholesterol (LDL-C) between the three groups were significantly different from the almond group (both p < 0.001). Within group analysis revealed that the almond-based diet induced significant reductions in TC (p < 0.05), LDL-C (p < 0.001), and the TC:HDL ratio (p < 0.001), while HDL-C levels were preserved. TC and HDL-C in the control diet were significantly increased from baseline (both p < 0.05), while the olive oil-based diet resulted in no significant changes over the study period. Weight did not change significantly.

Results suggest that the more favorable lipid-altering effects induced by the almond group may be due to interactive or additive effects of the numerous bioactive constituents found in almonds.

49. Kris-Etherton PM, Pearson TA, Wan Y, et al. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. Am J Clin Nutr. 1999;70(6):1009-1015.

Low-fat diets increase plasma triacylglycerol and decrease HDL-cholesterol concentrations, thereby potentially adversely affecting cardiovascular disease (CVD) risk. High-monounsaturated fatty acid (MUFA), cholesterol-lowering diets do not raise triacylglycerol or lower HDL cholesterol, but little is known about how peanut products, a rich source of MUFAs, affect CVD risk. The present study compared the CVD risk profile of an Average American diet (AAD) with those of 4 cholesterol-lowering diets: an American Heart

Association/National Cholesterol Education Program Step II diet and 3 high-MUFA diets [olive oil (OO), peanut oil (PO), and peanuts and peanut butter (PPB)].

A randomized, double-blind, 5-period crossover study design (n = 22) was used to examine the effects of the diets on serum lipids and lipoproteins: AAD [34% fat; 16% saturated fatty acids (SFAs), 11% MUFAs], Step II (25% fat; 7% SFAs, 12% MUFAs), OO (34% fat; 7% SFAs, 21% MUFAs), PO (34% fat; 7% SFAs, 17% MUFAs), and PPB (36% fat; 8% SFAs, 18% MUFAs). The high-MUFA diets lowered total cholesterol by 10% and LDL cholesterol by 14%. This response was comparable with that observed for the Step II diet. Triacylglycerol concentrations were 13% lower in subjects consuming the high-MUFA diets and were 11% higher with the Step II diet than with the AAD. The high-MUFA diets did not lower HDL cholesterol whereas the Step II diet lowered it by 4% compared with the AAD. The OO, PO, and PPB diets decreased CVD risk by an estimated 25%, 16%, and 21%, respectively, whereas the Step II diet lowered CVD risk by 12%.

A high-MUFA, cholesterol-lowering diet may be preferable to a low-fat diet because of more favorable effects on the CVD risk profile.

50. O'Byrne DJ, Knauft DA, Shireman RB. Low fat-monounsaturated rich diets containing high-oleic peanuts improve serum lipoprotein profiles. Lipids. 1997;32(7):687-695.

Postmenopausal hypercholesterolemic women are at risk for cardiovascular disease and are encouraged to follow low-fat (LF) (< or = 30% energy) diets. However, these diets may have undesirable effects on high density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (apo A-I) and triglycerides, whereas diets high in monounsaturated fats do not. Twenty postmenopausal hypercholesterolemic women previously consuming high-fat diets (34% energy) were placed on a low fat-monounsaturated rich diet (LFMR: 26%, 14% energy, respectively) for 6 men. Sixteen women already eating LF diets (24% energy) were also followed to monitor variations in serum lipids due to seasonal variations. Twenty-five women successfully completed the study (LFMR = 12, LF = 13). Serum cholesterol decreased 10% (264 to 238 mg/dL, P < or = 0.01) and low density lipoprotein cholesterol (LDL-C) decreased 12% (182 to 161 mg/dL, P < or = 0.01) in the LFMR group, but did not change in the LF group. The reduction in serum cholesterol in the LFMR group was greater than estimated by predictive formulas. Serum triglycerides and apo A-I did not change in the LFMR group. A modest decrease in HDL-C, HDL3-C, and apolipoprotein B (apo B) occurred in both groups, but only the LFMR group showed a trend toward beneficial changes in LDL-C/HDL-C and apo A-Vapo B ratios. Overall, the LFMR diet was well tolerated and resulted in an improved serum lipid and apolipoprotein profile.

51. Morgan WA, Clayshulte BJ. Pecans lower low-density lipoprotein cholesterol in people with normal lipid levels. J Am Diet Assoc. 2000;100(3):312-318.

The goal of this study was to compare serum lipid profiles and dietary intakes of people with normal lipid levels who consumed pecans and those who did not consume nuts. Eight-week, randomized, controlled study of pecan treatment group vs control group. Nineteen people with normal lipid levels completed the study; 10 had been randomly assigned to the pecan treatment group (7 women, 3 men, mean age = 45 +/- 10 years) and 9 to the control group (8 women, 1 man, mean age = 37 +/- 12 years). The pecan treatment group consumed 68 g pecans per day for 8 weeks plus self-selected diets. The pecans contributed 459 kcal and 44 g fat daily. The control group avoided nuts and consumed self-selected diets. Total serum cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total triglyceride levels were measured at the time of entrance to the study (baseline), week 4, and week 8. Computer analyses were done on five 3-day food records.Comparisons were made using analysis of variance or paired t test.

LDL-C was lowered in the pecan treatment group from 2.61 +/- 0.49 mmol/L at baseline to 2.35 +/- 0.49 at week 4 (P < .05) and to 2.46 +/- 0.59 at week 8 (P < .05). At week 8, total cholesterol and HDL-C in the pecan treatment group were significantly lower (P < .05) than in the control group (total cholesterol: 4.22 +/- 0.83 vs 5.02 +/- 0.54 mmol/L; HDL-C: 1.37 +/- 0.23 vs 1.47 +/- 0.34 mmol/L). Dietary fat, monounsaturated fat, polyunsaturated fat, insoluble fiber, magnesium, and energy were significantly higher in the pecan treatment group than in the control group. Body mass indexes and body weights were unchanged in both groups.

Pecans can be included in a healthful diet when energy intake and potential weight gain are addressed.

52. Hyson DA, Schneeman BO, Davis PA. Almonds and almond oil have similar effects on plasma lipids and LDL oxidation in healthy men and women. J Nutr. 2002;132(4):703-707.

Epidemiologic and clinical studies have shown that nut consumption is associated with favorable plasma lipid profiles and reduced cardiovascular risk. These effects may result from their high monounsaturated fat (MUFA) content but nuts contain constituents other than fatty acids that might be cardioprotective. We conducted a study to compare the effects of whole-almond vs. almond oil consumption on plasma lipids and LDL oxidation in healthy men and women. Using a randomized crossover trial design, 22 normolipemic men and women replaced half of their habitual fat (approximately 14% of approximately 29% energy) with either whole almonds (WA) or almond oil (AO) for 6-wk periods. Compliance was ascertained by monitoring dietary intake via biweekly 5-d food records, return of empty almond product packages and weekly meetings with a registered dietitian. Fat replacement with either WA and AO resulted in a 54% increase in percentage of energy as MUFA with declines in both saturated fat and cholesterol intake and no significant changes in total energy, total or polyunsaturated fat intake. The effects of WA and AO on plasma lipids did not differ compared with baseline; plasma triglyceride, total and LDL cholesterol significantly decreased, 14, 4 and 6% respectively, whereas HDL cholesterol increased 6%. Neither treatment affected in vitro LDL oxidizability. We conclude that WA and AO do not differ in their beneficial effects on the plasma lipid variables measured and that this suggests that the favorable effect of almonds is mediated by components in the oil fraction of these nuts.

53. Abbey M, Noakes M, Belling GB, Nestel PJ. Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol. Am J Clin Nutr. 1994;59(5):995-999.

Sixteen normolipidemic male volunteers aged 41 +/- 9 y (mean +/- SD) consumed a diet providing 36% of energy as fat (92 g fat/d) for 9 wk. A daily supplement of nuts (providing half of the total fat intake) was provided against a common background diet. In the first 3-wk period the background diet was supplemented with raw peanuts (50 g/d), coconut cubes (40 g/d), and a coconut confectionary bar (50 g/d), designed to provide 47 g fat with a ratio of polyunsaturated to monounsaturated to saturated fatty acids (P:M:S) to match the Australian diet (reference diet). During the following 3 wk the background diet was supplemented with monounsaturated fatty acid-rich raw almonds (84 g/d), equivalent to 46 g fat, and during the final 3-wk period the background diet was supplemented with polyunsaturated fatty acid-rich walnuts (68 g/d), equivalent to 46 g fat. Compared with the reference diet there were significant reductions in total and LDL cholesterol, 7% and 10%, respectively, after supplementation with almonds, and 5% and 9%, respectively, after supplementation with walnuts.

54. Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. Am J Clin Nutr. 2001;74(1):72-79.

Epidemiologic studies show an inverse relation between nut consumption and coronary heart disease. We determined the effects of walnut intake on plasma fatty acids, lipoproteins, and lipoprotein subclasses in patients with combined hyperlipidemia. Participants sequentially adhered to the following diets: 1) a habitual diet (HD), 2) a habitual diet plus walnuts (HD+W), 3) a low-fat diet (LFD), and 4) a low-fat diet plus walnuts (LFD+W).

In 13 postmenopausal women and 5 men (+/- SD age 60 +/- 8 y), walnut supplementation did not increase body weight despite increased energy intake and the LFD caused weight loss (1.3 +/- 0.5 kg; $P < 0.01$). When comparing the HD with the HD+W, linoleic acid concentrations increased from 29.94 +/- 1.14% to 36.85 +/- 1.13% and alpha-linolenic acid concentrations increased from 0.78 +/- 0.04% to 1.56 +/- 0.11%. During the LFD+W, plasma total cholesterol concentrations decreased by 0.58 +/- 0.16 mmol/L when compared with the HD and by 0.46 +/- 0.14 mmol/L when compared with the LFD. LDL-cholesterol concentrations decreased by 0.46 +/- 0.15 mmol/L when compared with the LFD. Measurements of lipoprotein subclasses and particle size suggested that walnut supplementation lowered cholesterol preferentially in small LDL (46.1 +/- 1.9% compared with 33.4 +/- 4.3%, HD compared with HD+W, respectively; $P < 0.01$). HDL-cholesterol concentrations decreased from 1.27 +/- 0.07 mmol/L during the HD to 1.14 +/- 0.07 mmol/L during the HD+W and to 1.11 +/- 0.08 mmol/L during the LFD. The decrease was seen primarily in the large HDL particles.

Walnut supplementation may beneficially alter lipid distribution among various lipoprotein subclasses even when total plasma lipids do not change. This may be an additional mechanism underlying the antiatherogenic properties of nut intake.

55. Chisholm A, Mann J, Skeaff M, et al. A diet rich in walnuts favourably influences plasma fatty acid profile in moderately hyperlipidaemic subjects. Eur J Clin Nutr. 1998;52(1):12-16.

To compare two low fat diets one rich in walnuts on parameters of lipid metabolism in a group of hyperlipidaemic subjects. Twenty one men with mean (s.d.) levels of total and LDL cholesterol of 6.58 (0.60) and 4.63 (0.58) respectively were asked to consume two low fat diets (fat 30% total energy), one containing, on average, 78 g/d walnuts for two periods of four weeks.

Participants reported a higher total fat intake on the walnut diet (38% compared with 30% on the low fat diet $P < 0.01$) The most consistent change in fatty acid profile of triacylglycerol, phospholipid and cholesterol ester on the walnut diet was a significant ($P < 0.01$) increase in linoleic acid. Triacylglycerol linolenate also increased significantly ($P < 0.01$). Total and LDL cholesterol were lower on both experimental diets than at baseline, 0.25 mmol/l and 0.36 mmol/l respectively on the walnut diet and 0.13 mmol/l and 0.20 mmol/l respectively on the low fat diet. High density lipoprotein cholesterol was higher on both the walnut and low fat diets when compared to baseline (0.15 mmol/l and 0.12 mmol/l, respectively). When comparing the walnut and low fat diets only apo B was significantly lower ($P < 0.05$) on the walnut diet.

Despite an unintended increase in the total fat intake on the walnut diet, fatty acid profile of the major lipid fractions showed changes which might be expected to reduce risk of cardiovascular disease. The reduction of apolipoprotein B suggests a reduction in lipoprotein mediated risk, the relatively low myristic acid content of both diets perhaps explaining the absence of more extensive differences in lipoprotein levels on the two diets.

56. Sabate J, Fraser GE, Burke K, Knutsen SF, Bennett H, Lindsted KD. Effects of walnuts on serum lipid levels and blood pressure in normal men. N Engl J Med. 1993;328(9):603-607.

In a recent six-year follow-up study, we found that frequent consumption of nuts was associated with a reduced risk of ischemic heart disease. To explore possible explanations for this finding, we studied the effects of nut consumption on serum lipids and blood pressure. We randomly placed 18 healthy men on two mixed natural diets, each diet to be followed for four weeks. Both diets conformed to the National Cholesterol Education Program Step 1 diet and contained identical foods and macronutrients, except that 20 percent of the calories of one diet (the walnut diet) were derived from walnuts (offset by lesser amounts of fatty foods, meat, and visible fat [oils, margarine, and butter]).

With the reference diet, the mean (+/- SD) serum values for total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol were, respectively, 182 +/- 23, 112 +/- 16, and 47 +/- 11 mg per deciliter (4.71 +/- 0.59, 2.90 +/- 0.41, and 1.22 +/- 0.28 mmol per liter). With the walnut diet, the mean total cholesterol level was 22.4 mg per deciliter (0.58 mmol per liter) lower than the mean level with the reference diet (95 percent confidence interval, 28 to 17 mg per deciliter [0.72 to 0.44 mmol per liter]); the LDL and HDL cholesterol levels were, respectively, 18.2 mg per deciliter (0.47 mmol per liter) (P < 0.001) and 2.3 mg per deciliter (0.06 mmol per liter) (P = 0.01) lower. These lower values represented reductions of 12.4, 16.3, and 4.9 percent in the levels of total, LDL, and HDL cholesterol, respectively. The ratio of LDL cholesterol to HDL cholesterol was also lowered (P < 0.001) by the walnut diet. Mean blood-pressure values did not change during either dietary period.

Incorporating moderate quantities of walnuts into the recommended cholesterol-lowering diet while maintaining the intake of total dietary fat and calories decreases serum levels of total cholesterol and favorably modifies the lipoprotein profile in normal men. The long-term effects of walnut consumption and the extension of this finding to other population groups deserve further study.

57. Zambon D, Sabate J, Munoz S, et al. Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. A randomized crossover trial. Ann Intern Med. 2000;132(7):538-546.

It has been reported that walnuts reduce serum cholesterol levels in normal young men.To assess the acceptability of walnuts and their effects on serum lipid levels and low-density lipoprotein (LDL) oxidizability in free-living hypercholesterolemic persons, 55 men and women (mean age, 56 years) with polygenic hypercholesterolemia were fed a cholesterol-lowering Mediterranean diet and a diet of similar energy and fat content in which walnuts replaced approximately 35% of the energy obtained from monounsaturated fat. Patients followed each diet for 6 weeks.

49 persons completed the trial. The walnut diet was well tolerated. Planned and observed diets were closely matched. Compared with the Mediterranean diet, the walnut diet produced mean changes of -4.1% in total cholesterol level, -5.9% in LDL cholesterol level, and -6.2% in lipoprotein(a) level. The mean differences in the changes in serum lipid levels were -0.28 mmol/L (95% CI, -0.43 to -0.12 mmol/L) (-10.8 mg/dL [-16.8 to -4.8 mg/dL]) (P<0.001) for total cholesterol level, -0.29 mmol/L (CI, -0.41 to -0.15 mmol/L) (-11.2 mg/dL [-16.3 to -6.1 mg/dL]) (P<0.001) for LDL cholesterol level, and -0.021 g/L (CI, -0.042 to -0.001 g/L) (P = 0.042) for lipoprotein(a) level. Lipid changes were similar in men and women except for lipoprotein(a) levels, which decreased only in men. Low-density lipoprotein particles were enriched with polyunsaturated fatty acids from walnuts, but their resistance to oxidation was preserved.

Substituting walnuts for part of the mono-unsaturated fat in a cholesterol-lowering Mediterranean diet further reduced total and LDL cholesterol levels in men and women with hypercholesterolemia.

58. Puglisi MJ, Mutungi G, Brun PJ, McGrane MM, Labonte C, Volek JS, Fernandez ML. Raisins and walking alter appetite hormones and plasma lipids by modifications in lipoprotein metabolism and up-regulation of the low-density lipoprotein receptor. Metabolism. 2009 Jan;58(1):120-8.

The purpose of this study was to determine the effects of consuming raisins, increasing steps walked, or a combination of these interventions on lipoprotein metabolism and appetite hormones by assessing plasma apolipoprotein concentrations, cholesterol ester transfer protein activity, low-density lipoprotein (LDL) receptor messenger RNA (mRNA) abundance, and plasma ghrelin and leptin concentrations. Thirty-four subjects (17 men and 17 postmenopausal women) were matched for weight and sex and randomly assigned to consume 1 cup raisins per day (RAISIN), increase the amount of steps walked per day (WALK), or a combination of both interventions (RAISIN + WALK). The subjects completed a 2-week run-in period, followed by a 6-week intervention. Ribonucleic acid was extracted from mononuclear cells, and LDL receptor mRNA abundance was quantified by use of reverse transcriptase polymerase chain reaction. Plasma apolipoproteins were measured by Luminex (Austin, TX) technology. Apoproteins A-1, B, C-II, and E and cholesterol ester transfer protein activity were not altered for any of the groups. In contrast, apolipoprotein C-III was significantly decreased by 12.3% only in the WALK group (P < .05). Low-density lipoprotein receptor mRNA abundance was increased for all groups after the intervention (P < .001). There was a significant group effect for plasma leptin (P = .026). Plasma concentrations increased for RAISIN and RAISIN + WALK. Similarly, plasma ghrelin concentrations were elevated postintervention for both groups consuming raisins (P < .05). These data suggest that walking and raisin consumption decrease plasma LDL cholesterol by up-regulating the LDL receptor and that raisin consumption may reduce hunger and affect dietary intake by altering hormones influencing satiety.

59. Puglisi MJ, Vaishnav U, Shrestha S, Torres-Gonzalez M, Wood RJ, Volek JS, Fernandez ML. Raisins and additional walking have distinct effects on plasma lipids and inflammatory cytokines. Lipids Health Dis. 2008 Apr 16;7:14.

Raisins are a significant source of dietary fiber and polyphenols, which may reduce cardiovascular disease (CVD) risk by affecting lipoprotein metabolism and inflammation. Walking represents a low intensity exercise intervention that may also reduce CVD risk. The purpose of this study was to determine the effects of consuming raisins, increasing steps walked, or a combination of these interventions on blood pressure, plasma lipids, glucose, insulin and inflammatory cytokines.

Thirty-four men and postmenopausal women were matched for weight and gender and randomly assigned to consume 1 cup raisins/d (RAISIN), increase the amount of steps walked/d (WALK) or a combination of both interventions (RAISINS + WALK). The subjects completed a 2 wk run-in period, followed by a 6 wk intervention. Systolic blood pressure was reduced for all subjects ($P = 0.008$). Plasma total cholesterol was decreased by 9.4% for all subjects ($P < 0.005$), which was explained by a 13.7% reduction in plasma LDL cholesterol (LDL-C) ($P < 0.001$). Plasma triglycerides (TG) concentrations were decreased by 19.5% for WALK ($P < 0.05$ for group effect). Plasma TNF-alpha was decreased from 3.5 ng/L to 2.1 ng/L for RAISIN ($P < 0.025$ for time and group x time effect). All subjects had a reduction in plasma sICAM-1 ($P < 0.01$).

This research shows that simple lifestyle modifications such as adding raisins to the diet or increasing steps walked have distinct beneficial effects on CVD risk.

60. Sudano I, Flammer AJ, Roas S, Enseleit F, Ruschitzka F, Corti R, Noll G. Curr Hypertens Rep. 2012 Aug;14(4):279-84. Cocoa, blood pressure, and vascular function.

The consumption of a high amount of fruits and vegetables was found to be associated with a lower risk of coronary heart disease and stroke. Epidemiologically, a similar relationship has been found with cocoa, a naturally polyphenol-rich food. Obviously, double blind randomized studies are difficult to perform with cocoa and chocolate, respectively. However, intervention studies strongly suggest that cocoa has several beneficial effects on cardiovascular health, including the lowering of blood pressure, the improvement of vascular function and glucose metabolism, and the reduction of platelet aggregation and adhesion. Several potential mechanisms through which cocoa might exert its positive effects have been proposed, among them activation of nitric oxide synthase, increased bioavailability of nitric oxide as well as antioxidant, and anti-inflammatory properties. It is the aim of this review to summarize the findings of cocoa and chocolate on blood pressure and vascular function.

61. Zomer E, Owen A, Magliano DJ, Liew D, Reid CM. BMJ. 2012 May 30;344:e3657. The effectiveness and cost effectiveness of dark chocolate consumption as prevention therapy in people at high risk of cardiovascular disease: best case scenario analysis using a Markov model.

The objective was to model the long term effectiveness and cost effectiveness of daily dark chocolate consumption in a population with metabolic syndrome at high risk of cardiovascular disease using data from the Australian Diabetes, Obesity and Lifestyle study. 2013 people with hypertension who met the criteria for metabolic syndrome, with no history of cardiovascular disease and not receiving antihypertensive therapy were included in the study. Treatment effects associated with dark chocolate consumption derived from published meta-analyses were used to determine the absolute number of cardiovascular events with and without treatment. Costs associated with cardiovascular events and treatments were applied to determine the potential amount of funding required for dark chocolate therapy to be considered cost effective.

Daily consumption of dark chocolate (polyphenol content equivalent to 100 g of dark chocolate) can reduce cardiovascular events by 85 (95% confidence interval 60 to 105) per 10,000 population treated over 10 years. $A40 (£25; €31; $42) could be cost effectively spent per person per year on prevention strategies using dark chocolate. These results assume 100% compliance and represent a best case scenario.

The blood pressure and cholesterol lowering effects of dark chocolate consumption are beneficial in the prevention of cardiovascular events in a population with metabolic syndrome. Daily dark chocolate consumption could be an effective cardiovascular preventive strategy in this population.

62. Monahan KD. Arch Biochem Biophys. 2012 Nov 15;527(2):90-4. Effect of cocoa/chocolate ingestion on brachial artery flow-mediated dilation and its relevance to cardiovascular health and disease in humans.

Prospective studies indicate that high intake of dietary flavanols, such as those contained in cocoa/chocolate, are associated with reduced rates of cardiovascular-related morbidity and mortality in humans. Numerous mechanisms may underlie these associations such as favorable effects of flavanols on blood pressure, platelet aggregation, thrombosis, inflammation, and the vascular endothelium. The brachial artery flow-mediated dilation (FMD) technique has emerged as a robust method to quantify endothelial function in humans.

Collectively, the preponderance of evidence indicates that FMD is a powerful surrogate measure for firm cardiovascular endpoints, such as cardiovascular-related mortality, in humans. Thus, literally thousands of studies have utilized this technique to document group differences in FMD, as well as to assess the effects of various interventions on FMD. In regards to the latter, numerous studies indicate that both acute and chronic ingestion of cocoa/chocolate increases FMD in humans. Increases in FMD after cocoa/chocolate ingestion appear to be dose-dependent such that greater increases in FMD are observed after ingestion of larger quantities. The mechanisms underlying these responses are likely diverse, however most data suggest an effect of increased nitric oxide bioavailability. Thus, positive vascular effects of cocoa/chocolate on the endothelium may underlie (i.e., be linked mechanistically to) reductions in cardiovascular risk in humans.

63. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A. Am J Clin Nutr. 2012 Mar;95(3):740-51. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials.

There is substantial interest in chocolate and flavan-3-ols for the prevention of cardiovascular disease (CVD). The objective of this study was to systematically review the effects of chocolate, cocoa, and flavan-3-ols on major CVD risk factors. We searched Medline, EMBASE, and Cochrane databases for randomized controlled trials (RCTs) of chocolate, cocoa, or flavan-3-ols. We contacted authors for additional data and conducted duplicate assessment of study inclusion, data extraction, validity, and random-effects meta-analyses. We included 42 acute or short-term chronic (≤18 wk) RCTs that comprised 1297 participants. Insulin resistance (HOMA-IR: -0.67; 95% CI: -0.98, -0.36) was improved by chocolate or cocoa due to significant reductions in serum insulin. Flow-mediated dilatation (FMD) improved after chronic (1.34%; 95% CI: 1.00%, 1.68%) and acute (3.19%; 95% CI: 2.04%, 4.33%) intakes. Effects on HOMA-IR and FMD remained stable to sensitivity analyses. We observed reductions in diastolic blood pressure (BP; -1.60 mm Hg; 95% CI: -2.77, -0.43 mm Hg) and mean arterial pressure (-1.64 mm Hg; 95% CI: -3.27, -0.01 mm Hg) and marginally significant effects on LDL (-0.07 mmol/L; 95% CI: -0.13, 0.00 mmol/L) and HDL (0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L) cholesterol. Chocolate or cocoa improved FMD regardless of the dose consumed, whereas doses >50 mg epicatechin/d resulted in greater effects on systolic and diastolic BP. GRADE (Grading of Recommendations, Assessment, Development and Evaluation, a tool to assess quality of evidence and strength of recommendations) suggested low- to moderate-quality evidence of beneficial effects, with no suggestion of negative effects. The strength of evidence was lowered due to unclear reporting for allocation concealment, dropouts, missing data on outcomes, and heterogeneity in biomarker results in some studies.

We found consistent acute and chronic benefits of chocolate or cocoa on FMD and previously unreported promising effects on insulin and HOMA-IR. Larger, longer-duration, and independently funded trials are required to confirm the potential cardiovascular benefits of cocoa flavan-3-ols.

64. Curtis PJ, Sampson M, Potter J, Dhatariya K, Kroon PA, Cassidy A. Diabetes Care. 2012 Feb;35(2):226-32. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: a 1-year, double-blind, randomized, controlled trial.

Despite being medicated, patients with type 2 diabetes have elevated CVD risk, particularly postmenopausal women. Although dietary flavonoids have been shown to reduce CVD risk factors in healthy participants, no long-term trials have examined the additional benefits of flavonoids to CVD risk in medicated postmenopausal women with type 2 diabetes. We conducted a parallel-design, placebo-controlled trial with type 2 diabetic patients randomized to consume 27 g/day (split dose) flavonoid-enriched chocolate (containing 850 mg flavan-3-ols [90 mg epicatechin] and 100 mg isoflavones [aglycone equivalents)]/day) or matched placebo for 1 year. Ninety-three patients completed the trial, and adherence was high (flavonoid 91.3%; placebo 91.6%). Compared with the placebo group, the combined flavonoid intervention resulted in a significant reduction in estimated peripheral insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR] -0.3 ± 0.2; P = 0.004) and improvement in insulin sensitivity (quantitative insulin sensitivity index [QUICKI] 0.003 ± 0.00; P = 0.04) as a result of a significant decrease in insulin levels (-0.8 ± 0.5 mU/L; P = 0.02). Significant reductions in total cholesterol:HDL-cholesterol (HDL-C) ratio (-0.2 ± 0.1; P = 0.01) and LDL-cholesterol (LDL-C) (-0.1 ± 0.1 mmol/L; P = 0.04) were also observed. Estimated 10-year total coronary heart disease risk (derived from UK Prospective Diabetes Study algorithm) was attenuated after flavonoid intervention (flavonoid +0.1 ± 0.3 vs. placebo 1.1 ± 0.3; P = 0.02). No effect on blood pressure, HbA(1c), or glucose was observed.

One-year intervention with flavan-3-ols and isoflavones improved biomarkers of CVD risk, highlighting the additional benefit of flavonoids to standard drug therapy in managing CVD risk in postmenopausal type 2 diabetic patients.

65. Tokede OA, Gaziano JM, Djoussé L. Eur J Clin Nutr. 2011 Aug;65(8):879-86. Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis.

Cocoa products, which are rich sources of flavonoids, have been shown to reduce blood pressure and the risk of cardiovascular disease. Dark chocolate contains saturated fat and is a source of dietary calories; consequently, it is important to determine whether consumption of dark chocolate adversely affects the blood lipid profile. The objective was to examine the effects of dark chocolate/cocoa product consumption on the lipid profile using published trials. A detailed literature search was conducted via MEDLINE (from 1966 to May 2010), CENTRAL and ClinicalTrials.gov for randomized controlled clinical trials assessing the effects of flavanol-rich cocoa products or dark chocolate on lipid profile. The primary effect measure was the difference in means of the final measurements between the intervention and control groups. In all, 10 clinical trials consisting of 320 participants were included in the analysis. Treatment duration ranged from 2 to 12 weeks. Intervention with dark chocolate/cocoa products significantly reduced serum low-density lipoprotein (LDL) and total cholesterol (TC) levels (differences in means (95% CI) were -5.90 mg/dl (-10.47, -1.32 mg/dl) and -6.23 mg/dl (-11.60, -0.85 mg/dl), respectively). No statistically significant effects were observed for high-density lipoprotein (HDL) (difference in means (95% CI): -0.76 mg/dl (-3.02 to 1.51 mg/dl)) and triglyceride (TG) (-5.06 mg/dl (-13.45 to 3.32 mg/dl)). These data are consistent with beneficial effects of dark chocolate/cocoa products on total and LDL cholesterol and no major effects on HDL and TG in short-term intervention trials.

66. Shrime MG, Bauer SR, McDonald AC, Chowdhury NH, Coltart CE, Ding EL. J Nutr. 2011 Nov;141(11):1982-8. Flavonoid-rich cocoa consumption affects multiple cardiovascular risk factors in a meta-analysis of short-term studies.

A growing body of evidence suggests that the consumption of foods rich in polyphenolic compounds, particularly cocoa, may have cardioprotective effects. No review, however, has yet examined the effect of flavonoid-rich cocoa (FRC) on all major cardiovascular risk factors or has examined potential dose-response relationships for these effects. A systematic review and meta-analysis of randomized, controlled trials was performed to evaluate the effect of FRC on cardiovascular risk factors and to assess a dose-response relationship. Inclusion and exclusion criteria as well as dependent and independent variables were determined a priori. Data were collected for: blood pressure, pulse, total cholesterol, HDL cholesterol, LDL cholesterol, TG, BMI, C-reactive protein, flow-mediated vascular dilation (FMD), fasting glucose, fasting insulin, serum isoprostane, and insulin sensitivity/resistance indices. Twenty-four papers, with 1106 participants, met the criteria for final analysis. In response to FRC consumption, systolic blood pressure decreased by 1.63 mm Hg (P = 0.033), LDL cholesterol decreased by 0.077 mmol/L (P = 0.038), and HDL cholesterol increased by 0.046 mmol/L (P = 0.037), whereas total cholesterol, TG, and C-reactive protein remained the same. Moreover, insulin resistance decreased (HOMA-IR: -0.94 points; P < 0.001), whereas FMD increased (1.53%; P < 0.001). A nonlinear dose-response relationship was found between FRC and FMD (P = 0.004), with maximum effect observed at a flavonoid dose of 500 mg/d; a similar relationship may exist with HDL cholesterol levels (P = 0.06). FRC consumption significantly improves blood pressure, insulin resistance, lipid profiles, and FMD. These short-term benefits warrant larger long-term investigations into the cardioprotective role of FRC.

67. Buitrago-Lopez A, Sanderson J, Johnson L, Warnakula S, Wood A, Di Angelantonio E, Franco OH. BMJ. 2011 Aug 26;343:d4488. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis.

To evaluate the association of chocolate consumption with the risk of developing cardiometabolic disorders through a systematic review and meta-analysis of randomised controlled trials and observational studies. From 4576 references seven studies met the inclusion criteria (including 114,009 participants). None of the studies was a randomised trial, six were cohort studies, and one a cross sectional study. Large variation was observed between these seven studies for measurement of chocolate consumption, methods, and outcomes evaluated. Five of the seven studies reported a beneficial association between higher levels of chocolate consumption and the risk of cardiometabolic disorders. The highest levels of chocolate consumption were associated with a 37% reduction in cardiovascular disease (relative risk 0.63 (95% confidence interval 0.44 to 0.90)) and a 29% reduction in stroke compared with the lowest levels.

Based on observational evidence, levels of chocolate consumption seem to be associated with a substantial reduction in the risk of cardiometabolic disorders. Further experimental studies are required to confirm a potentially beneficial effect of chocolate consumption.

68. Westphal S, Luley C. Heart Vessels. 2011 Sep;26(5):511-5. Flavanol-rich cocoa ameliorates lipemia-induced endothelial dysfunction.

Consumption of flavanols improves chronic endothelial dysfunction. We investigated whether it can also improve acute lipemia-induced endothelial dysfunction. In this randomized, placebo-controlled, double-blind, crossover trial, 18 healthy subjects received a fatty meal with cocoa either rich in flavanols (918 mg) or flavanol-poor. Flow-mediated dilation (FMD), triglycerides, and free fatty acids were then determined over 6 h. After the flavanol-poor fat loading, the FMD deteriorated over 4 h. The consumption of flavanol-rich cocoa, in contrast, improved this deterioration in hours 2, 3, and 4 without abolishing it completely. Flavanols did not have any influence on triglycerides or on free fatty acids. Flavanol-rich cocoa can alleviate the lipemia-induced endothelial dysfunction, probably through an improvement in endothelial NO synthase.

69. Djoussé L, Hopkins PN, North KE, Pankow JS, Arnett DK, Ellison RC. Clin Nutr. 2011 Apr;30(2):182-7. Chocolate consumption is inversely associated with prevalent coronary heart disease: the National Heart, Lung, and Blood Institute Family Heart Study.

Epidemiologic studies have suggested beneficial effects of flavonoids on cardiovascular disease. Cocoa and particularly dark chocolate are rich in flavonoids and recent studies have demonstrated blood pressure lowering effects of dark chocolate. However, limited data are available on the association of chocolate consumption and the risk of coronary heart disease (CHD). We sought to examine the association between chocolate consumption and prevalent CHD. We studied in a cross-sectional design 4970 participants aged 25-93 years who participated in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. Chocolate intake was assessed through a semi-quantitative food frequency questionnaire. We used generalized estimating equations to estimate adjusted odds ratios.

Compared to subjects who did not report any chocolate intake, odds ratios (95% CI) for CHD were 1.01 (0.76-1.37), 0.74 (0.56-0.98), and 0.43 (0.28-0.67) for subjects consuming 1-3 times/month, 1-4 times/week, and 5+ times/week, respectively (p for trend <0.0001) adjusting for age, sex, family CHD risk group, energy intake, education, non-chocolate candy intake, linolenic acid intake, smoking, alcohol intake, exercise, and fruit and vegetables. Consumption of non-chocolate candy was associated with a 49% higher prevalence of CHD comparing 5+/week vs. 0/week [OR = 1.49 (0.96-2.32)].

These data suggest that consumption of chocolate is inversely related with prevalent CHD in a general United States population.

70. Djoussé L, Hopkins PN, Arnett DK, Pankow JS, Borecki I, North KE, Curtis Ellison R. Clin Nutr. 2011 Feb;30(1):38-43. Chocolate consumption is inversely associated with calcified atherosclerotic plaque in the coronary arteries: the NHLBI Family Heart Study.

While a diet rich in anti-oxidant has been favorably associated with coronary disease and hypertension, limited data have evaluated the influence of such diet on subclinical disease. Thus, we sought to examine whether chocolate consumption is associated with calcified atherosclerotic plaque in the coronary arteries (CAC). In a cross-sectional design, we studied 2217 participants of the NHLBI Family Heart Study. Chocolate consumption was assessed by a semi-quantitative food frequency questionnaire and CAC was measured by cardiac CT. We defined prevalent CAC using an Agatston score of at least 100 and fitted generalized estimating equations to calculate prevalence odds ratios of CAC.

There was an inverse association between frequency of chocolate consumption and prevalent CAC. Odds ratios (95% CI) for CAC were 1.0 (reference), 0.94 (0.66-1.35), 0.78 (0.53-1.13), and 0.68 (0.48-0.97) for chocolate consumption of 0, 1-3 times per month, once per week, and 2+ times per week, respectively (p for trend 0.022), adjusting for age, sex, energy intake, waist-hip ratio, education, smoking, alcohol consumption, ratio of total-to-HDL-cholesterol, non-chocolate candy, and diabetes mellitus. Controlling for additional confounders did not alter the findings. Exclusion of subjects with coronary heart disease or diabetes mellitus did not materially change the odds ratio estimates but did modestly decrease the overall significance (p = 0.07).

These data suggest that chocolate consumption might be inversely associated with prevalent CAC.

71. Buijsse B, Feskens EJM, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen elderly study. Arch Intern Med 2006;166:411-7.

Small, short-term, intervention studies indicate that cocoa-containing foods improve endothelial function and reduce blood pressure. We studied whether habitual cocoa intake was cross-sectionally related to blood pressure and prospectively related with cardiovascular mortality. Data used were of 470 elderly men participating in the Zutphen Elderly Study and free of chronic diseases at baseline. Blood pressure was measured at baseline and 5 years later, and causes of death were ascertained during 15 years of follow-up. Habitual food consumption was assessed by the cross-check dietary history method in 1985, 1990, and 1995. Cocoa intake was estimated from the consumption of cocoa-containing foods.

One third of the men did not use cocoa at baseline. The median cocoa intake among users was 2.11 g/d. After adjustment, the mean systolic blood pressure in the highest tertile of cocoa intake was 3.7 mm Hg lower (95% confidence interval [CI], -7.1 to -0.3 mm Hg; P = .03 for trend) and the mean diastolic blood pressure was 2.1 mm Hg lower (95% CI, -4.0 to -0.2 mm Hg; P = .03 for trend) compared with the lowest tertile. During follow-up, 314 men died, 152 of cardiovascular diseases. Compared with the lowest tertile of cocoa intake, the adjusted relative risk for men in the highest tertile was 0.50 (95% CI, 0.32-0.78; P = .004 for trend) for cardiovascular mortality and 0.53 (95% CI, 0.39-0.72; P < .001) for all-cause mortality.

In a cohort of elderly men, cocoa intake is inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality.

72. Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. J Hypertens 2003;21:2281-6.

Consumption of flavonoid-rich beverages, including tea and red wine, has been associated with a reduction in coronary events, but the physiological mechanism remains obscure. Cocoa can contain extraordinary concentrations of flavanols, a flavonoid subclass shown to activate nitric oxide synthase in vitro. The study prospectively assessed the effects of Flavanol-rich cocoa, using both time and beverage controls. Participants were blinded to intervention; the endpoint was objective and blinded.

Pulse wave amplitude was measured on the finger in 27 healthy people with a volume-sensitive validated calibrated plethysmograph, before and after 5 days of consumption of Flavanol-rich cocoa [821 mg of flavanols/day, quantitated as (-)-epicatechin, (+)-catechin, and related procyanidin oligomers]. The specific nitric oxide synthase inhibitor, NG-nitro-L-arginine methyl ester (L-NAME) was infused intravenously on day 1, before cocoa, and on day 5, after an acute ingestion of cocoa.

Four days of flavanol-rich cocoa induced consistent and striking peripheral vasodilation (P = 0.009). On day 5, pulse wave amplitude exhibited a large additional acute response to cocoa (P = 0.01). L-NAME completely reversed this vasodilation (P = 0.004). In addition, intake of flavanol-rich cocoa augmented the vasodilator response to ischemia. Flavanol-poor cocoa induced much smaller responses (P = 0.005), and none was induced in the time-control study. Flavanol-rich cocoa also amplified the systemic pressor effects of L-NAME (P = 0.005).

In healthy humans, flavanol-rich cocoa induced vasodilation via activation of the nitric oxide system, providing a plausible mechanism for the protection that flavanol-rich foods induce against coronary events.

73. Grassi D, Necozione S, Lippi C, et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 2005;46:398-405.

Consumption of flavanol-rich dark chocolate (DC) has been shown to decrease blood pressure (BP) and insulin resistance in healthy subjects, suggesting similar benefits in patients with essential hypertension (EH). Therefore, we tested the effect of DC on 24-hour ambulatory BP, flow-mediated dilation (FMD), and oral glucose tolerance tests (OGTTs) in patients with EH. After a 7-day chocolate-free run-in phase, 20 never-treated, grade I patients with EH (10 males; 43.7+/-7.8 years) were randomized to receive either 100 g per day DC (containing 88 mg flavanols) or 90 g per day flavanol-free white chocolate (WC) in an isocaloric manner for 15 days. After a second 7-day chocolate-free period, patients were crossed over to the other treatment. Noninvasive 24-hour ambulatory BP, FMD, OGTT, serum cholesterol, and markers of vascular inflammation were evaluated at the end of each treatment. The homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and insulin sensitivity index (ISI) were calculated from OGTT values. Ambulatory BP decreased after DC (24-hour systolic BP -11.9+/-7.7 mm Hg, P<0.0001; 24-hour diastolic BP -8.5+/-5.0 mm Hg, P<0.0001) but not WC. DC but not WC decreased HOMA-IR (P<0.0001), but it improved QUICKI, ISI, and FMD. DC also decreased serum LDL cholesterol (from 3.4+/-0.5 to 3.0+/-0.6 mmol/L; P<0.05). In summary, DC decreased BP and serum LDL cholesterol, improved FMD, and ameliorated insulin sensitivity in hypertensives. These results suggest that, while balancing total calorie intake, flavanols from cocoa products may provide some cardiovascular benefit if included as part of a healthy diet for patients with EH.