Review

Dietary Effects on Cardiovascular Disease Risk Factors: Beyond Saturated Fatty Acids and Cholesterol

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Hypercholesterolemia represents a significant risk for cardiovascular disease (CVD). While diet intervention remains the initial choice for the prevention and treatment of CVD, the nature of the dietary modification remains controversial. For example, reducing calories from total fat, without decreasing saturated fat intake results in insignificant changes in low density lipoprotein cholesterol (LDL-C). Similarly, diet interventions that focus solely on lowering dietary cholesterol and saturated fat intake not only decrease LDL-C, but also high density lipoprotein cholesterol (HDL-C) and therefore may not improve the lipoprotein profile. This brief review summarizes dietary interventions that lower LDL-C without affecting HDL-C levels. These interventions include soy protein, soluble fiber, soy lecithin and plant sterols. This review also includes some of the reported dietary interventions, such as polyphenols, isoflavones, folic acid and vitamins B_6 and B_{12}, which reduce the risk of CVD without changes in lipoprotein cholesterol.

Key teaching points:

- Hypercholesterolemia is one of several risk factors for coronary heart disease (CHD).
- Dietary interventions should be designed to produce optimal lipoprotein profiles which decrease LDL-C without reductions in HDL-C.
- In general, dietary interventions which focus on reducing saturated fatty acids and cholesterol lower both LDL-C and HDL-C, thereby not improving the lipoprotein profile.
- Interventions including soy protein, soluble fiber, soy lecithin and plant sterols, especially sterol or stanol esters, are nutrients which reduce LDL-C without associated reductions in HDL-C and may be prescribed for individuals with low HDL-C.
- Polyphenols in fruits, vegetables and minimally-processed vegetable oils are antioxidants which could reduce the incidence and severity of CHD.
- Recent intervention studies which utilize vitamin E supplements have not demonstrated efficacy in humans as it relates to preventing or treating CHD.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in the United States. High blood cholesterol, which affects more than 90 million adults, is a risk factor for this disease. To lower blood cholesterol levels and the risk for CHD, diets reduced in saturated fat and cholesterol and increased in unsaturated fat are recommended [1–5]. The American Heart Association's recently revised dietary guidelines advocate a population-wide limitation of saturated fat to <10% of energy and cholesterol <300 mg/day to reduce the risk for CHD [1]. Most saturated fats (SFA) increase serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C); polyunsaturated fatty acids (PUFA) lower serum cholesterol concentrations [6]; and monounsaturated fats (MUFA) either lower [3] or have no influence on plasma TC or LDL-C [6].

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For many individuals, a mean reduction of 10% in plasma cholesterol, as noted in the Adult Treatment Panel (ATP) II report of the National Cholesterol Education Program (NCEP) Expert Panel, is insufficient to avoid drug intervention [2]. Equally important, dietary interventions that focus on reducing dietary saturated fat and cholesterol can also reduce high density lipoprotein cholesterol (HDL-C) concentrations, thereby failing to improve the lipoprotein profile, i.e., TC/HDL-C or LDL-C/HDL-C ratios [7,8].

DIETARY INTERVENTIONS FOCUSING ON LOWERING BLOOD CHOLESTEROL LEVELS

As discussed below, several dietary interventions have been demonstrated to lower plasma total cholesterol, predominantly LDL-C, without affecting HDL-C levels.

Soy Protein

According to many reports, consuming a diet high in vegetable products versus animal products reduces plasma cholesterol concentrations and risk for developing CHD [9–11]. Dietary plant proteins such as soy protein appear to lower plasma cholesterol concentrations in humans and animals [9,12,13], although the mechanism by which soy protein lowers blood cholesterol levels remains unclear. According to one hypothesis, soy protein's effect on serum cholesterol concentrations is due largely to its amino acid composition. However, in studies in which amino acids patterned after soy protein or casein were fed to experimental animals, other nonprotein components present in soy appeared to be partially responsible for this protein's hypocholesterolemic effect [14].

A number of non-amino acid components in soy products, in particular phytoestrogens, have been associated with lowering blood lipids. In studies of nonhuman primates conducted by Anthony *et al.* [15], alcohol-extracted soy protein, from which phytoestrogens have been removed, was less effective at lowering plasma cholesterol levels and preventing the development of atherosclerosis than water-washed soy protein diets. Similar studies in humans by Crouse *et al.* [16] demonstrated that isolated soy protein containing 62 mg of isoflavones fed to hypercholesterolemic individuals resulted in reductions of 9% and 10%, respectively, for TC and LDL-C compared to casein-fed individuals.

Soluble Fibers

According to studies in laboratory rats, diets containing high amounts of soluble fibers such as pectin, guar gum and oat bran, as well as viscous non-fermentable fibers such as psyllium, can lower plasma cholesterol concentrations in rats when fed up to 60 g/kg diet/day (Fig. 1) [17]. These diets not only are effective at lowering plasma LDL-C concentrations, but they do so without affecting HDL-C levels [17]. This same group of investigators also demonstrated in human studies that oat bran feeding relative to wheat bran was associated with a 12% decrease in LDL-C without any significant changes in HDL-C [18]. A recent study from our laboratory demonstrated that Fibercel,™ a high β-glucan-containing fiber isolated from yeast cell walls, resulted in a 7% to 9% decrease in TC and LDL-C, respectively, when fed to hypercholesterolemic humans at 15 g/day (Fig. 2) [19].

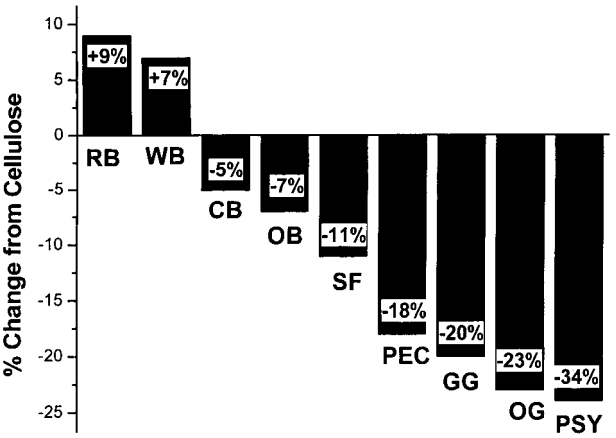

Fig. 1. Effect of rice bran (RB), wheat bran (WB), corn bran (CB), oat bran (OB), soy fiber (SF), pectin (PEC), guar gum (GG), oat gum (OG) and psyllium (PSY) on serum cholesterol levels in rats. The soluble and viscous fibers SF, PEC, GG, OG, and PSY produce significant cholesterol-lowering in rats [17].

Lecithin

Several studies indicate that lecithin, a phosphatidylcholine-containing phospholipid, has hypocholesterolemic properties.

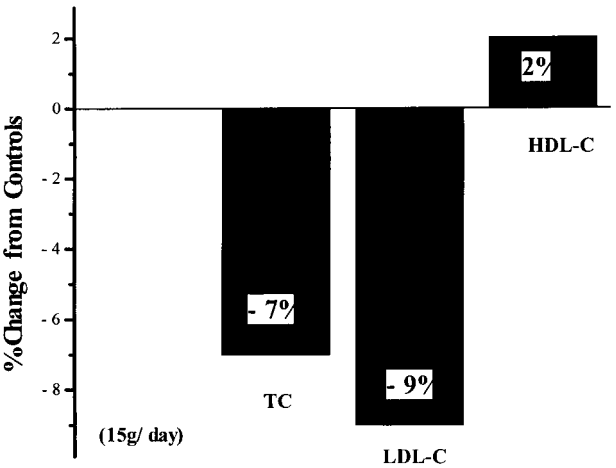

Fig. 2. Effect of Fibercel™ on lipoprotein cholesterol levels in humans. A dose of 15 g/day of this high β-glucan fiber was associated with 7% to 9% reductions in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) without significantly affecting HDL-C [19].

Data on its hypocholesterolemic properties, however, are inconsistent, possibly as a result of differences in the degree of initial hypercholesterolemia of the population studied, and/or the type and level of lecithin fed. For example, the cholesterol-lowering effects of lecithin have been mainly observed in hyperlipidemic animals [20–23] and humans [24–26] and not in animals or humans with normal blood lipid levels [25,27]. Lecithin-induced reductions in LDL-C were not associated with changes in HDL-C. One remarkable study [26] found that feeding 10 g/day of lecithin to very hypercholesterolemic individuals resulted in a 36% reduction of LDL-C and a 46% increase in HDL-C. The underlying mechanism(s) for the hypocholesterolemic effect of lecithin in hypercholesterolemic individuals has yet to be elucidated. While our studies in hamsters and monkeys [22] indicate a cholesterol-lowering effect of lecithin beyond its linoleate content, this finding remains controversial.

Plant Sterols (Stanol/Sterol Esters)

The cholesterol-lowering effect of phytosterols has been studied since the 1950s and is well known [28]. Phytosterols interfere with the uptake of both dietary and biliary cholesterol from the intestinal tract in humans [29]. The mechanism(s) for this activity is not well known. However, phytosterols appear to decrease the solubility of cholesterol in the oil and micellar phases, thus displacing cholesterol from bile salt micelles and interfering with its absorption [30]. Phytosterols differ from cholesterol by the presence of an extra methyl or ethyl group on the cholesterol side chain [31]. The major dietary phytosterols are sitosterol, campesterol, and stigmasterol. The most common dietary phytostanol, sitostanol, is a saturated derivative of sitosterol [32].

Studies in animals [33–36] and humans [37–48] have demonstrated the predominant LDL cholesterol-lowering effects of plant sterols, in particular sterol and stanol esters, without accompanying alterations in HDL-C levels. Earlier studies in humans indicated that the stanols were more effective than the sterols [37–39]. However, in many of these studies, crystalline preparations of the sterols and stanols were used in the free, unesterified form and incorporated into oil or margarine-like vehicles. More recent human studies [39,49] indicate that both plant stanol and sterol esters are equally efficacious in reducing LDL-C (Fig. 3). The mechanism(s) of action is reported to be inhibition of cholesterol absorption [28–30,35,36,38,46,47].

Rice Bran Oil

For several years, it has been known that rice bran oil contains unsaponifiables that are poorly absorbed and characterized as ferulate esters of triterpene alcohols. In a human feeding trial comparing several vegetable oils [50], rice bran oil consumption was associated with significant LDL-C lowering when compared to an olive oil-containing diet (Fig. 4). Similarly, corn fiber oil containing both fatty acid and ferulate esters

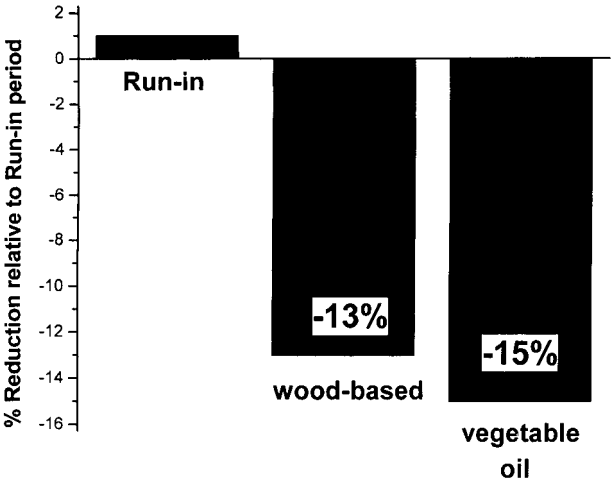

Fig. 3. Stanol ester effects on LDL-C. Stanol esters produced from either a wood-based or a vegetable oil source give comparable low density lipoprotein cholesterol (LDL-C) lowering in humans [39].

of stanols had significant cholesterol-lowering activity in hamsters (Fig. 5) that was associated with increased fecal cholesterol excretion (Fig. 6) [51].

NUTRIENTS INFLUENCING CARDIOVASCULAR DISEASE RISK INDEPENDENT OF BLOOD CHOLESTEROL-LOWERING

Up until now, our focus has been on nutrients that affect elevated cholesterol as the predominant risk factor for cardiovascular disease (CVD). However, some nutrients can dramatically influence CVD risk independent of their cholesterol-lowering effects.

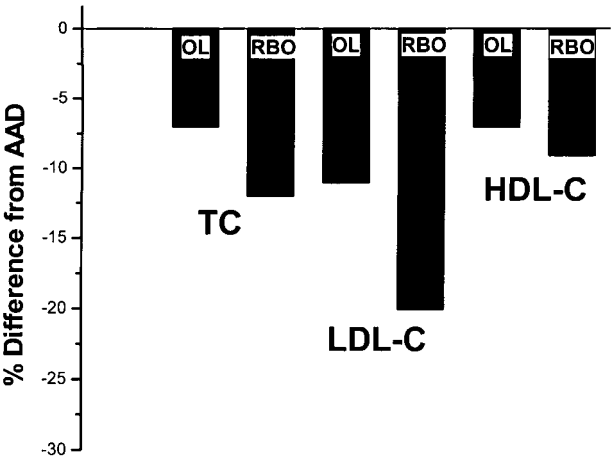

Fig. 4. Comparative effects of olive oil (OL) and rice bran oil (RBO) substitution on lipoprotein cholesterol levels in humans consuming an average American diet (AAD). RBO feeding significantly reduced total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) relative to OL feeding [50].

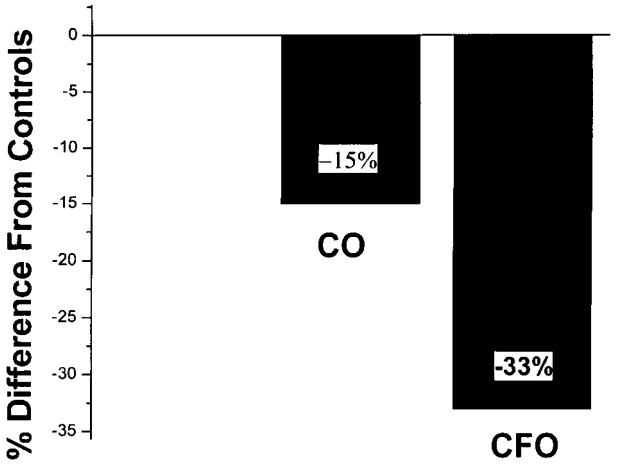

Fig. 5. Comparative effects of corn oil (CO) and corn fiber oil (CFO) on non-HDL-C in hamsters. CFO feeding was twofold greater in reducing non-HDL-C compared to corn oil [51].

Flavonoids

Epidemiological studies in Zutphen by Hertog *et al.* [52] demonstrate an inverse association between the flavonoid content of fruits, vegetables, and beverages and risk for CHD. A nearly 50% reduction in relative risk for CHD and incidence of first myocardial infarction was found between individuals consuming the highest and lowest tertiles of flavonoids (Fig. 7). Flavonoids are naturally occurring, water-soluble anti-oxidant substances found in fruits, vegetables, and beverages such as tea and wine.

Isoflavones

A recent review article [53] summarizes evidence indicating that isoflavones from soy protein may reduce cardiovascular disease risk. Potential mechanisms, in addition to the reported cholesterol-lowering activity of the isoflavones, genistein and daidzein, include their effects on estrogenic activity, thyroxine activity, anti-oxidant activity, and arterial compliance.

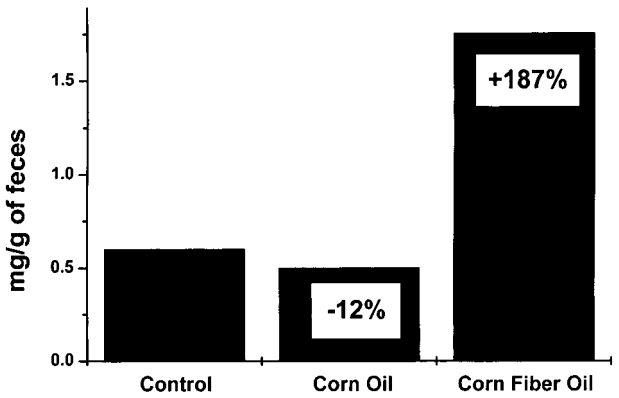

Fig. 6. Fecal cholesterol excretion in hamsters fed corn oil or corn fiber oil. Note the striking increase (+187%) in fecal cholesterol excretion in the hamsters fed corn fiber oil relative to the control or corn oil diet [51].

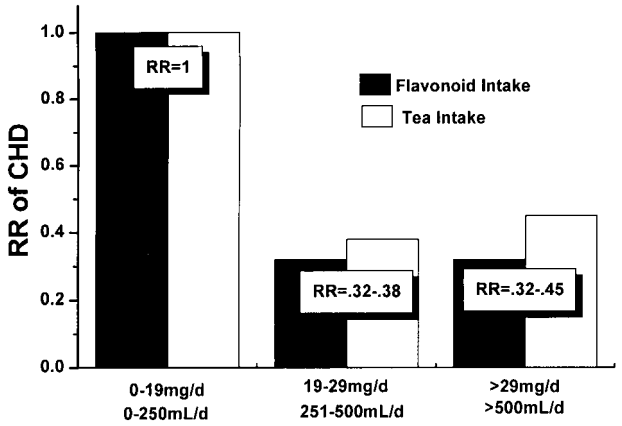

Fig. 7. Effect of flavonoids and tea intake on relative risk (RR) of coronary heart disease (CHD) in the Zutphen Study. Note the 60% decrease in RR in subjects consuming flavonoids and tea [52].

Vitamin E

Evidence for a protective role for vitamin E in CVD is controversial. In general, animal data support the anti-oxidant activity of vitamin E and reduced atherosclerosis [54–56]. Similarly, prospective cohort studies support an inverse association between reported intake of vitamin E and relative risk of CVD in women [57] and men [58]. However, with the exception of one intervention study entitled the Cambridge Heart Anti-Oxidant Study (CHAOS) [59], other investigations have

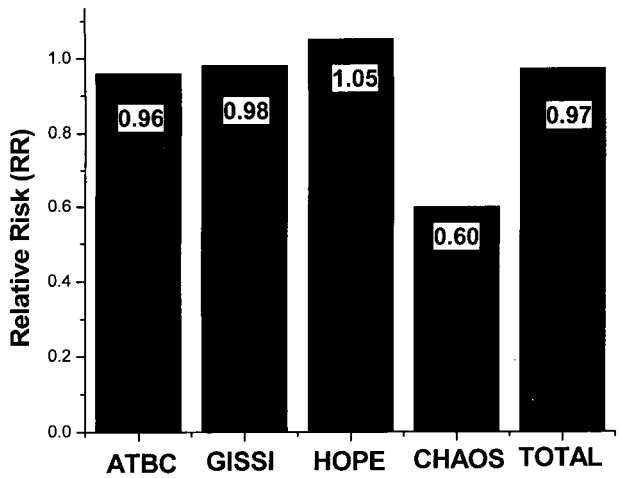

Fig. 8. Effects of vitamin E on relative risk (RR) of myocardial infarcts (MI), stroke or death from cardiovascular disease (CVD). ATBC = Alpha Tocopherol, Beta Carotene Cancer Prevention Study Group; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto miocardico. Hope = Heart Outcomes Prevention Evaluation. CHAOS = Cambridge Heart Antioxidant Study. Note that only the CHAOS study showed an association between vitamin E intake and reduced RR.

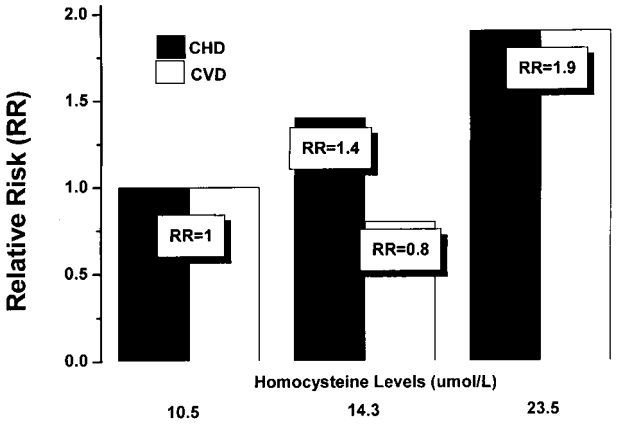

Fig. 9. Relative Risk (RR) for mortality from coronary heart disease (CHD) and cardiovascular disease (CVD) according to tertiles of homocysteinemia. Note the increase in RR at increasing homocysteine levels [65].

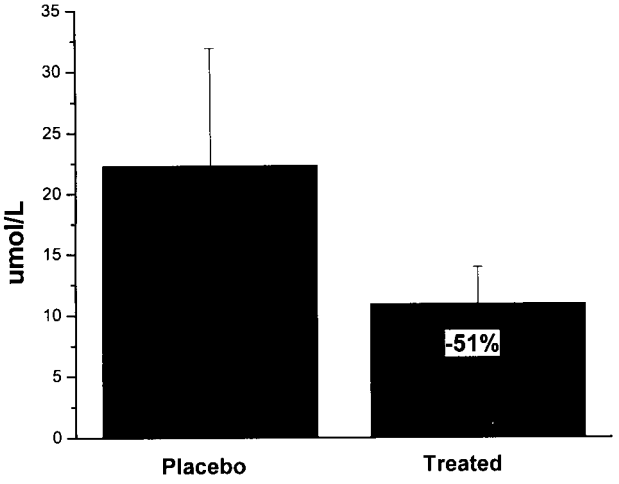

Fig. 10. Effect of folic acid (1 mg/d), vitamin B_6 (10 mg/d) and vitamin B_{12} (0.4 mg/d) on homocysteine levels. The treated group had a 51% reduction in homocysteine levels [69].

failed to demonstrate a protective effect for vitamin E against CVD (Fig. 8) [60–62]. Multiple reasons may explain this inconsistency, including differences in dosages used, time on supplement, primary *vs.* secondary prevention, and outcomes measured.

B Vitamins and Homocysteine Lowering

Evidence supporting hyperhomocysteinemia as an independent risk factor for atherosclerotic disease is growing (Fig. 9) [63–65]. Although the mechanism(s) by which elevated levels of homocysteine increase risk of vascular disease remains to be elucidated, several dietary interventions, including folic acid alone or with various combinations of vitamins B_6 and B_{12}, have been reported to reduce homocysteine levels (Fig. 10) [66–70].

CONCLUSION

Several dietary interventions are reported to have profound effects on hypercholesterolemia and other risk factors associated with CVD. While these dietary interventions have important implications for prevention and treatment of many diseases, the need for more investigations related to their mechanism(s) of action and possible synergistic interactions is recognized.

REFERENCES

1. Krauss RM, Eckel RH, Howard B, et al: AHA dietary guidelines. Revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 102:2284–2299, 2000.
2. NCEP Expert Panel: Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 269:3015–3023, 1993.
3. Mattson FH, Grundy, SM: Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. J Lipid Res 26:194–202, 1985.
4. McDonald BE, Gerrard JM, Bruce VM, Corner EJ: Comparison of the effect of canola oil and sunflower oil on plasma lipids and lipoproteins and on in vivo thromboxane A_2 and prostacyclin production in healthy young men. Am J Clin Nutr 50:1382–1388, 1989.
5. Mensink RP, Katan MB: Effect of a diet enriched with monounsaturated or polyunsaturated fatty acids on levels of low-density and high-density lipoprotein cholesterol in healthy women and men. N Engl J Med 321:436–441, 1989.
6. Hegsted DM, Ausman LM, Johnson JA, Dallal GE: Dietary fat and serum lipids: an evaluation of the experimental data. Am J Clin Nutr 57:875–883, 1993.
7. Barr SL, Ramakrishnan R, Johnson C, Holleran S, Dell RB, Ginsberg HN: Reducing total dietary fat without reducing saturated fatty acids does not significantly lower total plasma cholesterol concentrations in normal males. Am J Clin Nutr 55:675–681, 1992.
8. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Goldin BR, Rasmussen H, McNamara JR, Ordovas JM: Effects of National Cholesterol Education Program Step 2 diets relatively high or relatively low in fish-derived fatty acids on plasma lipoproteins in middle-aged and elderly subjects. Am J Clin Nutr 63:234–241, 1996.
9. Anderson JW, Johnstone BM, Cook-Newell ML: Meta-Analysis of the effects of soy protein intake on serum lipids. N Engl J Med 333:276–282, 1995.
10. Carroll KK: Review of clinical studies on cholesterol-lowering response to soy protein. J Am Dietetic Assoc 91:820–827, 1991.
11. Meinertz H, Nilausen K, Faergeman O: Soy protein and casein in cholesterol-enriched diets: effects on plasma lipoproteins in normolipidemic subjects. Am J Clin Nutr 50:786–793, 1989.
12. Potter SM, Bakhit RM, Essex-Sorlie D, Weingartner KE, Chapman KM, Nelson RA, Prabhudesai M, Savage WD, Nelson AI, Winter LW, Erdman Jr JW: Depression of plasma cholesterol in men by

consumption of baked products containing soy protein. Am J Clin Nutr 58:501–506, 1993.
13. Gooderham MJ, Aldercreutz H, Ojala ST, Wahala K, Holub BJ: A soy protein isolate rich in genistein and daidzein and its effects on plasma isoflavone concentrations, platelet aggregation, blood lipids and fatty acid composition of plasma phospholipid in normal men. J Nutr 126:2000–2006, 1996.
14. Potter SM: Overview of proposed mechanisms for the hypocholesterolemic effect of soy. J Nutr 125(Suppl):606–611, 1995.
15. Anthony MS, Clarkson TB, Bullock BC, Wagner JD: Soy protein versus soy phytoestrogens in the prevention of diet-induced coronary artery atherosclerosis on male cynomolgus monkeys. Arterioscler Thromb Vasc Biol 17:2524–2531, 1997.
16. Crouse JR, Morgan T, Terry JG, Ellis J, Vitolins M, Burke GL: A randomized trial comparing the effect of casein with that of soy protein containing varying amounts of isoflavones on plasma concentrations of lipids and lipoproteins. Arch Intern Med 159:2020–2076, 1999.
17. Anderson JW, Jones AE, Riddell-Mason S: Ten different dietary fibers have significantly different effects on serum and liver lipids of cholesterol-fed rats. J Nutr 124:78–83, 1994.
18. Anderson JW, Spencer DB, Hamilton CC, Smith SF, Tietyen J, Bryant CA, Oeltgen D: Oat bran cereal lowers serum total and LDL cholesterol in hypercholesterolemic men. Am J Clin Nutr 52:495–499, 1990.
19. Nicolosi RJ, Bell SJ, Bistrian BR, Greenberg I, Forse AF, Blackburn GL: Plasma lipid changes after supplementation with β-glucan fiber. Am J Clin Nutr 70:208–212, 1999.
20. Clark SB, Clark VE, Small DM: Effects of lecithin ingestion on plasma and lymph lipoproteins of normo- and hyperlipemic rats. Am J Physiol 241:422–430, 1981.
21. Hunt CE, Duncan LA: Hyperlipoproteinaemia and atherosclerosis in rabbits fed low-level cholesterol and lecithin. Br J Exp Pathol 66:35–46, 1985.
22. Wilson TA, Meservey CM, Nicolosi RJ: Soy lecithin reduces plasma lipoprotein cholesterol and early atherosclerosis in hypercholesterolemic monkeys and hamsters:beyond linoleate. Atherosclerosis 140:147–153, 1998.
23. Wong EK, Nicolosi RJ, Low PA, Herd JA, Hayes K: Lecithin influence on hyperlipemia in rhesus monkeys. Lipids 15:428–433, 1980.
24. Blaton V, Soetewey F, Vandamme D, Declerq B, Peeters H: Effect of polyunsaturated phosphatidylcholine on human types II and IV hyperlipoproteinemias. Artery 2:309–325, 1976.
25. Childs MT, Bowlin JA, Oglivie JT, Hazzard WR, Albers JJ: The contrasting effects of a dietary soya lecithin product and corn oil on lipoprotein lipids in normolipidemic and familial hypercholesterolemic subjects. Atherosclerosis 38:217–222, 1981.
26. Wojcickl J, Pawlik A, Samochawiee L, Katdenska M, Mysliwiec Z: Clinical evaluation of lecithin as a lipid-lowering agent. Short communication. Phytother Res 9:597–599, 1995.
27. Cobb M, Turkki P, Linscheer W, Raheja K: Lecithin supplementation in healthy volunteers. Nutr Metab 24:228–237, 1980.
28. Pollak OJ, Kritchevsky D: Sitosterol. In Clarkson TB, Kritchevsky D, Pollak OJ (eds): "Monographs on Atherosclerosis," vol. 10. Basel (Switzerland):Karger, pp 60–113, 1981.
29. Heinemann T, Kullak-Ublick GA, Pietruck BJ: Mechanisms of action of plant sterols on inhibition of cholesterol absorption. Comparison of sitosterol and sitostanol. Eur J Clin Pharmacol 40(Suppl 1):59S–63S, 1991.
30. Ikeda I, Sugano M: Inhibition of cholesterol absorption by plant sterols for mass intervention. Curr Opin Lipidol 9:527–531, 1998.
31. Jenkins DJA, Kendall CWC: Plant sterols, health claims, and strategies to reduce cardiovascular disease risk. J Am Coll Nutr 18:559–562, 1999.
32. Nguyen TT: The cholesterol-lowering action of plant stanol esters. J Nutr 129:2109–2112, 1999.
33. Sugano M, Morioka H, Ikeda I: A comparison of hypocholesterolemic activity of β-sitosterol and β-sitostanol in rats. J Nutr 107:2011–2019, 1977.
34. Ikeda I, Kawasaki A, Samezima K, Sugano M: Antihypercholesterolemic activity of β-sitostanol in rabbits. J Nutr Sci Vitaminol 27:243–251, 1981.
35. Ikeda I, Sugano M: Comparison of absorption and metabolism of beta-sitosterol and beta-sitostanol in rats. Atherosclerosis 30:227–237, 1978.
36. Ntanios FY, Jones PJH: Dietary sitostanol reciprocally influences cholesterol absorption and biosynthesis in hamsters and rabbits. Atherosclerosis 143:341–351, 1999.
37. Becker M, Staab D, von Bergmann K: Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol. J Pediatr 122:292–296, 1993.
38. Heinemann T, Axtmann G, von Bergmann K: Comparison of intestinal absorption of cholesterol with different plant sterols in man. Eur J Clin Invest 23:827–831, 1993.
39. Westrate JA, Meijer GW: Plant sterol-enriched margarines and reduction of plasma total and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. Eur J Clin Nutr 52:334–343, 1998.
40. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartainen E: Serum cholesterol lowering by sitostanol ester margarine in a mildly hypercholesterolemic random population. N Engl J Med 333:1308–1312, 1995.
41. Williams CL, Bollella MC, Strobino BA, Boccia L, Campanaro L: Plant stanol ester and bran fiber in childhood: effects on lipids, stool weight, and stool frequency in preschool children. J Am Coll Nutr 18:572–581, 1999.
42. Jones PJH, MacDougall DE, Ntanios F, Vanstone CA: Dietary phytosterols as cholesterol-lowering agents in humans. Can J Physiol Pharmacol 75:217–227, 1997.
43. Hallikainen MA, Uusitupa MIJ: Effects of 2 low-fat stanol ester-containing margarines as part of a low-fat diet in hypercholesterolemic subjects. Am J Clin Nutr 69:403–410, 1999.
44. Gylling H, Radhakrishnan R, Miettinen TA: Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine. Circulation 96:4226–4231, 1997.
45. Gylling H, Miettinen TA: Serum cholesterol and cholesterol and lipoprotein metabolism in hypercholesterolaemic NIDDM patients before and during sitostanol ester-margarine treatment. Diabetologia 37:773–780, 1994.
46. Gylling H, Miettinen TA: The effects of inhibiting cholesterol synthesis and absorption on cholesterol and lipoprotein metabolism in hypercholesterolemic non-insulin dependent diabetic men. J Lipid Res 31:1776–1785, 1996.
47. Mattson FH, Volpenhein RA, Erickson BA: Effect of plant sterol

esters on the absorption of dietary cholesterol. J Nutr 107:1139–1146, 1977.
48. Heinemann T, Pietruck B, Kullak-Ublick G, von Bergmann K: Comparison of sitosterol and sitostanol inhibition of intestinal cholesterol absorption. Agents Actions 26:117S–122S, 1988.
49. Jones PJ, Sarjaz-Raeini M, Ntanios FY, Vanstone CA, Feng JY, Parsons WE: Modulation of plasma lipid levels and kinetics by phytosterol versus phytostanol esters. J Lipid Res 41:697–705, 2000.
50. Lichtenstein AH, Ausman LM, Carrasco W, Gualtieri LJ, Jenner JL, Ordovas JM, Nicolosi RJ, Goldin BR, Schaefer EJ: Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans. Arterioscler Thromb 14:1549–1556, 1994.
51. Wilson TA, DeSimone AP, Romano CA, Nicolosi RJ: Corn fiber oil lowers plasma cholesterol levels and increases cholesterol excretion greater than corn oil and similar diets containing soy sterols and soy stanols. J Nutr Biochem 11:443–449, 2000.
52. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D: Dietary antioxidant flavonoids and risk of coronary heart disease. The Zutphen elderly study. Lancet 342:1007–1011, 1993.
53. Lichtenstein AH: Soy protein, isoflavones and cardiovascular disease risk. J Nutr 128:1589–1592, 1998.
54. Wojcicki J, Rozewicka L, Barcew-Wiszniewska B et al: Effect of selenium and vitamin E on the development of experimental atherosclerosis in rabbits. Atherosclerosis 87:9–16, 1991.
55. Keaney JF, Gaziano JM, Xu A, Frei B, Curran-Celentano J, Shwaery GT, Loscalzo J, Vita JA: Low dose α-tocopherol improves and high dose α-tocopherol worsens endothelial vasodilator function in cholesterol-fed rabbits. J Clin Invest 93:844–851, 1994.
56. Verlangieri AJ, Bush MJ: Effects of α-tocopherol supplementation on experimentally induced primate atherosclerosis. J Am Coll Nutr 11:131–138, 1992.
57. Stampfer MJ, Hennekens CH, Manson JE et al: Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 328:1444–1449, 1993.
58. Rimm EB, Stampfer J, Ascherio A, et al: Vitamin E consumption and risk of coronary heart disease in men. N Engl J Med 328: 1450–1456, 1993.
59. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ: Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 347:781–786, 1996.
60. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330:1029–1035, 1994.
61. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction:results of the GISSI-Prevenzione trial. Lancet 354:447–455, 1999.
62. The HOPE Study Investigators. The HOPE (Heart Outcomes Prevention Evaluation) Study: Vitamin E supplementation and cardiovascular events in high risk patients. N Engl J Med 342:154–160, 2000.
63. Stampfer MJ, Malinow R, Willett WC, Newcomer LM, Upson B, Ullmann D, Tishler PV, Hennekens CH: A prospective study of plasma homocysteine and risk of myocardial infarction in US Physicians. JAMA 268:877–881, 1992.
64. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, Graham I: Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 324:1149–1155, 1991.
65. Coen DA, Weijenberg MP, van den Berg M, Jakobs C, Feskens JM, Kromhout D: Serum homocysteine and risk of coronary heart disease and cerebrovascular disease in elderly men—A 10 year follow-up. Arterioscler Thromb Vasc Biol 18:1895–1901, 1998.
66. Jacques PF, Selhub J, Bostom AG, Wilson PWF, Rosenberg IH: The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med 340:1449–1454, 1999.
67. Brattstrom LE, Israelsson B, Jeppson JO, Hultberg BL: Folic acid—an inocuous means to reduce plasma homocysteine. Scand J Clin Invest 48:215–221, 1988.
68. Van der Griend R, Haas FJLM, Biesma DH, Duran M, Meuwissen OJATh, Banga JD: Combination of low-dose folic acid and pyridoxine for treatment of hyperhomocysteinaemia in patients with pre-mature arterial disease and their relatives. Atherosclerosis 143: 177–183, 1999.
69. Ubbink JB, Vermaak WJH, van der Merwe A, Becker PJ: Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinaemia. Am J Clin Nutr. 57:47–53, 1993.
70. Olszewski AJ, Szostak WB, Bialkowska M, Rudnicki S, McCully KS: Reduction of plasma lipid and homocysteine levels by pyridoxine, folate, cobalamin, choline, riboflavin, and troxerutin in atherosclerosis. Atherosclerosis 75:1–6, 1989.

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