

Omega-6 Fatty Acids and Risk for Cardiovascular Disease A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention

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A large body of literature suggests that higher intakes of omega-6 (or n-6) polyunsaturated fatty acids (PUFAs) reduce risk for coronary heart disease (CHD). However, for the reasons outlined below, some individuals and groups have recommended substantial reductions in omega-6 PUFA intake.¹⁻⁴ The purpose of this advisory is to review evidence on the relationship between omega-6 PUFAs and the risk of CHD and cardiovascular disease.

Omega-6 PUFAs

Omega-6 PUFAs are characterized by the presence of at least 2 carbon-carbon double bonds, with the first bond at the sixth carbon from the methyl terminus. Linoleic acid (LA), an 18-carbon fatty acid with 2 double bonds (18:2 omega-6), is the primary dietary omega-6 PUFA. LA cannot be synthesized by humans, and although firm minimum requirements have not been established for healthy adults, estimates derived from studies in infants and hospitalized patients receiving total parenteral nutrition suggest that an LA intake of $\approx 0.5\%$ to 2% of energy is likely to suffice. After consumption, LA can be desaturated and elongated to form other omega-6 PUFAs such as γ -linolenic and dihomo- γ -linolenic acids. The latter is converted to the metabolically important omega-6 PUFA arachidonic acid (AA; 20:4 omega-6), the substrate for a wide array of reactive oxygenated metabolites. Because LA accounts for 85% to 90% of the dietary omega-6 PUFA, this advisory focuses primarily on this fatty acid, recognizing that dietary AA, which can affect tissue AA

levels,⁵ may have physiological sequelae.⁶⁻⁸ LA comes primarily from vegetable oils (eg, corn, sunflower, safflower, soy). The average US intake of LA, according to National Health and Nutrition Examination Survey 2001 to 2002 data for adults ≥ 19 years of age, is 14.8 g/d.⁹ On the basis of an average intake of 2000 kcal/d, LA intake is 6.7% of energy. AA (≈ 0.15 g/d) is consumed preformed in meat, eggs, and some fish.

Omega-6 PUFAs and Inflammation

Arguments for reduced LA intakes are based on the assumption that because CHD has an inflammatory component¹⁰ and because the omega-6 fatty acid, AA, is the substrate for the synthesis of a variety of proinflammatory molecules, reducing LA intakes should reduce tissue AA content, which should reduce the inflammatory potential and therefore lower the risk for CHD. The evidence, derived primarily from human studies, regarding this line of reasoning is examined below.

AA is the substrate for the production of a wide variety of eicosanoids (20-carbon AA metabolites). Some are proinflammatory, vasoconstrictive, and/or proaggregatory, such as prostaglandin E₂, thromboxane A₂, and leukotriene B₄. However, others are antiinflammatory/antiaggregatory, such as prostacyclin, lipoxin A₄,¹¹ and epoxyeicosatrienoic acids.¹² Epoxyeicosatrienoic acids are fatty acid epoxides produced from AA by a cytochrome P450 epoxygenase. Epoxyeicosatrienoic acids also have important vasodilator properties via

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hyperpolarization and relaxation of vascular smooth muscle cells.¹³ Importantly, because the production of AA from LA is tightly regulated,¹⁴ wide variations in dietary LA (above minimal essential intakes) do not materially alter tissue AA content.¹⁵ In tracer studies, the extent of conversion of LA to AA is $\approx 0.2\%$.¹⁶

In studies with vascular endothelial cells, omega-6 PUFA had antiinflammatory properties, suppressing the production of adhesion molecules, chemokines, and interleukins, all key mediators of the atherosclerotic process.¹⁷ In human studies, higher plasma levels of omega-6 PUFAs, mainly AA, were associated with decreased plasma levels of serum proinflammatory markers, particularly interleukin-6 and interleukin-1 receptor antagonist, and increased levels of antiinflammatory markers, particularly transforming growth factor- β .¹⁸ When healthy volunteers were given ≈ 7 times the usual intake of AA (ie, 1.5 g/d) in a 7-week controlled feeding study, no effects on platelet aggregation, bleeding times, the balance of vasoactive metabolites, serum lipid levels, or immune response were observed.⁵⁻⁸ Likewise, in a recent study from Japan, AA supplementation (840 mg/d for 4 weeks) had no effect on any metabolic parameter or platelet function.¹⁹ Consistent with this, in observational studies, higher omega-6 PUFA consumption was associated with unaltered or lower levels of inflammatory markers.²⁰

Diets high in LA can increase the *ex vivo* susceptibility of low-density lipoprotein (LDL) to oxidation,²¹ and oxidized LDL can promote vascular inflammation.²² Therefore, oxidized LDL may play some role in the etiology of CHD.²³ However, the extent of LDL oxidation at higher LA intakes (5% to 15% of energy) has not been established, and its clinical relevance is in question owing to the general failure of antioxidant treatments to mitigate CHD risk in most randomized trials.²⁴ At present, little direct evidence supports a net proinflammatory, proatherogenic effect of LA in humans.^{22,25,26}

Omega-6 PUFA Consumption and Other CHD Risk Factors/Markers

The cholesterol-lowering effect of LA is well established from human trials. In a meta-analysis of 60 feeding studies including 1672 volunteers, the substitution of PUFA (largely omega-6, varying from 0.6% to 28.8% energy) for carbohydrates had more favorable effects on the ratio of total to high-density lipoprotein cholesterol (perhaps the best lipid predictor of CHD risk) than any class of fatty acids.²⁷ Higher plasma PUFA levels are associated with a reduced ratio of total to high-density lipoprotein cholesterol,²⁸ and epidemiologically, the replacement of 10% of calories from saturated fatty acid with omega-6 PUFA is associated with an 18-mg/dL decrease in LDL cholesterol, greater than that observed with similar replacement with carbohydrate.²⁹ These findings confirm an LDL-lowering effect of omega-6 PUFA beyond that produced by the removal of saturated fatty acids. Favorable effects of LA on cholesterol levels are thus well documented and would predict significant reductions in CHD risk. Additionally, higher LA intakes may improve insulin resistance³⁰ and reduce the incidence of diabetes mellitus,³¹ and higher serum LA levels are associated with lower blood

pressure.³² Nevertheless, not all studies support a beneficial effect of LA on CHD risk markers. For example, an angiographic study reported a direct association between PUFA intakes and luminal narrowing in women with CHD.³³ However, effects on markers do not always translate into effects on actual clinical end points; thus, it is essential to evaluate the relations between LA consumption and CHD events.

Omega-6 PUFA Consumption and CHD Events: Observational Studies

Ecological Studies

Cross-cultural, cross-sectional, and time-trend studies examining omega-6 PUFA intake and CHD risk demonstrate equivocal results.^{34,35} Among the 4584 subjects in the National Heart, Lung, and Blood Institute Family Heart Study, the prevalence of coronary artery disease was $\approx 66\%$ higher at LA intakes of 1.8% compared with 5.3%.³⁶ The weaknesses of these study designs for evaluating diet-disease relations are well documented,³⁷ and most evaluated only total PUFA intake, failing to distinguish between omega-3 and omega-6 PUFAs and their potentially distinct effects. Given these limitations, firm conclusions cannot be drawn from these studies.

Case-Control Studies

In a meta-analysis of 25 case-control studies (including 1998 cases and 6913 controls) evaluating blood/tissue omega-6 PUFA content and CHD events, LA content was inversely associated with CHD risk, whereas AA was unrelated to CHD risk.³⁸ Even very high LA intakes have been associated with lower risk; in 1 study in Israel,³⁹ where 25% of the population consumes $>12\%$ of energy as omega-6 PUFA, an inverse association was found between adipose LA and acute myocardial infarction after controlling for other omega-6 PUFAs.

Prospective Cohort Studies

These observational studies use the strongest designs, minimizing both selection and recall bias. No significant associations between LA or omega-6 PUFA intake and CHD risk were seen in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,⁴⁰ Lipid Research Clinics study,⁴¹ or Honolulu Heart Program.⁴² Modest, nonsignificant inverse associations were observed in the Multiple Risk Factor Intervention Trial,⁴³ the Irish-Boston Heart Study,⁴⁴ and the Health Professionals Follow-Up Study.⁴⁵ In the Health Professionals Follow-Up Study, CHD rates were lowest in participants with higher intake of both omega-3 and omega-6 PUFAs,⁴⁶ and in the Western Electric Study⁴⁷ and the Kupio Heart Study,⁴⁸ higher LA intakes or serum levels were associated with lower risk of CHD or total mortality. In the Nurses' Health Study, in which diet was assessed multiple times over 20 years,⁴⁹ CHD risk was $\approx 25\%$ lower comparing the 95th and 5th percentiles of LA intake (7.0% versus 2.8% of energy, respectively). Most prospective cohort studies have not found significant associations between omega-6 fatty acid intakes and ischemic⁵⁰⁻⁵² or hemorrhagic^{50,51,53} stroke or stroke mortality.⁵⁴ In 1 prospective study, serum

LA levels predicted lower risk of stroke, particularly ischemic stroke.⁵⁵ LA intakes are not associated with risk for cancer.²⁶ Therefore, observational studies generally suggest an overall modest benefit of omega-6 PUFA intake on CHD risk and no significant effect on stroke or cancer. These studies, some of which included LA intakes of up to 10% to 12% of energy, contradict the supposition that higher omega-6 PUFA intakes increase risk for CHD.

Omega-6 PUFA Consumption and CHD Events: Randomized Controlled Trials

Several randomized trials have evaluated the effects of replacing saturated fatty acids with PUFAs on CHD events.^{56–65} Intakes of PUFA (almost entirely omega-6 PUFA) ranged from 11% to 21%. In addition to the inability to double-blind these studies, many had design limitations such as small sample size ($n=54$),⁶⁵ the provision of only $\approx 50\%$ of meals,⁵⁶ outcomes composed largely of “soft” ECG end points,^{59,60} randomization of sites rather than individuals with open enrollment and high turnover of subjects,^{59,60} use of vegetable oils that also contained the plant omega-3 fatty acid α -linolenic acid,^{57,59,60} and simultaneous recommendations to increase fish and cod liver oil use.⁵⁸ Nevertheless, a meta-analysis including 6 of these trials^{56–60,62–64} indicated that replacing saturated fatty acids with PUFAs lowered the risk for CHD events by 24%.⁶⁶ Of the remaining 4 studies, 1 reported a significant 45% reduction in risk,⁵⁹ whereas no significant effect was seen in the others.^{60,61,65}

These trials tested the effect of replacing saturated fatty acids; no randomized trial has reported the effects of replacing carbohydrate or protein with omega-6 PUFAs on CHD risk. Although limitations are present for each trial, the combined results of these studies and the observational trials provide evidence that replacing saturated fatty acid or refined carbohydrate (eg, sugars, white bread, white rice, potatoes) with omega-6 PUFAs reduces CHD risk. On the basis of the intakes of omega-6 PUFAs used in the randomized trials, metabolic studies, and nonhuman primate studies discussed below, reductions in CHD risk might be expected with omega-6 PUFA intakes of 10% to 21% of energy compared with lower intakes, with no clinical evidence for adverse events.

Recommended Intakes of Omega-6 Fatty Acids

Dietary recommendations for omega-6 PUFAs traditionally focused on the prevention of essential fatty acid deficiency but are now increasingly seeking to define “optimal” intakes to reduce risk for chronic disease, particularly CHD. The Institute of Medicine’s Food and Nutrition Board, in their Dietary Reference Intake Report for Energy and Macronutrients,⁶⁷ defines an adequate intake of LA as 17 g/d for men and 12 g/d for women (5% to 6% of energy) 19 to 50 years of age, approximately the current median US intake. Both the Dietary Reference Intake Report and the 2005 Dietary Guidelines for Americans⁶⁸ support an acceptable macronutrient distribution range (the range of intakes for a particular energy source

that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients) of 5% to 10% dietary energy from omega-6 PUFAs. The Third Adult Treatment Panel of the National Cholesterol Education Program recommends PUFA consumption up to 10%, noting that “there are no large populations that have consumed large quantities of polyunsaturated fatty acids for long periods. Thus, high intakes have not been proven safe in large populations; this introduces a note of caution for recommending high intakes.”⁶⁹ On the other hand, evidence from trials in nonhuman primates has demonstrated cardiovascular benefits and no evidence of harm with LA intakes of 25% of energy for up to 5 years,^{70,71} and randomized trials in humans have shown reduced CHD risk with omega-6 PUFA intakes of 11% to 21% of energy for up to 11 years with no evidence of harm.

Other governmental health recommendations for omega-6 fatty acid intakes (on a percent energy basis) are as follows: European Commission, 4% to 8%⁷²; Food and Agriculture Organization/World Health Organization, 5% to 8%⁷³; British Nutrition Foundation, 6% to 6.5% (maximum, 10%)⁷⁴; the Department of Health and Ageing, Australia and New Zealand, 4% to 5% (maximum, 10%)⁷⁵; and the American Dietetic Association/Dietitians of Canada, 3% to 10%.⁷⁶ The American Heart Association places primary emphasis on healthy eating patterns rather than on specific nutrient targets.

Advice to reduce omega-6 PUFA intakes is typically framed as a call to lower the ratio of dietary omega-6 to omega-3 PUFAs.^{1–4} Although increasing omega-3 PUFA tissue levels does reduce the risk for CHD,^{77,78} it does not follow that decreasing omega-6 levels will do the same. Indeed, the evidence considered here suggests that it would have the opposite effect. Higher omega-6 PUFA intakes can inhibit the conversion of α -linolenic acid to eicosapentaenoic acid,⁷⁹ but such conversion is already quite low,⁸⁰ and whether additional small changes would have net effects on CHD risk after the other benefits of LA consumption are taken into account is not clear. The focus on ratios, rather than on levels of intake of each type of PUFA, has many conceptual and biological limitations.⁸¹

Conclusions

This advisory was undertaken to summarize the current evidence on the consumption of omega-6 PUFAs, particularly LA, and CHD risk. Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the consumption of at least 5% to 10% of energy from omega-6 PUFAs reduces the risk of CHD relative to lower intakes. The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low-saturated-fat, low-cholesterol diet). In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD.

Disclosures

Writing Group Disclosures

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*Modest.

†Significant.

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*Modest.

†Significant.

References

- Sears B. *The Omega Rx Zone: The Miracle of the New High-Dose Fish Oil*. New York, NY: HarperCollins; 2003.
- Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med (Maywood)*. 2008;233:674–688.
- Simopoulos AP, Leaf A, Salem N Jr. Essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. *Ann Nutr Metab*. 1999;43:127–130.
- Hamazaki T, Okuyama H. The Japan Society for Lipid Nutrition recommends to reduce the intake of linoleic acid: a review and critique of the scientific evidence. *World Rev Nutr Diet*. 2003;92:109–132.
- Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Phinney SD, Kyle D, Silbermann S, Schaefer EJ. The effect of dietary arachidonic acid on plasma lipoprotein distributions, apoproteins, blood lipid levels, and tissue fatty acid composition in humans. *Lipids*. 1997;32:427–433.
- Ferretti A, Nelson GJ, Schmidt PC, Kelley DS, Bartolini G, Flanagan VP. Increased dietary arachidonic acid enhances the synthesis of vasoactive eicosanoids in humans. *Lipids*. 1997;32:435–439.
- Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Mackey BE, Kyle D. Effects of dietary arachidonic acid on human immune response. *Lipids*. 1997;32:449–456.
- Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Kyle D. The effect of dietary arachidonic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids*. 1997;32:421–425.
- Moshfegh A, Goldman J, Cleveland L. What we eat in America: NHANES 2001–2002: usual nutrient intakes from food compared to

- dietary reference intakes. Beltsville, Md: US Department of Agriculture, Agricultural Research Service; 2005. Available at: <http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/usualintaketables2001-02.pdf>. Accessed December 20, 2008.
10. Libby P. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr*. 2006;83:456S–460S.
 11. Serhan CN. Lipoxins and aspirin-triggered 15-epi-lipoxins are the first lipid mediators of endogenous anti-inflammation and resolution. *Prostaglandins Leukot Essent Fatty Acids*. 2005;73:141–162.
 12. Node K, Huo Y, Ruan X, Yang B, Spiecker M, Ley K, Zeldin DC, Liao JK. Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science*. 1999;285:1276–1279.
 13. Oltman CL, Weintraub NL, VanRollins M, Dellsperger KC. Epoxyeicosatrienoic acids and dihydroxyeicosatrienoic acids are potent vasodilators in the canine coronary microcirculation. *Circ Res*. 1998;83:932–939.
 14. Mohrhauer H, Holman RT. The effect of dose level of essential fatty acids upon fatty acid composition of rat liver. *J Lipid Res*. 1963;4:151–159.
 15. Sarkkinen ES, Agren JJ, Ahola I, Ovaskainen ML, Uusitupa MI. Fatty acid composition of serum cholesterol esters, and erythrocyte and platelet membranes as indicators of long-term adherence to fat-modified diets. *Am J Clin Nutr*. 1994;59:364–370.
 16. Hussein N, Ah-Sing E, Wilkinson P, Leach C, Griffin BA, Millward DJ. Long-chain conversion of [¹³C]linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in men. *J Lipid Res*. 2005;46:269–280.
 17. De Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. *Am J Clin Nutr*. 2000;71:213S–223S.
 18. Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U, Guralnik JM. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab*. 2006;91:439–446.
 19. Kusumoto A, Ishikura Y, Kawashima H, Kiso Y, Takai S, Miyazaki M. Effects of arachidonate-enriched triacylglycerol supplementation on serum fatty acids and platelet aggregation in healthy male subjects with a fish diet. *Br J Nutr*. 2007;98:626–635.
 20. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation*. 2003;108:155–160.
 21. Tsimikas S, Philis-Tsimikas A, Alexopoulos S, Sigari F, Lee C, Reaven PD. LDL isolated from Greek subjects on a typical diet or from American subjects on an oleate-supplemented diet induces less monocyte chemotaxis and adhesion when exposed to oxidative stress. *Arterioscler Thromb Vasc Biol*. 1999;19:122–130.
 22. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320:915–924.
 23. Tsimikas S. Oxidative biomarkers in the diagnosis and prognosis of cardiovascular disease. *Am J Cardiol*. 2006;98:9P–17P.
 24. Bleyys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2006;84:880–887.
 25. Galassetti P, Pontello A. Dietary effects on oxidation of low-density lipoprotein and atherogenesis. *Curr Atheroscler Rep*. 2006;8:523–529.
 26. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. *Am J Clin Nutr*. 1998;68:142–153.
 27. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146–1155.
 28. Siguel E. A new relationship between total/high density lipoprotein cholesterol and polyunsaturated fatty acids. *Lipids*. 1996;31(suppl):S51–S56.
 29. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. *Arterioscler Thromb*. 1992;12:911–919.
 30. Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. *Diabetologia*. 2002;45:369–377.
 31. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2001;73:1019–1026.
 32. Grimsgaard S, Bonna KH, Jacobsen BK, Bjerve KS. Plasma saturated and linoleic fatty acids are independently associated with blood pressure. *Hypertension*. 1999;34:478–483.
 33. Mozaffarian D, Rimm EB, Herrington DM. Dietary fats, carbohydrate, and progression of coronary atherosclerosis in postmenopausal women. *Am J Clin Nutr*. 2004;80:1175–1184.
 34. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH. The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol*. 1986;124:903–915.
 35. Hegsted DM, Ausman LM. Diet, alcohol and coronary heart disease in men. *J Nutr*. 1988;118:1184–1189.
 36. Djousse L, Pankow JS, Eckfeldt JH, Folsom AR, Hopkins PN, Province MA, Hong Y, Ellison RC. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr*. 2001;74:612–619.
 37. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
 38. Harris WS, Poston WC, Haddock CK. Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. *Atherosclerosis*. 2007;193:1–10.
 39. Kark JD, Kaufmann NA, Binka F, Goldberger N, Berry EM. Adipose tissue n-6 fatty acids and acute myocardial infarction in a population consuming a diet high in polyunsaturated fatty acids. *Am J Clin Nutr*. 2003;77:796–802.
 40. Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol*. 1997;145:876–887.
 41. Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: Lipid Research Clinics Prevalence Follow-Up Study. *J Clin Epidemiol*. 1996;49:211–216.
 42. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. *Am J Epidemiol*. 1984;119:667–676.
 43. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc Soc Exp Biol Med*. 1992;200:177–182.
 44. Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R. Diet and 20-year mortality from coronary heart disease: the Ireland-Boston Diet-Heart Study. *N Engl J Med*. 1985;312:811–818.
 45. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ*. 1996;313:84–90.
 46. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. *Circulation*. 2005;111:157–164.
 47. Shekelle RB, Shryock AM, Paul O, Lepper M, Stamler J, Liu S, Raynor WJ Jr. Diet, serum cholesterol and death from coronary heart disease: the Western Electric Study. *N Engl J Med*. 1981;304:65–70.
 48. Laaksonen DE, Nyyssonen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. *Arch Intern Med*. 2005;165:193–199.
 49. Oh K, Hu FB, Manson JE, Stampfer JM, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol*. 2005;161:672–679.
 50. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hu F, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of fat and protein intake and risk of intraparenchymal hemorrhage in women. *Circulation*. 2001;103:856–863.
 51. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ*. 2003;327:777–782.
 52. Gillman MW, Cupples LA, Millen BE, Ellison RC, Wolf PA. Inverse association of dietary fat with development of ischemic stroke in men. *JAMA*. 1997;278:2145–2150.
 53. Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol*. 2003;157:32–39.
 54. Sauvaget C, Nagano J, Hayashi M, Yamada M. Animal protein, animal fat, and cholesterol intakes and risk of cerebral infarction mortality in the Adult Health Study. *Stroke*. 2004;35:1531–1537.
 55. Iso H, Sato S, Umemura U, Kudo M, Koike K, Kitamura A, Imano H, Okamura T, Naito Y, Shimamoto T. Linoleic acid, other fatty acids, and the risk of stroke. *Stroke*. 2002;33:2086–2093.
 56. Dayton S, Pearce ML, Goldman H, Harnish A, Plotkin D, Shickman M, Winfield M, Zager A, Dixon W. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *Lancet*. 1968;2:1060–1062.
 57. Controlled trial of soya-bean oil in myocardial infarction. *Lancet*. 1968; 2:693–699.
 58. Leren P. The Oslo Diet-Heart Study: eleven-year report. *Circulation*. 1970;42:935–942.
 59. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. *Int J Epidemiol*. 1979;8:99–118.

60. Miettinen M, Turpeinen O, Karvonen MJ, Pekkarinen M, Paavilainen E, Elosuo R. Dietary prevention of coronary heart disease in women: the Finnish Mental Hospital Study. *Int J Epidemiol.* 1983;12:17–25.
61. Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. *Arteriosclerosis.* 1989;9:129–135.
62. Woodhill JM, Palmer AJ, Leelarthaeapin B, McGilchrist C, Lackett RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol.* 1978;109:317–330.
63. Watts GF, Lewis B, Brunt JN, Lewis ES, Coltart DJ, Smith LD, Mann JI, Swan AV. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). *Lancet.* 1992;339:563–569.
64. Low fat diet in myocardial infarction: a controlled trial. *Lancet.* 1965;2:501–504.
65. Rose GA, Thomson WB, Williams RT. Corn oil in the treatment of ischemic heart disease. *BMJ.* 1965;1:1531–1533.
66. Gordon DJ. Lowering cholesterol and total mortality. In: Rifkin BM, ed. *Lowering Cholesterol in High-Risk Individuals and Populations.* New York, NY: Marcel Dekker, Inc; 1995:33–48.
67. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Washington, DC: National Academies Press; 2002. Available at: http://books.nap.edu/catalog.php?record_id=10490. Accessed December 20, 2008.
68. Department of Health and Human Services and the USDA. Dietary guidelines for Americans: The report of the Dietary Guidelines Advisory Committee on Dietary Guidelines for Americans, 2005. Available at: <http://www.health.gov/dietaryguidelines/dga2005/report/default.htm>. Accessed December 20, 2008.
69. National Heart, Lung, and Blood Institute. Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>. Accessed December 20, 2008.
70. Wolfe MS, Parks JS, Morgan TM, Rudel LL. Childhood consumption of dietary polyunsaturated fat lowers risk for coronary artery atherosclerosis in African green monkeys. *Arterioscler Thromb.* 1993;13:863–875.
71. Wolfe MS, Sawyer JK, Morgan TM, Bullock BC, Rudel LL. Dietary polyunsaturated fat decreases coronary artery atherosclerosis in a pediatric-aged population of African green monkeys. *Arterioscler Thromb.* 1994;14:587–597.
72. Eurodiet Core Report. Available at: <http://eurodiet.med.uoc.gr/eurodietcorereport.pdf>. Accessed December 20, 2008.
73. Joint WHO/FAO Expert Consultation. Diet, nutrition and the prevention of chronic diseases. Geneva, Switzerland: World Health Organization; 2003. Available at: http://www.who.int/hpr/NPH/docs/who_fao_expert_report.pdf. Accessed December 20, 2008.
74. British Nutrition Foundation. Nutrient requirements and recommendations. Available at: [http://www.nutrition.org.uk/upload/Nutrient%20Requirements%20and%20recommendations%20pdf\(1\).pdf](http://www.nutrition.org.uk/upload/Nutrient%20Requirements%20and%20recommendations%20pdf(1).pdf). Accessed December 20, 2008.
75. National Health and Medical Research Council. Nutrient reference values for Australia and New Zealand Including Recommended Dietary Intakes. Available at: <http://www.nhmrc.gov.au/publications/synopses/n35syn.htm>. Accessed December 20, 2008.
76. Kris-Etherton PM, Innis S, for the American Dietetic Association, Dietitians of Canada. Position of the American Dietetic Association and Dietitians of Canada: dietary fatty acids. *J Am Diet Assoc.* 2007;107:1599–1611.
77. Kris-Etherton PM, Harris WS, Appel LJ, for the American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002;106:2747–2757.
78. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA.* 2006;296:1885–1899.
79. Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. *J Nutr.* 2007;137:945–952.
80. Brenna JT. Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. *Curr Opin Clin Nutr Metab Care.* 2002;5:127–132.
81. Harris WS. The omega-6/omega-3 ratio and cardiovascular disease risk: uses and abuses. *Curr Atheroscler Rep.* 2006;8:453–459.

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Omega-6 Fatty Acids and Risk for Cardiovascular Disease: A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention

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