

Dietary Omega-3 Fatty Acid Intake and Cardiovascular Risk

Tricia L. Psota, Sarah K. Gebauer, and Penny Kris-Etherton, PhD, RD*

Dietary omega-3 fatty acids decrease the risk of cardiovascular disease (CVD). Both epidemiologic and interventional studies have demonstrated beneficial effects of omega-3 fatty acids on many CVD end points, including all CVD (defined as all coronary artery disease [CAD], fatal and nonfatal myocardial infarction [MI], and stroke combined), all CAD, fatal and nonfatal MI, stroke, sudden cardiac death, and all-cause mortality. Much of the evidence comes from studies with fish oil and fish; to a lesser extent, data relate to plant-derived omega-3 fatty acids. Cardioprotective benefits have been observed with daily consumption of as little as 25 to 57 g (~1 to 2 oz) of fish high in omega-3 fatty acids, an intake equivalent to ≥ 1 fish meal weekly or even monthly, with greater intakes decreasing risk further in a dose-dependent manner, up to about 5 servings per week. Fish, including farm-raised fish and their wild counterparts, are the major dietary sources of the longer-chain omega-3 fatty acids. Sources of plant-derived omega-3 fatty acids include flaxseed, flaxseed oil, walnuts, canola oil, and soybean oil. Because of the remarkable cardioprotective effects of omega-3 fatty acids, consumption of food sources that provide omega-3 fatty acids—especially the longer-chain fatty acids (≥ 20 carbons) from marine sources—should be increased in the diet to decrease CVD risk significantly. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98[suppl]:3i–18i)

Omega-3 polyunsaturated fatty acids (PUFAs) are one of a number of dietary components that have demonstrated cardioprotective benefits. Among populations in which total fat intake is considerably $>30\%$ of total energy, yet mortality from cardiovascular disease (CVD) is low, fish and plant oils are the primary sources of fat consumed. Dietary patterns associated with low CVD mortality, initially identified among the Greenland Eskimos who subsisted on large amounts of fish, have since been identified in populations residing in Mediterranean regions. Subsequent studies include large numbers of men and women from diverse populations, ranging in age from 25 to 103 years, residing in >30 countries, who were either free of CVD at baseline or had clinical evidence of coronary artery disease (CAD).^{1–5} The findings of longitudinal cohort and cross-sectional ecologic studies, together with data from case-control and dietary intervention studies, have confirmed that significant reductions in mortality due to myocardial infarction (MI), ischemic heart disease, stroke, sudden cardiac death, and total CVD can be attributed to consumption of fish and other dietary sources of omega-3 fatty acids, as estimated from 24-hour recalls, dietary histories, food records, semiquantitative food-frequency questionnaires, or agricultural food balance data, as well as from measurement of serum, membrane, and tissue omega-3 fatty acid concentrations. The inverse relationship between dietary sources of omega-3 fatty acids, and

fish in particular, with CVD mortality has been demonstrated as strong, graded, consistent, and independent of saturated fat intake, other dietary components, and known risk factors of CVD and can be explained by a number of plausible biologic mechanisms favoring antiatherogenic, antithrombotic, and antiarrhythmic effects. With few exceptions, cardioprotective benefits have been found with consumption of modest amounts of omega-3 fatty acids provided by an average intake of 25 to 57 g (~1 to 2 oz) of fish high in omega-3 fatty acids consumed daily or an intake of an equivalent amount consumed in ≥ 1 meal weekly or even monthly.^{2,4,6–9}

In most of the populations examined, reductions in CVD mortality have been associated with fish consumption. Because high intakes of omega-3 fatty acids are characteristic of fish-consuming populations, attention has focused largely on the benefits of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to explain the protective effects on CVD risk observed in these studies. Results from several meta-analyses and interventional studies also have demonstrated that regular consumption of a variety of omega-3 fatty acid sources—including fish oils, nuts, and soybean oil, in addition to dietary supplements that provide concentrated amounts of purified EPA and DHA—was inversely associated with CVD mortality or promoted significant reductions of 30% to 60% in CVD mortality.^{3,4,7,8,10–13} In a recent evaluation of data from 97 randomized, placebo-controlled trials of different lipid-lowering interventions that included omega-3 fatty acids and diet in addition to pharmacologic therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), fibrates, resins, and niacin, the most favorable effects of treatment compared with controls were observed with statins and omega-3 fatty acids. Omega-3 fatty acids were associated with

Department of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania, USA.

*Address for reprints: Penny Kris-Etherton, PhD, RD, Department of Nutritional Sciences, Pennsylvania State University, S-126 Henderson Building, University Park, Pennsylvania 16802.

E-mail address: pmk3@psu.edu.

reductions of 23% in all-cause mortality and 32% in cardiac mortality compared with reductions of 13% and 22% in all-cause and cardiac mortality, respectively, for statins.¹⁴ This study is an excellent demonstration of the cardioprotective potency that omega-3 fatty acids can have. This article summarizes the epidemiologic and randomized, controlled trial evidence of studies that evaluated the effects of dietary omega-3 fatty acids on various CVD end points. Thus, fish oil studies are not included in this review.

The Dietary Fat Conundrum

The appropriate amount and distribution of dietary fatty acids required to achieve the most favorable impact on CVD risk has been a subject of recent discussion. The need to reduce dietary saturated fat from meats and dairy products as well as *trans* fatty acids from hydrogenated vegetable oils is universally accepted. Questions remain about the optimal levels of total fat and unsaturated fatty acids, specifically monounsaturated fatty acids and omega-3 and omega-6 fatty acids. With respect to omega-3 fatty acids, there are additional questions about how much plant- and marine-derived fatty acids should be recommended. The very early studies conducted with modified-fat diets, which emphasized quite high levels of PUFA and reduced levels of saturated fat, were effective in markedly reducing plasma levels of total and low-density lipoprotein (LDL) cholesterol, but those diets did not prevent the accompanying reduction in high-density lipoprotein (HDL) cholesterol, nor were they effective in significantly lowering serum triglyceride (TG) levels.^{15–18} These diets did not place an emphasis on a balance between sources of omega-6 PUFAs that dominate dietary patterns in the United States, among other Western industrialized countries, and sources of omega-3 fatty acids that dominate diets in countries associated with low CVD risk. In addition, the other early studies that reduced dietary total fat as a means to lower saturated fat, and correspondingly increased dietary carbohydrate (as a means to maintain energy balance), resulted in increases in serum TG levels and decreases in HDL cholesterol levels, with adverse effects on glycemic control, particularly among individuals with type 2 diabetes mellitus.^{19–22}

Traditional fat-modified diets characterized by low intake of total fat, saturated fat, and dietary cholesterol, and including a relatively high proportion of omega-6 fatty acids, have been highly effective in managing plasma levels of total and LDL cholesterol, but they have not been as successful in optimizing levels of HDL cholesterol and TG. Replacing some portion of PUFA with monounsaturated fatty acids from olive oil or other rich sources, while adding incrementally to total fat (ie, a Mediterranean dietary approach), attenuates or prevents the HDL cholesterol decrease but does not have a clinically significant impact on management of hypertriglyceridemia. The discussion about the optimal composition of fat-modified diets has been reopened by emerging data that support the concept of the favorable biochemical effects of omega-3 fatty acids

differing quantitatively and qualitatively from the effects of both omega-6 and monounsaturated fatty acids, as well as being cardioprotective at relatively high total-fat intakes (40% of energy). These data suggest that increasing total fat intake by increasing intake of omega-3 fatty acids, while maintaining currently recommended intakes of omega-6 and monounsaturated fatty acids and keeping total saturated fat and *trans* fatty acid intake low, may result in a more favorable CVD risk profile.

Metabolism of Omega-3 Fatty Acids and Role in Cardiovascular Function

Individual fatty acids have a wide range of effects on biochemical and physiologic functions that are determined by a combination of chain length, number and placement of double bonds, and isomerism around these bonds. The nutritionally important omega-6 fatty acids—linoleic acid (LA) (18 carbons with 2 double bonds) and arachidonic acid (AA) (20 carbons with 4 double bonds)—differ substantially from their omega-3 counterparts, α -linolenic acid (ALA) (18 carbons with 3 double bonds) and EPA (20 carbons with 5 double bonds), in their impact on plasma lipids and lipoproteins, blood pressure, and other prominent biomarkers of CVD risk such as fasting plasma glucose and insulin, lipoprotein (a), inflammatory markers, and clotting factors. In addition, DHA, an omega-3 fatty acid with 22 carbons and 6 double bonds, contributes substantially to total bioactivity of omega-3 fatty acids, but does not appear to have an omega-6 fatty acid counterpart with comparable biologic activity. The structure, function, and metabolic fate of the primary omega-6 and omega-3 fatty acids are presented in Figure 1.

The metabolic utilization of omega-3 fatty acids differs from omega-6 fatty acid metabolism. Both types of fatty acids are substrates for lipid mediators and are incorporated as structural components to form the lipid bilayers of cell membranes; however, it is the structural differences between these classes of fatty acids that determine the specific properties of the lipid mediators and cell membranes associated with each. The long-chain 20- and 22-carbon fatty acids within each class—AA, EPA, and DHA—are biologically more active than are the 18-carbon fatty acids LA and ALA, which serve primarily as substrates for synthesis of the longer-chain, more highly unsaturated counterparts. As components of cell membranes, omega-3 fatty acids increase membrane fluidity, thereby influencing a host of membrane functions, including eicosanoid signaling, pinocytosis, ion channel modulation, and regulation of gene expression.²³ Whereas omega-6 fatty acids generally exert their cardioprotective effects through changes in lipids and lipoproteins, omega-3 fatty acids contribute benefits through their antiarrhythmic, anti-inflammatory, and anti-thrombotic effects.²⁴

Despite differences in metabolic utilization and the bioactive lipid mediators synthesized, a balance between omega-3 and omega-6 fatty acid intakes is important because these fatty

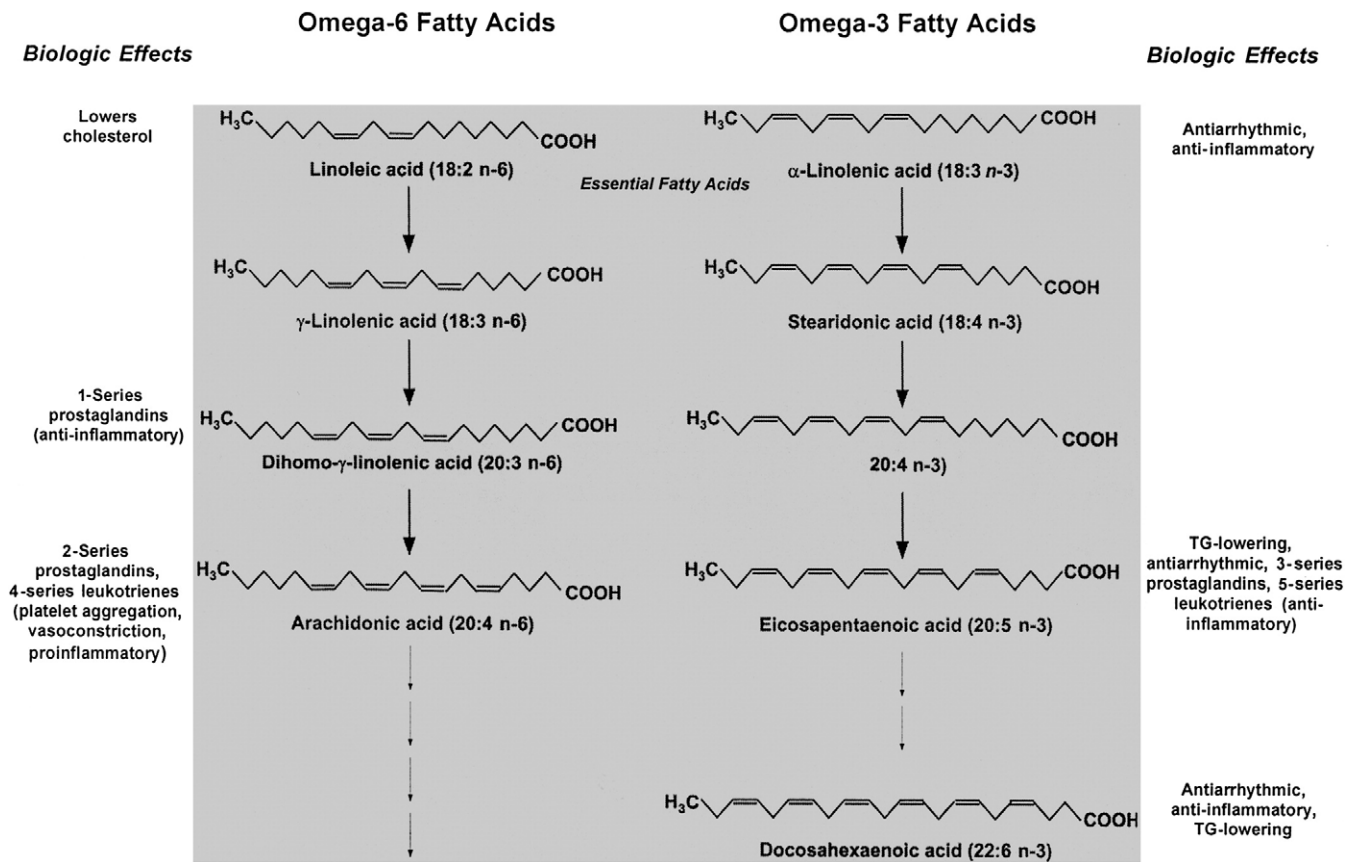


Figure 1. Structure, function, and metabolic fate of the primary omega-6 (n-6) and omega-3 (n-3) fatty acids. TG = triglycerides.

acids compete for the same enzyme systems involved in elongation and desaturation to synthesize the longer-chain, more unsaturated, and more biologically active fatty acids. They also compete for cyclooxygenases and lipoxygenases involved in the production of prostaglandins and leukotrienes that mediate a range of cell functions important to cardiovascular function, including vasodilation and vasoconstriction, cellular adhesion processes, inflammatory responses, and platelet aggregation. Competition between omega-3 and omega-6 fatty acids for cyclooxygenases and lipoxygenases will therefore determine the physiologic effects that will dominate. The 2- and 4-series eicosanoids produced from AA promote proinflammatory and prothrombotic effects, whereas the corresponding 3- and 5-series eicosanoids produced from EPA have either the opposite effects or exhibit much lower levels of biologic activity.

Excessive intake of LA relative to ALA increases production of AA compared with that of EPA and DHA, and large adipose tissue reservoirs of LA slow down conversion of ALA to EPA and DHA. Compensation for this imbalance can be achieved in part by increasing consumption of EPA and DHA, but this does not completely satisfy the biologic requirements for omega-3 fatty acids, indicating that ALA has important biologic effects that are independent of its being a precursor for EPA and DHA.²⁴ Each of these fatty acids has a different metabolic role, with DHA preferentially taken up by cell membranes and EPA utilized as a substrate for eicosanoid synthesis.

Approximately 5% to 10% of dietary ALA is converted to EPA, and an additional 2% to 5% is converted to DHA in healthy adults.²⁴ Recent evidence from tracer kinetic studies revealed that approximately 7% of ALA is converted to EPA.²⁵ The conversion of ALA to DHA typically is <5% in humans²⁶ and may be as low as 1%.²⁵ Experimental evidence also suggests that excess intakes of *trans* fatty acids may create an imbalance in omega-3 fatty acids by inhibiting the conversion of EPA to DHA at the δ -6 desaturase-dependent step, which reduces the amount of DHA available from ingestion of either ALA or EPA.²⁷

Dietary Omega-3 Fatty Acids and CVD Risk: Epidemiologic and Interventional Studies

Studies designed to assess omega-3 fatty acid intake and CVD risk: Numerous epidemiologic and interventional studies have evaluated the associations and effects of omega-3 fatty acids^{9,10,28–34} and fish,^{1–4,6,7,13,35–39} as well as markers of omega-3 fatty acid intake,⁴⁰ on CVD end points in a variety of populations (Tables 1 and 2^{1,2,4,6–9,28–36,39–43} and Tables 3 and 4^{3,10,11,13,37,38}). Healthy subjects and subjects at high risk for coronary disease, including those who had an MI, have been evaluated. Many different study designs for both epidemiologic and interventional studies have been used. In addition, a number of diet-assessment

Table 1
Epidemiologic studies assessing omega-3 fatty acid consumption and cardiovascular disease (CVD) risk: study design

Study	Omega-3 Intake	Subjects (n, age)	Baseline Status	Follow-Up (yr)
NHANES I Follow-up Study ²	Fish: never, <1×/wk, 1×/wk, >1×/wk	8,825 M + W, 25–74 yr	Healthy	Mean 18.8 (≤ 22.1)
Physicians Health Study ⁶	Fish: none, <1×/mo, 1×/wk	20,551 M, 40–84 yr	Healthy	11
Seven Countries Study ³⁰	Average omega-3 intake in each country	12,763 M, middle-aged	Healthy	25
Zutphen Study ⁴¹	Fish (g/day): >20, <20	552 M, 50–69 yr	Healthy	10
Zutphen Elderly Study ²⁹	ALA (% kcal): <0.45, 0.45–0.58, ≥0.58	667 M, 64–84 yr, subjects added	Healthy	10
Health Professionals Follow-Up Study ³⁴	ALA (mg/day): 790 (10 th percentile)–1,470 (90 th percentile)	45,722 M, 40–75 yr	Healthy	14
Nurses Health Study ²⁸	ALA means across quintiles (g/day): 0.71, 0.86, 0.98, 1.12, 1.36	76,283 W, 30–55 yr	Healthy	10
Nurses Health Study ⁷	Fish: <1×/mo, 1–3×/mo, 1×/wk, 2–4×/wk, ≥5×/wk	84,688 W, 34–59 yr	Healthy	16
Nurses Health Study ⁴³	Fish: <1×/mo, 1–3×/mo, 1×/wk, 2–4×/wk, ≥5×/wk	5,103 W	Diabetes, no CAD	CAD within 4–20
Cardiovascular Health Study ³²	Cases fatal IHD: EPA/DHA (% total kcal) = 3.3 ± 0.8, ALA = 0.16 ± 0.06, LA = 20.1 ± 2.3 Cases nonfatal MI: EPA/DHA = 3.6 ± 1.1, ALA = 0.17 ± 0.06, LA = 20.3 ± 2.5	179 cases, 179 controls, ≥65 yr	Cases: fatal MI, IHD death, nonfatal MI	≤4
Cardiovascular Health Study ³¹	Fish: <1×/mo, 1–3×/mo, 1–4×/wk, ≥5×/wk	4,775 M + W, ≥65 yr (mean 72.7)	Free of CVD	12
Danish adults ³⁵	Fish: <1×/mo, 2×/mo, <1×/wk, 2×/wk vs 1×/wk	4,513 M, 3,984 W, 30–70 yr	Healthy, no CAD ≥5 yr	8–18
Japan Public Health Center–Based Study Cohort I ³⁹	Fish (g/day): 23, 51, 78, 114, 180	41,578 M + W, 40–59 yr	Healthy	477,325 person-yr
CWES ⁹	Fish (g/day): none, 1–17, 18–34, ≥35	1,822 M, 40–56 yr	Healthy	30
CWES ³³	Fish (g/day): none, 1–17, 18–34, ≥35	1,847 M, 40–55 yr	Healthy	30
EURAMIC ⁴⁰	NA*	M, 639 cases, 700 controls	Patients with MI	NR
Honolulu Heart Program ³⁶	Fish: <2×/wk, >2×/wk	8,006 JA M, 45–65 yr	Smokers	23
36-country FAO and WHO data ¹	Fish: 0.23–10.43% kcal (mean 1.53 ± 1.93)	M + W, 45–74 yr	Varied	Assessed 1961–1991
Meta-analysis of cohort studies, CAD mortality ⁴	Fish: <1×/mo, 1–3×/mo, 1×/wk, 2–4×/wk, ≥5×/wk	222,364 M + W	Apparently healthy	Mean 11.8
Meta-analysis of cohort studies, stroke ⁸	Fish: <1×/mo, 1–3×/mo, 1×/wk, 2–4×/wk, ≥5×/wk	200,575 M + W, 34–103 yr	Apparently healthy	Mean 12.8
Meta-analysis of observational studies ⁴²	Fish: any, <2×/wk, 2–4×/wk, ≥4×/wk	M + W, 22–87 yr	Cases: MI	5–30

ALA = α -linolenic acid; BI = black; CAD = coronary artery disease; CWES = Chicago Western Electric Study; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; EURAMIC = European Multicenter Case-control Study on Antioxidants, Myocardial Infarction, and Breast Cancer; FAO = Food and Agriculture Organization of the United Nations; IHD = ischemic heart disease; JA = Japanese American; LA = linoleic acid; M = men; MI = myocardial infarction; NA = not applicable; NHANES = National Health and Nutrition Examination Survey; NR = not reported; W = women; Wh = white; WHO = World Health Organization.

*Adipose levels of omega-3 fatty acids were measured.

methods have been employed to evaluate omega-3 fatty acid intake, and different diet designs have been implemented in the interventional studies. The following discussion is organized by first describing the study designs used and then presenting the study results organized by specific CVD outcomes for the epidemiologic and interventional studies reviewed.

EPIDEMIOLOGIC STUDY METHODS. Eight epidemiologic studies are discussed that assess the relationship between omega-3 fatty acids and CVD risk in individuals who were healthy at baseline. Some studies assessed risk solely in men^{6,9,29,30,33,34,41} or women,^{7,28} while others determined risk in a mixed population.^{2,31,32,35,39}

The Physicians' Health Study (PHS), a prospective cohort study, was conducted in a population of 20,551 healthy male physicians ranging in age from 40 to 84 years at baseline to compare men who consumed no fish with less than once a month and once weekly. Fish consumption was estimated in this study by a semiquantitative food-frequency questionnaire. Kromhout and colleagues³⁰ examined CAD mortality rates among 12,763 healthy middle-aged men from 16 cohorts in the Seven Countries Study (SCS) using laboratory analyses of representative foods from each country to estimate average omega-3 fatty acid intakes. In the Zutphen Elderly Study (ZES), a prospective population-based study, ALA intakes were estimated as a percentage of energy on the basis of data from dietary histories of 667 healthy survivors of the Dutch cohort of the SCS aged 64 to 84 years.^{29,41} Analyses were adjusted for body mass index, smoking status, alcohol intake, use of vitamin supplements, and dietary intakes of saturated fat, *trans* fatty acids, *cis* fatty acids, LA, EPA, DHA, protein (percentage of energy), energy, dietary cholesterol, fiber, vitamin E, vitamin C, and beta carotene.^{29,41} Another cohort study, the Health Professionals Follow-Up Study, assessed omega-3 intake by a semiquantitative food-frequency questionnaire in 45,722 men aged 40 to 75 years over 14 years of follow-up.³⁴ The Chicago Western Electric Study (CWES),^{9,33} a prospective study in 1,847 healthy men aged 40 to 55 years, assessed the impact of fish consumption, determined by diet history questionnaires, across tertiles (1 to 17 g/day, 18 to 34 g/day, and ≥ 35 g/day) on CVD end points over 30 years of follow-up.

In the Nurses' Health Study (NHS), a longitudinal study, food-frequency questionnaires were used to assess dietary intake of omega-3 fatty acids and fish consumption prospectively in a large cohort of healthy women for 10 to 16 years of follow-up.^{7,28}

The National Health and Nutrition Examination Survey (NHANES) I Follow-Up Study was conducted over an average of 18.8 years in 8,825 healthy white and African American men and women aged 25 to 74 years.² Fish intake was estimated at baseline from food-frequency data over 3 months. Analyses were adjusted for age, smoking, history of diabetes, education, systolic blood pressure, total serum cholesterol, body mass index, alcohol intake, and level of

activity. The Cardiovascular Health Study (CVHS), a prospective study with 12 years of follow-up in 4,775 men and women aged ≥ 65 years and free of CVD, assessed fish consumption by food-frequency questionnaire and verified consumption by plasma EPA and DHA concentrations.³¹ In the Japan Public Health Center-Based (JPHC) Study Cohort I, a population-based study in 41,578 healthy Japanese men and women aged 40 to 59 years, fish intakes were determined by food-frequency questionnaires over 477,325 person-years of follow-up.³⁹ A prospective cohort study by Osler and associates³⁵ was conducted in 4,513 Danish men and 3,984 women aged 30 to 70 years, who were free of CAD at baseline, to determine the relationship between fish consumption and CAD after 8 to 18 years of follow-up. A semiquantitative food-frequency questionnaire was used to assess fish intake across 4 categories: ≤ 1 time per month, 2 times per month, 1 time per week, and ≥ 2 times per week.

Two prospective studies that assessed CVD risk based on omega-3 fatty acid status in populations at high risk are the European Multicenter Case-control Study on Antioxidants, Myocardial Infarction and Breast Cancer (EURAMIC) study and the Honolulu Heart Program (HHP).^{36,40} In the EURAMIC study,⁴⁰ comparisons were made between adipose tissue fatty acid concentrations of 639 men with previous MI and 700 control subjects in 8 European countries and Israel. The HHP, a prospective study in 8,006 Japanese American men aged 45 to 65 years an average follow-up of 23 years, classified fish intake as < 2 times per week or > 2 times per week as determined by food-frequency questionnaire.³⁶

In an ecologic study by Zhang and colleagues,¹ fish consumption was estimated as a percentage of total energy on the basis of food balance sheets of men and women of varying health status, aged 45 to 74 years, residing in 36 countries. Using Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) data, this information was collected during periods between 1961 and 1991.

INTERVENTIONAL STUDY METHODS. Two key interventional studies assessed the impact of an increased fish intake on CVD end points in men who were at elevated risk for CVD.^{13,37} In the Multiple Risk Factor Intervention Trial (MRFIT),¹³ fish consumption data were obtained from 4 sequentially administered 24-hour recalls, and average baseline omega-3 fatty acid intakes were calculated for 6,250 men at high risk for CVD. In an interventional study in 3,114 Welsh men < 70 years of age with baseline angina, dietary advice to increase omega-3 fatty acid intake by consuming oily fish 2 times per week or ≤ 3 g of fish oil supplements daily was compared.³⁷

Secondary prevention trials have assessed the effects of increased omega-3 fatty acid intake via fish alone³ or in combination with supplements³⁸ or supplemented foods.¹⁰ In the Finnish cohort of the secondary prevention interventional study, European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE),³

Table 2
Epidemiologic studies assessing omega-3 fatty acid consumption and cardiovascular disease (CVD) risk: results

Study	All CVD*	Coronary Artery Disease (CAD)			Stroke*	Sudden Cardiac Death*	All-Cause Mortality*
		Nonfatal MI*	Fatal MI*	All*			
NHANES I Follow-Up Study ²	Fatal CVD [†]	NR	NR	M Wh: 0.86 (0.65–1.13); Bl: 1.05 (0.50–2.19), NS [‡] W Wh: 0.97 (0.74–1.28); Bl: 0.90 (0.51–1.6), NS	NR	NR	M Wh: 0.85 (0.68, 1.06), p [‡] = 0.01; Bl: 1.11 (0.68, 1.81), NS [‡] W Wh: 0.90 (0.71, 1.15); Bl: 0.82 (0.52–1.28), NS [‡]
Physicians Health Study ⁶	Fatal: no protection	No protection	NR	NR	NR	0.43 (0.2, 0.93)	0.71 (0.55, 0.91) NS
Seven Countries Study ³⁰	NR	NR	NR	NR	NR	NR	NR
Zutphen Study ⁴¹	NR	NR	NR	NR	HR = 0.49 (0.24–0.99)	NR	NR
Zutphen Elderly Study ²⁹	NR	NR	1.59 (0.62–4.08), p [‡] = 0.26	1.68 (0.86–3.29), p [‡] = 0.17	NR	NR	NR
Health Professionals Follow-Up Study ³⁴	NR	HR = 0.82 (0.67–1.02)	NR	HR = 0.84 (0.71–1.0)	NR	HR = 1.15 (0.69, 1.03)	NR
Nurses Health Study ²⁸	NR	0.85 (0.61–1.19), p [‡] = 0.50	NR	Fatal: 0.55 (0.32–0.94), p [‡] = 0.01	NR	NR	NR
Nurses Health Study ⁷	NR	0.73 (0.51–1.04)	0.55 (0.33–0.90)	0.66 (0.50–0.89), p [‡] = 0.001	NR	NR	NR
Nurses Health Study ⁴³	NR	NR	NR	0.36 (0.20–0.66), p [‡] = 0.002	NR	NR	0.48 (0.29, 0.80), p [‡] = 0.005
Cardiovascular Health Study ³²	NR	EPA/DHA: OR = 0.97 (0.71–1.33), NS; ALA: OR = 1.07 (0.81–1.41), NS; LA: 2.42 (1.07–5.43), p = 0.03	NR	Fatal: EPA/DHA: OR = 0.30 (0.12–0.76), p = 0.01; ALA: 0.48 (0.24–0.96), p = 0.04; LA: 2.42 (1.07–5.43), p = 0.03	NR	NR	NR
Cardiovascular Health Study ³¹	NR	NR	NR	NR	0.77 (0.56–1.07), p [‡] = 0.06	NR	NR
Danish adults ³⁵	NR	NR	0.98 (0.62–1.52), NS	0.93 (0.88–1.27), NS	NR	NR	1.06 (0.88, 1.28), p [‡] = 0.02
Japan Public Health Center-Based Study Cohort I ³⁹	NR	HR = 0.44 (0.24–0.81), p [‡] = 0.03	NR	HR = 0.63 (0.38–1.04), p [‡] = 0.25	NR	HR = 1.14 (0.36, 3.63), p [‡] = 0.15	NR
Chicago Western Electric Study ⁹	Fatal: 0.74, p = 0.01	0.56, p [‡] = 0.02	NR	0.62, p [‡] = 0.04	NR	NR	0.85 (0.64, 1.10), NS
Chicago Western Electric Study ³³	NR	NR	NR	NR	1.26 (0.74–2.16), NS	NR	NR
EURAMIC ⁴⁰	NR	NR	NR	NR	0.88, NS	NR	NR
Honolulu Heart Program ³⁶	NR	NR	NR	High-smoking group: 0.5 (0.28–0.91), p < 0.01	NR	NR	NR

Table 2
Continued

Study	All CVD*	Coronary Artery Disease (CAD)			Stroke*	Sudden Cardiac Death*	All-Cause Mortality*
		Nonfatal MI*	Fatal MI*	All*			
36-Country FAO and WHO data ¹	NR	NR	NR	M, [§] 1961–1963: $r = -0.4$, $p < 0.05$; 1979–1981: $r = -0.39$, $p < 0.05$; 1989–1991: $r = -0.48$, $p < 0.01$ W, 1961–1963: $r = -0.42$, $p < 0.01$; 1979–1981: $r = -0.38$, $p < 0.05$; 1989–1991: $r = -0.51$, $p < 0.01$	M, [§] 1961–1963: $r = -0.34$, $p < 0.05$; 1979–1981: $r = -0.27$, NS; 1989–1991: $r = -0.29$, NS W, 1961–1963: $r = -0.35$, $p < 0.05$; 1979–1981: $r = -0.28$, NS; 1989–1991: $r = -0.33$, NS	NR	M, [§] 1961–1963: $r = -0.62$, $p < 0.001$; 1979–1981: $r = -0.54$, $p < 0.001$; 1989–1991: $r = -0.54$, $p < 0.001$ W, 1961–1963: $r = -0.6$, $p < 0.001$; 1979–1981: $r = -0.47$, $p < 0.01$; 1989–1991: $r = -0.56$, $p < 0.001$
Meta-analysis of cohort studies, CAD mortality ⁴	NR	NR	NR	Fatal: 0.62 (0.46–0.82)	NR	NR	NR
Meta-analysis of cohort studies, stroke ⁸	NR	NR	NR	NR	0.69 (0.54, 0.88)	NR	NR
Meta-analysis of observational studies ⁴²	NR	NR	Any fish: 0.83 (0.76–0.9), $p < 0.005$	Any fish: 0.86 (0.81–0.92), $p < 0.005$	NR	NR	NR

ALA = α -linolenic acid; BI = black; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; EURAMIC = European Multicenter Case-control Study on Antioxidants, Myocardial Infarction and Breast Cancer; FAO = Food and Agriculture Organization of the United Nations; HR = hazard ratio; LA = linoleic acid; M = men; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; NR = not reported; NS = not significant; OR = odds ratio; r = correlation coefficient; W = women; Wh = white; WHO = World Health Organization.

*Relative risk (RR) for highest intake versus lowest intake unless otherwise noted; confidence interval (CI) in parentheses.

[†]Fatal CVD in men, white: RR 0.95 (CI 0.68–1.33), p for trend 0.24; black: RR 1.08 (CI 0.52–2.21), p for trend 0.8; in women, white: RR 1.06 (CI 0.75–1.5); black: RR 0.99 (CI 0.51–1.93), NS for trends.

[‡] p value for trend.

[§]Range of dates, eg, 1961–1963.

Table 3
Interventional studies assessing omega-3 fatty acid consumption and cardiovascular disease risk: study design

Study	Omega-3 Intake	Subject Characteristics	Baseline Status	Follow-Up
MRFIT ¹³	Averaged individual omega-3 intakes	Usual care: 6,250 M	High risk	10.5 yr
Burr et al ³⁷	Fish: 2×/week, Fish oil: <3 g	3,114 Welsh M, age <70 yr	Angina	3–9 yr
EUROASPIRE ³	Fish (g/day): none, 1–57, >57	285 M, 130 W, age 33–74 yr	CAD	5 yr
DART ³⁸	Fish: 200–400 g/wk (500–800 mg/day)	2,033 Welsh M	MI	Intervention, 2 yr; follow-up, 10 yr
Lyon Diet Heart Study ¹⁰	ALA (g/day): 1.8 vs 0.67	333 control, 302 exp, M + W, age <70 yr (mean 53.5 yr)	post MI (≤6 mo)	46 mo
Meta-analysis of randomized controlled trials ¹¹	Enriched diet vs control or supplement vs placebo	7,855 control, 7,951 patients	CAD >6 mo	>6 mo

ALA = α -linoleic acid; CAD = coronary artery disease; DART = Diet and Reinfarction Trial; EUROASPIRE = European Action on Secondary Prevention Through Intervention to Reduce Events; exp = experimental group; M = men; MI = myocardial infarction; MRFIT = Multiple Risk Factor Intervention Trial; W = women.

Table 4
Interventional studies assessing omega-3 fatty acid consumption and cardiovascular disease (CVD) risk: results

Study	All CVD*	Coronary Artery Disease			Stroke*	Sudden Cardiac Death	All-Cause Mortality
		Nonfatal MI*	Fatal MI*	All*			
MRFIT ¹³	Inverse p <0.04	NR	NR	Inverse p <0.02	NR	NR	NR
Burr et al ³⁷	Fatal HR = 1.28 (1.0–1.58), p = 0.047	NR	NR	NR	NR	HR = 1.54 (1.06– 2.23), p = 0.025	NR
EUROASPIRE ³	0.45 (0.19–1.09), p [†] = 0.121	NR	NR	Fatal 1.04 (0.25–4.31), NS	NR	NR	0.37 (0.14–1.00), p [†] = 0.059
DART ³⁸	NR	NR	NR	After 2 yr: Mortality 0.7 (0.54–0.92)	NR	NR	NR
Lyon Diet Heart Study ¹⁰	NR	0.83	NR	NR	0 vs 4	0.35 (0.15–0.83)	0.44 (0.21–0.94)
Meta-analysis of randomized controlled trials ¹¹	NR	0.8 (0.5–1.2), p = 0.16	0.7 (0.6–0.8), p <0.001	NR	NR	0.7 (0.6–0.9), p <0.01	0.8 (0.7–0.9), p <0.001

DART = Diet and Reinfarction Trial; EUROASPIRE = European Action on Secondary Prevention Through Intervention to Reduce Events; HR = hazard ratio; MI = myocardial infarction; MRFIT = Multiple Risk Factor Intervention Trial; NR = not reported.

*Relative risk for highest intake versus lowest intake unless otherwise noted; confidence interval in parentheses.

[†]p value for trend.

frequency of fish consumption, determined by 4-day food records, was obtained from 285 men and 130 women aged 33 to 74 years who had clinically documented CAD. In the Diet and Reinfarction Trial (DART), a 2-year secondary prevention study, 2,033 Welsh men were randomized to the intervention group and consumed an average of 200 to 400 g of fatty fish weekly, estimated to provide 500 to 800 mg of omega-3 fatty acids daily.³⁸ The Lyon Diet Heart Study (LDHS), a randomized controlled single-blinded secondary prevention study, compared the Mediterranean diet with the National Cholesterol Education Program (NCEP) step 1 diet in adults with a mean age of 53.5 years who had suffered an MI within 6 months of randomization.¹⁰ The study was designed to compare the effects of a Mediterranean-style diet rich in ALA (ie, emphasizing more bread; more root vegetables and green vegetables; more fish; less beef, lamb, and pork [replaced with poultry]; daily fruit; butter and cream replaced with margarine high in ALA) with those of the NCEP step 1 diet on composite CVD end points at 46 months.

Omega-3 fatty acid intake and CVD risk study results:

ALL CVD. The risk for individual CVD end points is most often reported for all CAD, fatal and nonfatal MI, and stroke. Composite risk for all CVD includes these major events, as well as minor events such as stable and unstable angina, pulmonary and peripheral embolisms, postangioplasty restenosis, and heart failure. The relationship between omega-3 fatty acid intake and CVD mortality was demonstrated in 2 prospective studies to be beneficial in healthy men, with risk estimated at 25% to 30% lower with consumption as low as 1 fish meal weekly⁶ and ≤ 35 g/day of fish.^{9,33} This was confirmed by a 2-year interventional study with a 10-year follow-up that showed significant reduction in CVD mortality associated with baseline omega-3 fatty acid intake.¹³ However, fish consumption² and markers of omega-3 fatty acid intake³ were found to have no protection against CVD mortality in healthy men and women² and in individuals with CAD,³ and to increase risk in men with angina,³⁷ particularly in the fish oil capsule cohort compared with the group consuming fish.

Two prospective studies that found a benefit of omega-3 fatty acid intake on CVD mortality were the PHS and the CWES.^{6,9,33} In the CWES, CVD mortality was significantly lower among men consuming ≥ 35 g/day of fish compared with men consuming no fish (relative risk [RR], 0.74; $p = 0.01$ for trend).⁹ In MRFIT, an interventional study in men who were at greater than average risk for CAD, a significant inverse relationship was found between CVD mortality and baseline intake of dietary omega-3 fatty acids after 10.5 years of follow-up ($p < 0.04$).¹³ Four studies that did not find a cardioprotective effect of omega-3 fatty acid intake on CVD mortality were 2 epidemiologic studies, the NHANES I Follow-Up Study and PHS,² and 2 interventional studies, EUROASPIRE³ and a study by Burr and

associates³⁷ after 11 years, CVD mortality was unrelated to fish intake in healthy men.⁶ After an average of 18.8 years, the NHANES I Follow-Up Study found that CVD mortality for any race-gender group across quartiles of fish intake was not significantly different after adjustment between those who never consumed fish and those who consumed any fish (< 1 time per week, 1 time per week, > 1 time per week). In the Finnish cohort of the EUROASPIRE study, fish intake—estimated by dietary methods and measurement of omega-3 fatty acid concentrations in cholesteryl esters and red blood cell membrane phospholipids—was not associated with reductions in 5-year mortality due to CVD ($p = 0.121$ for trend).³ In an interventional study conducted by Burr and associates,³⁷ the hazard ratio (HR) for CVD mortality was 1.28 (95% CI, 1.00 to 1.58; $p = 0.047$) for individuals with angina advised to increase dietary omega-3 fatty acid intake; this was largely attributed to the taking of fish oil capsules. However, individuals who increased omega-3 fatty acids through increased fish consumption exhibited a lower HR for CVD mortality than individuals taking fish oil capsules.

ALL CAD. Numerous studies have demonstrated an inverse relationship between omega-3 fatty acid intake and CAD incidence and/or mortality (Figure 27.^{35,36,43}). Meta-analyses of epidemiologic studies have demonstrated a 7%⁴ and 14%⁴² decrease in CAD mortality for each 20 g/day increase of fish intake and for any amount of fish intake, respectively. Individual epidemiologic studies have indicated that fish intakes, ranging in frequency from > 2 times per week to 1 time per day, reduce risk 30% to 64%,^{7,9,33,36,43} with the largest reductions occurring in women with diabetes who consumed fish ≥ 5 times per week.⁴³ In addition, epidemiologic data indicate that for every 1 g/day increase in ALA intake, CAD incidence decreases by 16%.³⁴ Although some interventional studies^{13,38} confirmed the inverse relationship between fish consumption and risk for CAD mortality, other studies report no relationship^{2,3,35} or a harmful effect³⁷ of increased omega-3 fatty acid intake. Of note is that the studies demonstrating no association were conducted in healthy populations; therefore, the greatest benefit may be for individuals with a history of CVD or at risk for CV events. In addition, the 1 study showing an increased risk for CAD incidence assessed ALA, not marine-derived omega-3 fatty acid intake.²⁹

At 25-year follow-up of the SCS, a significant inverse relationship was found between omega-3 fatty acid intakes and CAD mortality, but the relationship was not independent of saturated fat intake.³⁰ The CWES, a study specifically examining fish intake, determined that fish intake ≥ 35 g/day, compared with no fish consumption, significantly reduced risk for CAD in healthy men (RR, 0.62; $p = 0.04$ for trend).⁹

In a cohort of 76,283 women aged 30 to 55 years in the NHS, a significant reduction in 10-year CAD mortality was associated with increasing intakes of ALA ($p = 0.01$ for

trend).²⁸ At the 16-year follow-up of the NHS in a cohort of 84,688 women aged 34 to 59 years, a significant reduction in CAD mortality of 34% was observed in the group of women who regularly consumed fish ≥ 5 times per week compared with women who consumed fish < 1 time per month ($p = 0.001$ for trend).⁷ Subgroup analysis was done in 5,103 women with diabetes, who were free of CAD at baseline but experienced a coronary event within 4 to 20 years of enrollment.⁴³ After adjustment for potential confounders, relative risk for CAD incidence was 30% to 36% lower among women who consumed fish 1 to 3 times per month, 1 time per week, and 2 to 4 times per week and 64% lower for women consuming fish ≥ 5 times per week, compared with women who consumed fish < 1 time per month ($p = 0.002$ for trend).

In a nested case control study of the CVHS, the relationship between CAD and PUFA concentration of plasma phospholipids in 179 cases and 179 control subjects was determined. Among cases, plasma EPA and DHA, expressed as a percentage of total fatty acids, was 3.3% ($\pm 0.8\%$) compared with 3.8% ($\pm 1.3\%$) for cases of fatal ischemic heart disease, and plasma ALA was 0.16% (± 0.06) compared with 0.17% ($\pm 0.06\%$) for control subjects. Linoleic acid was 20.1% ($\pm 2.3\%$) for cases and 19.2% ($\pm 2.4\%$) for control subjects. For ischemic heart disease death, the odds ratio corresponding to an increase of 1 standard deviation (SD) in plasma phospholipid fatty acid concentration over 4 years was 0.30 (95% CI, 0.12 to 0.76; $p = 0.01$) for combined EPA and DHA and 0.48 (95% CI, 0.24 to 0.96; $p = 0.04$) for ALA. In contrast, for LA, the odds ratio was 2.42 (95% CI, 1.07 to 5.43; $p = 0.03$).³²

In the HHP, a significant interaction was found among smokers between fish intake categories and CAD incidence and mortality. Among smokers, age-adjusted mortality rates significantly increased with the number of cigarettes smoked daily only among those who consumed fish < 2 times per week ($p < 0.0001$). In the subgroup of smokers who smoked the greatest number of cigarettes, the risk factor-adjusted relative risk for mortality due to CAD when fish was consumed > 2 times per week was 50% that observed when fish was consumed < 2 times per week (RR, 0.5; 95% CI, 0.28 to 0.91; $p < 0.01$). Among smokers who consumed fish > 2 times per week, CAD mortality was not increased.³⁶

In an ecologic study by Zhang and colleagues,¹ fish consumption, as a percentage of total energy, ranged from 0.23% to 10.43% with a mean of 1.53% ($\pm 1.93\%$). There was a significant inverse correlation after adjusting for confounders between ischemic heart disease and fish intake in men estimated during 1961 through 1963 (correlation coefficient [r] = -0.4 ; $p < 0.05$), 1979 through 1981 ($r = -0.39$; $p < 0.05$), and 1989 through 1991 ($r = -0.48$; $p < 0.01$). A similar pattern was seen among women, with the relationship significant for 1961 through 1963 ($r = -0.42$; $p < 0.01$), 1979 through 1981 ($r = -0.38$; $p < 0.05$), and 1989 through 1991 ($r = -0.51$; $p < 0.01$).¹

The results of a meta-analysis of 14 cohort and 5 case control studies with 5- to 30-year follow-up data that included men and women aged 22 to 87 years and quantified fish consumption as any, < 2 times per week, 2 to 4 times per week, and ≥ 4 times per week revealed that consumption of any amount of fish was associated with a reduction of 14% in CAD mortality (RR, 0.86; 95% CI, 0.81 to 0.92; $p < 0.005$).⁴² In a meta-analysis of 13 cohort studies, CAD mortality in apparently healthy men and women was 7% lower at a mean follow-up of 11.8 years for each 20 g/day increase in fish intake ($p = 0.03$ for trend).⁴ This dose-dependent response was based on the pooled multivariate RRs for CAD mortality and fish consumption: 0.89 (95% CI, 0.79 to 1.01) for fish intake 1 to 3 times per month, 0.85 (95% CI, 0.76 to 0.96) for 1 time per week, 0.77 (95% CI, 0.66 to 0.89) for 2 to 4 times per week, and 0.62 (95% CI, 0.46 to 0.82) for ≥ 5 times per week.

Two interventional studies conducted in men who had an MI³⁸ or were at risk for CVD¹³ are consistent with the findings of the epidemiologic studies above. MRFIT revealed a significant inverse relationship between fish consumption and CAD mortality in men who were at above-average risk ($p < 0.02$).¹³ In the DART, the RR for CAD mortality was 0.7 (95% CI, 0.54 to 0.92) after the 2-year intervention.³⁸ However, at the 10-year follow-up, this benefit was no longer apparent (RR, 0.98; 95% CI, 0.72 to 1.32).

Evidence from 3 epidemiologic studies, the NHANES I Follow-Up Study,² a study by Osler and associates,³⁵ and the JPHC Study Cohort I,³⁹ did not reveal any significant reduction in CAD incidence with increasing intakes of fish. In addition, the prospective cohort study in Danish men and women by Osler and associates³⁵ did not reveal a significant relationship between fish intake and CAD mortality. In a subgroup analysis of Danish adults at high risk for CVD based on gender-adjusted age (men aged > 50 years and women aged > 60 years), serum total cholesterol levels, and smoking, the RR for CAD incidence and mortality was not significant. Evidence from the Finnish cohort of the EUROASPIRE study, an interventional study, confirms these findings and demonstrated that fish intake was not associated with reductions in 5-year mortality due to CAD ($p = 0.731$ for trend).³

In contrast to most findings with omega-3 fatty acids, the ZES determined that age and energy-adjusted RR for 10-year CAD mortality and ALA intake was 1.26 (95% CI, 0.59 to 2.69) for individuals consuming 0.45% to 0.58% of energy from ALA and 1.95 (95% CI, 0.96 to 3.94) for individuals consuming $\geq 0.58\%$ of energy from ALA ($p = 0.05$ for trend).²⁹ The conflicting results may be attributed to confounding by associated *trans* fatty acid intake.⁴⁴ However, after adjustment for potential confounders, the relationship was no longer significant ($p = 0.17$ for trend).²⁹

FATAL AND NONFATAL MI. Fish consumption ≥ 5 times per week has been associated with significant reductions in the incidence of fatal and nonfatal MI ranging from 27% to 56% in both men and women.^{7,9,28,39,43} In the JPHC Study Cohort I, fish consumption of 8 times per week (median intake of 180

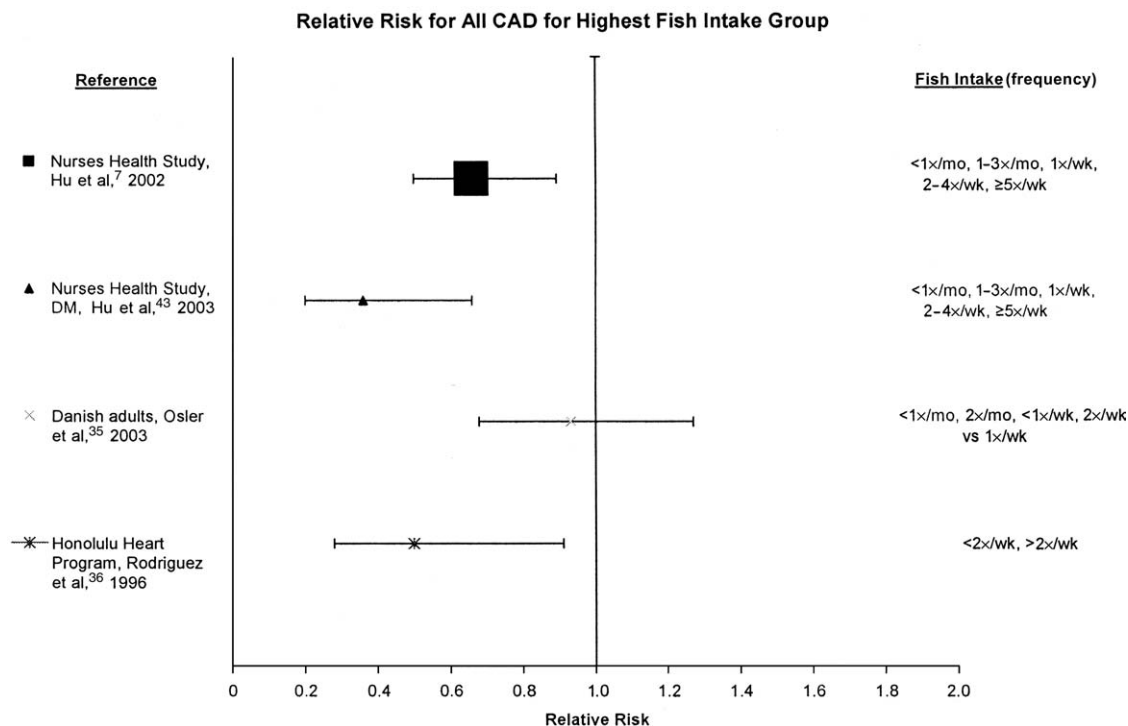


Figure 2. Relative risk for all coronary artery disease (CAD) for the highest fish intake groups in epidemiologic studies. DM = diabetes mellitus.

g/day) was associated with a 56% reduction in incidence of nonfatal MI and a 53% reduction in total MI when compared with fish intakes of 1 time per week (median intake of 23 g/day) in men and women.³⁹ In the CWES, risk for nonfatal MI was 44% lower among men consuming ≥ 35 g/day of fish in comparison with men with no fish consumption ($p = 0.02$ for trend).⁹ In the Health Professionals Follow-Up Study, ALA intake was associated with a trend toward lower risk of nonfatal MI (HR, 0.82; 95% CI, 0.67 to 1.02) at 14-year follow-up.³⁴ After 10 years of follow-up in the NHS, risk of nonfatal MI was not significantly related across quintiles of ALA intake ($p = 0.5$ for trend); however, the trend toward lower mortality due to MI across quintiles of ALA intake was borderline significant ($p = 0.06$ for trend).²⁸ At the 16-year follow-up, fish consumption ≥ 5 times per week, in comparison with < 1 time per month, was protective against nonfatal MI (RR, 0.73; 95% CI, 0.51 to 1.04) and associated with a 45% reduction in risk for fatal MI (RR, 0.55; 95% CI, 0.33 to 0.9).⁷ A beneficial effect was confirmed by a meta-analysis of 19 observational studies (14 cohort and 5 case control studies) with 5 to 30 years of follow up, of adults aged 22 to 87 years.⁴² A significant reduction of 17% in MI (RR, 0.83; 95% CI, 0.76 to 0.90; $p < 0.005$) was found among those who consumed fish compared with those who did not.⁴² A possible explanation for the difference in magnitude of the effect may be due to differences in how fish consumption was classified, such that in the study by Whelton and colleagues,⁴² any fish consumption was compared with no consumption, whereas the former studies used fish consumption ≥ 5 times per week compared with < 1 time per month.

Results of interventional studies demonstrate that a combination of plant and marine-derived omega-3 fatty acids reduce risk for MI.^{10,11} In the LDHS, patients receiving the supplemented margarine (1.8 g/day ALA) as part of a diet rich in fish had significantly greater plasma levels of ALA compared with control patients receiving the placebo margarine (0.67 g/day ALA; $p < 0.001$). After 46 months, the rate of nonfatal MI per 100 patients per year of follow-up was 0.83 for the experimental group compared with 2.7 for control subjects.¹⁰ A meta-analysis of 11 randomized controlled trials conducted in 7,951 patients with CAD for ≥ 6 months and 7,855 control subjects compared the effects on CVD end points of an omega-3 fatty acid-enriched diet against those of a control diet or of dietary supplements against placebo.¹¹ Two of the studies evaluated dietary intakes of omega-3 fatty acids, whereas the remaining 9 studies evaluated supplements containing only marine-derived omega-3 fatty acids (0.3 to 0.6 g/day EPA, 0.6 to 3.7 g/day DHA). Omega-3 fatty acid intervention was not associated with a significant reduction in incidence of nonfatal MI (RR, 0.8; 95% CI, 0.5 to 1.2; $p = 0.16$); however, it was associated with a significant reduction of 30% in incidence of fatal MI (RR, 0.7; 95% CI, 0.6 to 0.8; $p < 0.001$).¹¹

Baseline fish consumption, determined by food-frequency questionnaire and verified by adipose-tissue omega-3 fatty acid concentrations ($p = 0.001$), was not significantly associated with reduced risk of nonfatal MI at 11-year follow-up among healthy males in the PHS.⁶ The prospective cohort study by Osler and associates³⁵ confirmed these results in Danish men and women and did not reveal a significant relationship be-

tween fish consumption and MI. Another marker of omega-3 fatty acid intake, PUFA concentration of plasma phospholipids, showed no protection of omega-3 fatty acids against MI in a nested case-control study of the CVHS.³² PUFA concentration of plasma phospholipids was comparable in cases and control subjects for plasma EPA, DHA, ALA, and LA. For nonfatal MI, the odds ratio corresponding to an increase of 1 SD in plasma phospholipid fatty acid concentration over 4 years was 0.97 (95% CI, 0.71 to 1.33; $p = 0.8$) for combined EPA and DHA and 1.07 (95% CI, 0.81 to 1.41; $p = 0.6$) for ALA. In contrast, for LA, the odds ratio was 2.42 (95% CI, 1.07 to 5.43; $p = 0.03$).³²

Unlike other studies with omega-3 fatty acids, the ZES determined that the age and energy-adjusted relative risk of fatal MI was significantly greater among those with ALA intakes $>0.45\%$ of total energy ($p = 0.003$ for trend). After adjustment for potential confounders, the relationship was no longer significant ($p = 0.26$ for trend).²⁹

STROKE. Two prospective epidemiologic studies reported beneficial effects of fish consumption, with a wide range of intake, on stroke mortality in men⁴¹ as well as in men and women.³¹ The latter study reported a beneficial effect on ischemic stroke but no protection against hemorrhagic stroke. An ecologic study also reported a beneficial effect of fish on stroke mortality in men and women.¹ In addition, a large meta-analysis reported a beneficial effect of increased fish consumption on stroke mortality, as well as on the incidences of total stroke and ischemic stroke, but not on that of hemorrhagic stroke.⁸ However, fish consumption was not associated with incident stroke and stroke mortality in 1 prospective study conducted in men.³³ In a case-control study, ALA concentration in adipose tissue was not associated with stroke in men after adjusting for lifestyle factors.⁴⁰ Thus, the preponderance of epidemiologic evidence demonstrates a beneficial association of fish consumption with ischemic stroke.

Evidence from large epidemiologic studies, such as the Zutphen Study and the CVHS, demonstrates a reduction in stroke mortality, ranging from 11% to 51%, with increased fish consumption. At 10-year follow-up in the Zutphen Study,⁴¹ 51% fewer deaths due to stroke were found among a subgroup of men who consumed fish in amounts averaging ≥ 20 g/day compared with those who consumed <20 g/day (HR, 0.49; 95% CI, 0.24 to 0.99). The reduction in stroke mortality was 37% in the subset of 301 men with intakes classified as "always" compared with those classified as "never." This relationship was observed for intake of fatty fish, not lean fish, after adjustment for other dietary variables.²⁹ In the CVHS, fish consumption ≥ 1 time per month reduced stroke mortality among healthy men and women with borderline significance ($p = 0.06$ for trend).³¹ Classification of stroke as either ischemic or hemorrhagic revealed a significant decrease in ischemic stroke ranging from 11% to 28% with fish consumption ≥ 1 time per month compared with <1 time per month ($p = 0.03$ for trend); there was no protection against hemorrhagic stroke ($p = 0.63$).

Findings from a meta-analysis by He and associates⁸ confirm the inverse relationship between stroke risk and fish consumption. Fish intake was determined by in-person interviews with, or self-administered food-frequency questionnaires from, 9 cohorts in 8 studies of 200,575 healthy adults aged 34 to 103 years. At an average of 12.8 years of follow-up, RR of stroke was 0.87 (95% CI, 0.77 to 0.98) for those who consumed fish 1 time per week compared with those who consumed fish <1 time per month. This beneficial effect increased with increased consumption of fish (RR, 0.69; 95% CI, 0.54 to 0.88 for those who consumed fish ≥ 5 times per week). To account for the nonlinear relationship between fish intake and stroke mortality, intakes were classified as fish intakes ≥ 1 time per month or no fish consumption. Pooled relative risks for fish intake based on this classification were 0.85 for total stroke (95% CI, 0.79 to 0.91), 0.67 for ischemic stroke (95% CI, 0.58 to 0.78), and 1.06 for hemorrhagic stroke (95% CI, 0.82 to 1.37).⁸

In an ecologic study by Zhang and colleagues,¹ there was a significant inverse correlation after adjusting for confounders between stroke mortality and fish intake in men estimated during 1961 through 1963 ($r = -0.34$; $p < 0.05$). However, this relationship was not significant during the periods of 1979 through 1981 ($r = -0.27$) and 1989 through 1991 ($r = -0.29$). A similar pattern was seen among women, with the relationship being significant for the period of 1961 through 1963 ($r = -0.35$; $p < 0.05$) but not for the periods of 1979 through 1981 ($r = -0.28$) and 1989 through 1991 ($r = -0.33$).¹

In contrast, the EURAMIC case-control study⁴⁰ comparing the ALA concentration in adipose tissue (a marker of dietary ALA intake) between control subjects and patients with previous MI did not find a relationship with stroke risk after adjustment. The proportion of ALA in adipose tissue fatty acids in control subjects was significantly higher compared with men with previous MI ($p = 0.01$). A significant reduction in risk of MI was seen for the highest tertile of adipose fatty acid concentration compared with the lowest tertile (RR, 0.42; $p = 0.02$); however, after adjusting for lifestyle factors, the relationship was no longer significant. Findings of the 30-year follow-up of the CWES³³ indicate that there is also no significant relationship between fish consumption and incident stroke or stroke mortality in healthy men.

SUDDEN CARDIAC DEATH. One prospective cohort study in healthy men and 1 interventional study in men and women with previous MI demonstrate a protective association between fish consumption⁶ and ALA¹⁰ and sudden cardiac death. Evidence from a meta-analysis of 11 interventional studies also found that the incidence of sudden cardiac death was reduced as the result of fish consumption in patients with CAD. In contrast, Burr and colleagues reported that omega-3 fatty acids—principally fish oil supplements but not fish—increased the incidence of sudden cardiac death in patients with angina. However, the research

collectively shows beneficial effects of omega-3 fatty acids, from both marine and plant sources, on the incidence of sudden death.

Reduction in sudden cardiac death incidence ranged from 30% to 57% in interventional¹¹ and epidemiologic studies,⁶ respectively. In the PHS, fish consumption was found protective against sudden cardiac death at the 11-year follow-up; in contrast, there was no reduction in risk of fatal and nonfatal MI. The incidence of sudden cardiac death was 57% lower among those who consumed fish weekly compared with those who consumed fish <1 time per month (RR, 0.43; 95% CI, 0.20 to 0.93).⁶ A meta-analysis of randomized controlled trials involving either dietary intervention (n = 2) or omega-3 fatty acid supplements (n = 9) and including patients with CAD found a significant reduction of 30% in risk of sudden cardiac death (RR, 0.70; 95% CI, 0.6 to 0.9; p < 0.01).¹¹ At 46-month follow-up, the LDHS also demonstrated that an increased intake of ALA (1.8 g/day) is protective against sudden cardiac death in men and women with previous MI.¹⁰

Although a randomized controlled trial by Burr and colleagues³⁷ demonstrated an adverse effect of oily fish twice weekly or fish oil supplements ≤ 3 g/day on the incidence of sudden cardiac death in men with angina (HR, 1.54; 95% CI, 1.06 to 2.23; p = 0.025), the increase in risk was attributed to the fish oil capsules.

ALL-CAUSE MORTALITY. Four epidemiologic studies^{1,2,6,7} and 2 interventional studies^{3,10} reported a protective effect of fish consumption on all-cause mortality in men and women. Moreover, a meta-analysis of 11 randomized, controlled trials reported beneficial effects of omega-3 fatty acid intake on all-cause mortality.¹¹ However, 1 epidemiologic study reported no beneficial effect of fish consumption on all-cause mortality in men,⁹ and 1 prospective cohort study reported an increase in all-cause mortality in men and women that was associated with increasing fish consumption.³⁵ Despite these latter study findings, the majority of studies do indicate that fish consumption is associated with a decrease in all-cause mortality.

Although data from the NHANES I Follow-Up Study did not find a protective effect of fish consumption on CVD and CAD mortality, all-cause mortality was 24% lower in white men at a mean follow-up of 18.8 years (p < 0.01 for trend).² These trends were not statistically significant for white women or for African American men and women. The PHS also found a decreased risk for all-cause mortality associated with fish consumption in healthy men at 11-year follow-up (RR, 0.71; 95% CI, 0.55 to 0.91).⁶ The NHS demonstrated that women with diabetes also benefit from increased fish consumption. At 16-year follow-up, women who consumed fish ≥ 1 time per month had a significant reduction in mortality due to all causes compared with women who consumed fish <1 time per month (p = 0.005 for trend).⁴³ In an ecologic study in men and women by Zhang and colleagues,¹ there was a significant inverse correlation, after adjusting for confounders, between all-cause mortality and fish intake. Inverse correlations were demonstrated in men during 1961 through 1963 (r = -0.62;

p < 0.001), 1979 through 1981 (r = -0.54; p < 0.001), and 1989 through 1991 (r = -0.54; p < 0.001). A similar pattern was seen among women, with the relationship being significant during 1961 through 1963 (r = -0.6; p < 0.001), 1979 through 1981 (r = -0.47; p < 0.01), and 1989 through 1991 (r = -0.56; p < 0.001).¹

Interventional studies also have demonstrated a beneficial effect on all-cause mortality with intake of fish,³ ALA,¹⁰ or omega-3 fatty acid-enriched diets.¹¹ In the Finnish cohort of the EUROASPIRE study, the relationship between fish intake and 5-year all-cause mortality was borderline significant (p = 0.059 for trend).³ The only protective effect observed was for individuals with serum cholesteryl DHA concentrations (an indicator of dietary intake) in the highest tertile, who had 69% fewer deaths than those with DHA concentrations in the lowest tertile (p = 0.026). Serum cholesteryl ALA concentrations in the highest tertile appeared to be protective against all-cause mortality (RR, 0.33; p = 0.063). At 46-month follow-up, the LDHS demonstrated that daily ALA consumption of 1.8 g was associated with decreased risk for all-cause mortality in men and women with previous MI (RR, 0.44; 95% CI, 0.21 to 0.94).¹⁰ Furthermore, a meta-analysis of 11 randomized, controlled trials also found that all-cause mortality was significantly reduced by 20% in subjects with increased omega-3 fatty acid intakes through diet and supplementation (RR, 0.8; 95% CI, 0.7 to 0.9; p < 0.001).¹¹ The CWES, however, found that there was not a significant relationship between fish consumption and risk for all-cause mortality in healthy men at 30-year follow-up (p = 0.175 for trend).⁹

In contrast, a prospective cohort study in healthy adults, with a follow-up of 8 to 18 years, demonstrated an increase in all-cause mortality with increasing fish consumption (RR, 0.88 and 95% CI, 0.76 to 1.02 for <1 time per month; RR, 0.84 and 95% CI, 0.73 to 0.96 for 2 times per month; RR, 1.0 for <1 time per week; RR, 1.06 and 95% CI, 0.88 to 1.28 for >2 times per week; p = 0.02 for trend).³⁵ This effect on all-cause mortality was also seen in a subset of adults at high risk of CVD based on age and smoking status (p = 0.03 for trend).

Current Intake of Omega-3 Fatty Acids in the United States

Based on dietary estimates for fats and fatty acids by NHANES, for the US population aged 20 to 59 years in 1999 through 2000, the mean ALA intake for men is 1.7 g/day and for women it is 1.3 g/day.⁴⁵ For EPA, docosapentanoic acid (DPA), and DHA, the mean intake for men is 0.17 g/day and for women it is 0.11 g/day. Based on these same NHANES data, mean intake of fish is 81.76 g (2.92 oz)/week.⁴⁶ The majority of the fish consumed (63%) is finfish and shellfish containing <500 mg of omega-3 fatty acids per 3-oz serving. The most commonly consumed single fish is tuna (representing 22% of total fish consump-

Table 5
Finfish and shellfish most commonly consumed in the United States:
eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content*

Fish	EPA	DHA	EPA+DHA
Tuna, canned	0.198	0.535	0.733
Shrimp	0.145	0.122	0.267
Cod	0.003	0.131	0.134
Salmon	0.587	1.238	1.825
Clams	0.117	0.124	0.241
Flounder	0.207	0.219	0.426
Catfish	0.042	0.109	0.151
Flatfish	0.207	0.291	0.498
Pollock	0.077	0.383	0.46
Haddock	0.065	0.138	0.203

*Grams of fatty acid per 3 oz of fish, cooked.

Adapted from US Environmental Protection Agency⁴⁷ and US Department of Agriculture.⁴⁸

tion), with shrimp (16%), salmon (9%), mixed fish (8%), and crab (7%) also commonly reported (Table 5).^{46–48}

Dietary Recommendations for Omega-3 Fatty Acids

The Institute of Medicine of the National Academies⁴⁹ set a dietary recommendation as an adequate intake (an intake associated with a low prevalence of inadequacy) for ALA of 1.6 g/day for men and 1.1 g/day for women. This represents approximately 0.6% of energy intake for sedentary adults. The adequate intake for ALA is based on the median intakes in the United States and Canada—countries in which an ALA deficiency is nonexistent in healthy individuals. The Acceptable Macronutrient Distribution Range (the range of intake in a nutritionally adequate diet for a particular macronutrient that is associated with reduced risk of chronic disease) for ALA is 0.6% to 1.2% of calories. The lower boundary of the recommended range meets the adequate intake for ALA. The upper boundary corresponds to the highest reported ALA intake from foods consumed by individuals in the United States and Canada. In addition, $\leq 10\%$ of the adequate intake for ALA can be provided by EPA and/or DHA. Intakes of omega-3 fatty acids above the point of adequate intake confer health benefits, especially with respect to CVD. However, recommendations were not made for a greater intake for the prevention of CVD because of the lack of a robust database.

The Dietary Guidelines Advisory Committee (DGAC) Report 2005⁴⁶ recommended an ALA intake between 0.6% and 1.2% of calories. In addition, the report noted that consumption of 2 servings (approximately 8 oz total) per week of fish high in EPA and DHA is associated with reduced risk of both sudden death and CAD death in adults. To benefit from the potential cardioprotective effects of EPA and DHA, the weekly consumption of 2 servings of fish, particularly fish rich in EPA and DHA, was recommended. Table 6 lists species of fish that are rich in EPA and DHA.⁴⁸ In addition to the DGAC, other organizations have made similar recommendations for fish consumption:

Table 6
Best fish sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)*

Fish	EPA*	DHA*	EPA+DHA*
Salmon, Atlantic, farmed	0.587	1.238	1.825
Herring, Pacific	1.056	0.751	1.807
Mackerel, Pacific	0.555	1.016	1.571
Sablefish	0.737	0.782	1.519
White fish	0.345	1.025	1.37
Halibut, Greenland	0.573	0.428	1.001
Trout, farmed	0.284	0.697	0.981
Bluefish	0.275	0.565	0.84
Tuna, white, canned	0.198	0.535	0.733
Shark	0.219	0.366	0.585

*Grams of fatty acid per 3 oz of fish, cooked.

Adapted from US Department of Agriculture.⁴⁸

- The American Heart Association—consume fish, especially oily fish, at least twice a week^{50,51}
- NCEP—recommends fish as a food item for people to choose more often⁵²
- WHO—regular fish consumption, 1 to 2 servings per week; each serving should provide the equivalent of 200 to 500 mg of EPA and DHA⁵³
- European Society of Cardiology—oily fish and omega-3 fatty acids have particular protective properties for primary CVD prevention^{54–56}
- United Kingdom Scientific Advisory Committee on Nutrition—consume ≥ 2 portions of fish per week, of which 1 should be oily and provide 450 mg/day of EPA and DHA⁵⁷
- American Diabetes Association—2 to 3 servings of fish per week provide dietary omega-3 PUFAs and can be recommended.⁵⁸

Summary

The majority of epidemiologic and controlled interventional studies have demonstrated beneficial effects of omega-3 fatty acid consumption, whether marine or plant derived, on many CVD end points, including all CVD, defined as all CAD, fatal and nonfatal MI, and stroke; all CAD; fatal and nonfatal MI; stroke; sudden cardiac death; and all-cause mortality. Collectively, cardioprotective benefits have been found with consumption of modest amounts of omega-3 fatty acids provided by an average intake of 25 to 57 g (1 to 2 oz) of fish consumed daily or an intake of an equivalent amount consumed in ≥ 1 meal weekly or even monthly. Increasing fish consumption decreases risk in a dose-dependent manner. A meta-analysis of 13 cohort studies found a gradual beneficial effect of increasing fish dose and CAD mortality.⁴ Fish consumption 5 times per week decreased CAD mortality by 38%. There is evidence, albeit limited, that ALA also has cardioprotective effects.

The science progresses—A time for scrutiny: Scientific discoveries in the area of omega-3 fatty acids are happening at an ever-increasing rate. Research continually adds to the ex-

panding evidence base and contributes to our understanding of dietary omega-3 fatty acids and CVD. As would be expected, new studies sometimes challenge existing findings. One example is a recent Cochrane meta-analysis done by Hooper et al,⁵⁹ which concludes that: "long chain and shorter chain omega-3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer." As we have noted herein, the weight of evidence favors a beneficial effect of dietary omega-3 fatty acids on CVD. A critique of the Hooper meta-analysis written by von Schacky et al that appears in a recent International Society for the Study of Fatty Acids and Lipids (ISSFAL) Summer 2006 newsletter⁶⁰ questions the inclusion of the DART-2 trial. This trial, in men with angina, reported more sudden death in the intervention group provided dietary advice to eat fish or take fish oil capsules when compared with the control group.³⁷ Removal of DART-2 from the meta-analysis results in omega-3 consumption being associated with a decrease in relative risk. Removal of DART-2 is warranted due to inadequate methodology and analysis (ie, data were not collected for most participants at most time points⁶⁰ and use of composite end points⁶¹). Numerous criticisms of the meta-analysis are well-documented^{61–63} demonstrating support for current dietary recommendations for fish consumption for the prevention and treatment of CVD, including ones recently released by the American Heart Association.⁶⁴ In conclusion, the preponderance of data suggests that omega-3 fatty acids, both plant and marine-derived, are beneficial for cardiovascular health and should be recommended as part of a healthy diet.

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