

agents that are members of a larger family of substances called eicosanoids. Eicosanoids are localized tissue hormones that seem to be 1 of the fundamental regulatory classes of molecules in most higher forms of life. They do not travel in the blood, but are created in the cells to regulate a large number of processes, including the movement of calcium and other substances into and out of cells, dilation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division, and growth ⁴.

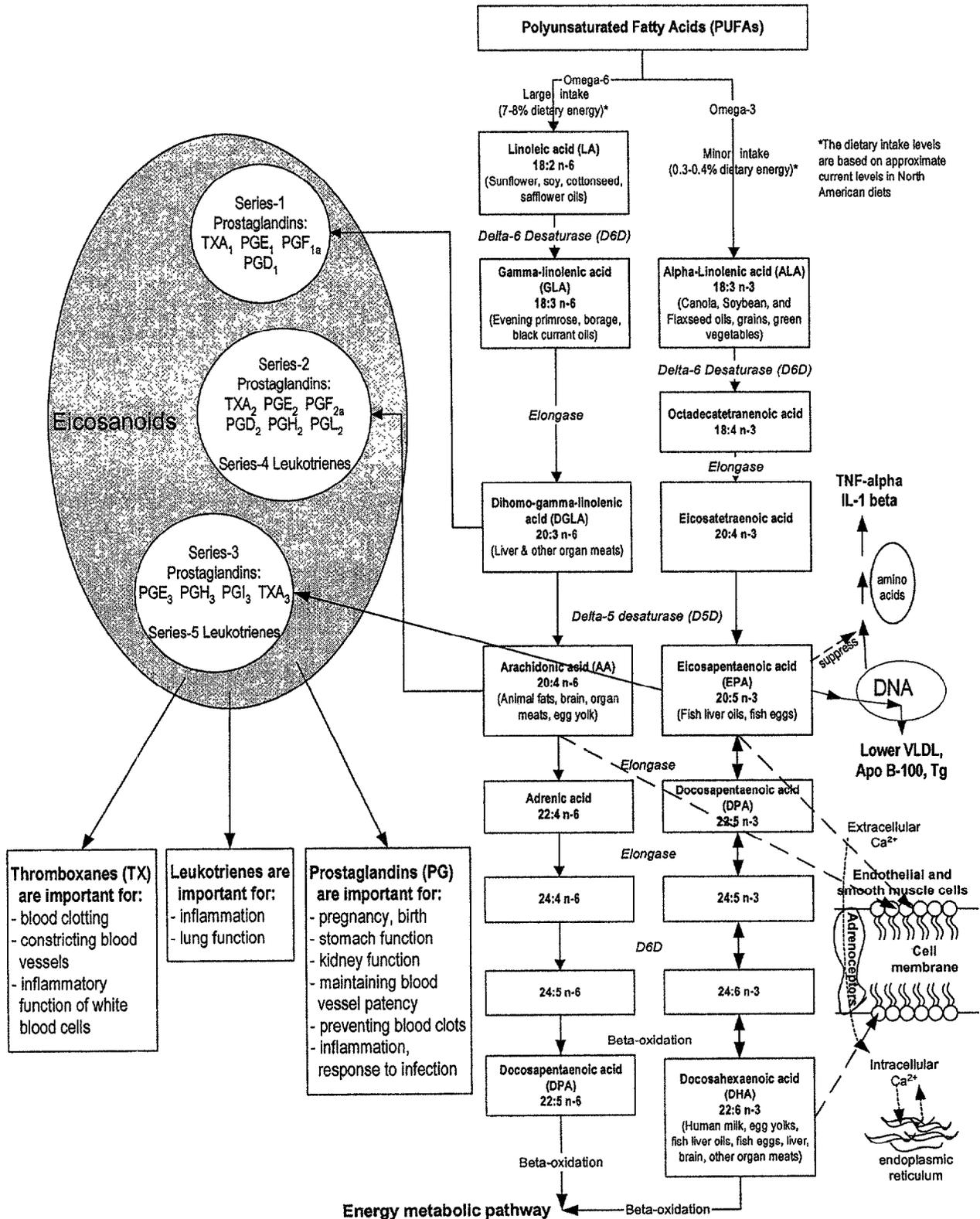
As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA, is the precursor of a group of eicosanoids including series-2 prostaglandins and series-4 leukotrienes. The omega-3 fatty acid, EPA, is the precursor to a group of eicosanoids including series-3 prostaglandins and series-5 leukotrienes. The series-2 prostaglandins and series-4 leukotrienes derived from AA are involved in intense actions (such as accelerating platelet aggregation and enhancing vasoconstriction and the synthesis of inflammatory mediators) in response to physiological stressors. The series-3 prostaglandins and series-5 leukotrienes that are derived from EPA are less physiologically potent than those derived from AA. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate excessive series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins, which are derived from the omega-3 fatty acid, EPA, may protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma ⁴. In addition, animal studies, have demonstrated that omega-3 LC PUFAs, such as EPA and DHA, engage in multiple cytoprotective activities that may contribute to antiarrhythmic mechanisms⁵. Arrhythmias are thought to be the cause of “sudden death” in heart disease.

In addition to affecting eicosanoid production as described above, EPA also affects lipoprotein metabolism and decreases the production of other compounds — including cytokines, interleukin 1 β (IL-1 β), and tumor necrosis factor α (TNF- α) —that have pro-inflammatory effects. These compounds exert pro-inflammatory cellular actions that include stimulating the production of collagenases and increasing the expression of adhesion molecules necessary for leukocyte extravasation ⁶. The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs remains unknown, although suppression of eicosanoid production by omega-3 fatty acids may be involved. EPA can also be converted into the longer chain omega-3 form of docosapentaenoic acid (DPA, 22:5 n-3), and then further elongated and oxygenated into DHA. EPA and DHA are frequently referred to as very long chain omega-3 fatty acids. DHA, which is thought to be important for brain development and functioning, is present in significant amounts in a variety of food products, including fish, fish liver oils, fish eggs, and organ meats. Similarly, AA can convert into an omega-6 form of DPA. Studies have reported that omega-3 fatty acids decrease triglycerides (Tg) and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, with a concomitant increase in high density lipoprotein (HDL). However, they appear to increase or have no effect on low density lipoprotein (LDL). Omega-3 fatty acids apparently lower Tg by inhibiting VLDL and apolipoprotein B-100 synthesis and decreasing post-prandial lipemia ⁷. Omega-3 fatty acids, in conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular Tg production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for Tg production ⁸.

As noted earlier, omega-6 fatty acids are consumed in larger quantities (>10 times) than omega-3 fatty acids. Maintaining a sufficient intake of omega-3 fatty acids is particularly

important since many of the body's physiologic properties depend upon their availability and metabolism.

Figure 1.1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acid in regulating health/disease markers.



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

The major source of omega-3 fatty acids is dietary intake of fish, fish oil, vegetable oils (principally canola and soybean), some nuts including walnuts, and dietary supplements. Two population-based surveys, the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main source of dietary intake data for the U.S. population. NHANES III collected information on the U.S. population aged ≥ 2 months. Mexican Americans and non-Hispanic African-Americans, children ≤ 5 years old, and adults ≥ 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall. Complete descriptions of the methods used and fuller analyses are later described in this report, under "Methods: Method to Assess the Dietary Intake of Omega-3 Fatty Acids in the US population" and "Results: Population Intake of Omega-3 Fatty Acids in the United States". CSFII 1994-96, popularly known as the What We Eat in America survey, addressed the requirements of the National Nutrition Monitoring and Related Research Act of 1990 (Public Law 101-445) for continuous monitoring of the dietary status of the American population. In CSFII 1994-96, an improved data-collection method known as the multiple-pass approach for the 24-hour recall was used. Given the large variation in intake from day-to-day, multiple 24-hour recalls are considered to be the best suited for most nutrition monitoring and will produce stable estimates of mean nutrient intakes from groups of individuals ⁹. In 1998, the Supplemental Children's Survey, a survey of food and nutrient intake by children under age of 10, was conducted as the supplement to the CSFII 1994-96. The CSFII 1994-96, 1998 surveyed 20,607 people of all ages with over-sampling of low-income population ($< 130\%$ of the poverty threshold). Dietary intake data by individuals of all ages were collected over 2 nonconsecutive days by use of two 1-day dietary recalls.

Table 1.1 reports the NHANES III survey mean intake \pm the standard error of the mean (SEM), as well as, the median and range for each omega-3 fatty acid. Distributions of EPA, DPA, and DHA were very skewed; therefore, the means and standard errors of the means should be used and interpreted with caution. Table 1.2 reports the CSFII survey mean and median intakes for each omega-3 fatty acid, along with SEMs, as reported in Dietary Reference Intakes by the Institute of Medicine ².

Table 1.1 Estimates of the mean \pm standard error of the mean (SEM) intake of linoleic acid (LA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the US population, based on analyses of a single 24-hour dietary recall of NHANES III data

	Grams/day		% Kcal/day	
	Mean \pm SEM	Median (range) ^a	Mean \pm SEM	Median (range) ^a
LA (18:2 n-6)	14.1 \pm 0.2	9.9 (0 - 168)	5.79 \pm 0.05	5.30 (0 - 39.4)
ALA (18:3 n-3)	1.33 \pm 0.02	0.90 (0 - 17)	0.55 \pm 0.004	0.48 (0 - 4.98)
EPA (20:5 n-3)	0.04 \pm 0.003	0.00 (0 - 4.1)	0.02 \pm 0.001	0.00 (0 - 0.61)
DHA (22:6 n-3)	0.07 \pm 0.004	0.00 (0 - 7.8)	0.03 \pm 0.002	0.00 (0 - 2.86)

^a The distributions are not adjusted for the over-sampling of Mexican Americans, non-Hispanic African-Americans, children ≤ 5 years old, and adults ≥ 60 years old in the NHANES III dataset.

Table 1.2 Mean, range, and median usual daily intakes of linoleic acid (LA), total omega-3 fatty acids (n-3 FA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in the US population, based on CSFII data (1994-1996, 1998)

	<u>Grams/day</u>	
	<u>Mean±SEM</u>	<u>Median±SEM</u>
LA (18:2 n-6)	13.0±0.1	12.0±0.1
Total n-3 FA	1.40±0.01	1.30±0.01
ALA (18:3 n-3)	1.30±0.01	1.21±0.01
EPA (20:5 n-3)	0.028	0.004
DPA (22:5 n-3)	0.013	0.005
DHA (22:6 n-3)	0.057±0.018	0.046±0.013

Dietary Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be found in many different sources of food, including fish, shellfish, some nuts, and various plant oils. Table 1.3 lists the amount of omega-3 fatty acids in some commonly consumed fish, shellfish, nuts, and edible oils, selected from the USDA website (accessed November 3, 2003) <http://www.nal.usda.gov/fnic/foodcomp> (Finfish and Shellfish Products, sr16fg15.pdf; Fats and Oils, sr16fg04.pdf; and Nut and Seed Products, sr16fg12.pdf)

Table 1.3 The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, and fish oils, and nuts and seeds, and plant oils that contain at least 5 g omega-3 fatty acids per 100 g (<http://www.nal.usda.gov/fnic/foodcomp>) .

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Raw ^a)				Fish, continued			
Anchovy, European	0.6	0.9	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.2	0.4	0.1	Tuna, Light, Canned in Oil ^e	trace	0.1	trace
Bass, Striped	0.2	0.6	trace	Tuna, Light, Canned in Water ^e	trace	0.2	trace
Bluefish	0.2	0.5	-	Tuna, White, Canned in Oil ^e	trace	0.2	0.2
Carp	0.2	0.1	0.3	Tuna, White, Canned in Water ^e	0.2	0.6	trace
Catfish, Channel	trace	0.2	0.1	Whitefish, Mixed Sp.	0.3	0.9	0.2
Cod, Atlantic	trace	0.1	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	trace	0.1	trace	Wolffish, Atlantic	0.4	0.3	trace
Eel, Mixed Sp.	trace	trace	0.4				
Flounder & Sole Sp.	trace	0.1	trace	Shellfish (Raw)			
Grouper, Mixed Sp.	trace	0.2	trace	Abalone, Mixed Sp.	trace	-	-
Haddock	trace	0.1	trace	Clam, Mixed Sp.	trace	trace	trace
Halibut, Atlantic and Pacific	trace	0.3	trace	Crab, Blue	0.2	0.2	-
Halibut, Greenland	0.5	0.4	trace	Crayfish, Mixed Sp., Farmed	trace	0.1	trace
Herring, Atlantic	0.7	0.9	0.1	Lobster, Northern	-	-	-
Herring, Pacific	1.0	0.7	trace	Mussel, Blue	0.2	0.3	trace
Mackerel, Atlantic	0.9	1.4	0.2	Oyster, Eastern, Farmed	0.2	0.2	trace
Mackerel, Pacific and Jack	0.6	0.9	trace	Oyster, Eastern, Wild	0.3	0.3	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Pacific	0.4	0.3	trace
Ocean Perch, Atlantic	trace	0.2	trace	Scallop, Mixed Sp.	trace	0.1	-
Pike, Northern	trace	trace	trace	Shrimp, Mixed Sp.	0.3	0.2	trace
Pike, Walleye	trace	0.2	trace	Squid, Mixed Sp.	0.1	0.3	trace
Pollock, Atlantic	trace	0.4	-				
Pompano, Florida	0.2	0.4	-	Fish Oils			
Roughy, Orange	trace	-	trace	Cod Liver Oil	6.9	11.0	0.9
Salmon, Atlantic, Farmed	0.6	1.3	trace	Herring Oil	6.3	4.2	0.8
Salmon, Atlantic, Wild	0.3	1.1	0.3	Menhaden Oil	13.2	8.6	1.5
Salmon, Chinook	1.0	0.9	trace	Salmon Oil	13.0	18.2	1.1
Salmon, Chinook, Smoked ^b	0.2	0.3	-	Sardine Oil	10.1	10.7	1.3
Salmon, Chum	0.2	0.4	trace				
Salmon, Coho, Farmed	0.4	0.8	trace	Nuts and Seeds			
Salmon, Coho, Wild	0.4	0.7	0.2	Butternuts, Dried	-	-	8.7
Salmon, Pink	0.4	0.6	trace	Flaxseed	-	-	18.1
Salmon, Pink, Canned ^c	0.9	0.8	trace	Walnuts, English	-	-	9.1
Salmon, Sockeye	0.6	0.7	trace				
Sardine, Atlantic, Canned in Oil ^d	0.5	0.5	0.5	Plant Oils			
Seabass, Mixed Sp.	0.2	0.4	-	Canola (Rapeseed)	-	-	9.3
Seatrout, Mixed Sp.	0.2	0.2	trace	Flaxseed Oil	-	-	53.3
Shad, American	1.1	1.3	0.2	Soybean Lecithin Oil	-	-	5.1
Shark, Mixed Sp.	0.3	0.5	trace	Soybean Oil	-	-	6.8
Snapper, Mixed Sp.	trace	0.3	trace	Walnut Oil	-	-	10.4
Swordfish	0.1	0.5	0.2	Wheatgerm Oil	-	-	6.9
Trout, Mixed Sp.	0.2	0.5	0.2				
Trout, Rainbow, Farmed	0.3	0.7	trace				
Trout, Rainbow, Wild	0.2	0.4	0.1				
Tuna, Fresh, Bluefin	0.3	0.9	-				
Tuna, Fresh, Skipjack	trace	0.2	-				

trace = <0.1; - = 0 or no data; Sp. = species.

a Except as indicated.

b Lox.

c Solids with bone and liquid.

d Drained solids with bone.

e Drained solids.

Overview of Effect of Omega-3 Fatty Acids on Cardiovascular Diseases

Since the first cross-cultural epidemiological studies in the 1970s^{11,12}, the body of evidence supporting a role for omega-3 fatty acids in the prevention of CVD risk has continued to increase. Dyerberg reported that disease patterns for the Greenland Inuit, when compared with those for the population of Denmark, exhibited a significantly lower rate of death from acute myocardial infarction (MI) despite only moderate differences in blood cholesterol levels¹². Similar results were found among inhabitants of Greenland and Denmark who were followed for over 25 years¹³.

Additional evidence was found in the Japanese population where it was demonstrated that higher fish intake was associated with considerably lower rates of MI, other ischemic heart diseases, and atherosclerosis¹⁴. In addition, studies among the Inuit of Nunavik, Quebec showed that progressive increases in levels of the omega-3 fatty acids EPA and DHA in plasma phospholipids reflected dietary intakes of these fatty acids and were beneficially associated with key risk factors for CVD¹³. However, the beneficial effects of omega-3 fatty acids are not consistently observed in all epidemiological studies. Data from 21 other countries showed no relation between fish consumption and mortality from coronary heart diseases¹⁵. Among countries participating in the Seven Countries Study, 15-year mortality from coronary heart disease was highest in Finland despite an average fish intake of about 60 grams per day¹⁶. Two other cohort studies carried out in Hawaii and Norway also found no relationship between fish consumption and CVD^{17,18}.

It should be noted, however, that some factors might confound the outcomes of all of these studies. Such factors include type of study design, the type of fish consumed, estimate of fish intake, study population, concomitant drugs, demographic features (e.g., sex, age), baseline diet, subject characteristics (e.g., lipid levels, weight, blood pressure), measurement errors, and environmental contaminants.

The effect of omega-3 fatty acids on risk factors, intermediate markers of CVD and how this effect relates to clinical outcomes, is addressed in another report *Effects of Omega-3 Fatty Acids on Cardiovascular Disease Risk Factors*. The report on risk factors also examines how the effects of omega-3 fatty acids on risk factors and intermediate markers can be modified by various factors, including concomitant drugs, demographic features (e.g., sex, age), baseline diet, subject characteristics (e.g., lipid levels, weight, blood pressure) and omega-3 fatty acids relates to different measures of tissue and plasma fatty acid levels.

This report reviews information from experimental and observational studies that investigate the effect of dietary or supplemental omega-3 fatty acids on CVD outcomes.

Ultimately, the most important questions relating to omega-3 fatty acids pertain to their effect on clinical outcomes such as mortality, myocardial infarction, and stroke. These questions are addressed in this report, which primarily summarizes evidence of human clinical outcomes. More specifically, this report answers the question of how dietary or supplemental omega-3 fatty acids affect each type of CVD outcomes, including mortality (all cause mortality, CVD death, cardiac death, sudden death), nonfatal MI, angina incidence, stroke, and others. The report also draws on the NHANES III database to determine the mean intake of omega-3 fatty acids in the US population and various sub-populations, and to determine whether there is a difference in the mean intake of omega-3 fatty acids between adults with and without cardiovascular disease. Finally, it investigates adverse events and drug interactions associated with omega-3 fatty acids

and whether omega-3 fatty acids can play a role in primary and secondary prevention of CVD events.

Fish accounts for a large part of omega-3 fatty acid consumption in the US and around the world. Due to the effect of environmental pollution, various types of contaminants such as methylmercury, PCBs (Polychlorinated Biphenyls), dioxins, chlordane and DDT (Dichloro-diphenyl-trichloroethane) have been reported in fish caught in lakes, rivers, estuaries, and oceans. Although methylmercury occurs naturally in nature and trace amounts are found in all fish and this amount is believed to have no harmful effects on human consumption, very high levels of methylmercury that may have serious health implications have been reported in certain types of fish. The Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and state government agencies have issued consumer advisories cautioning women who are pregnant and women of childbearing age who may become pregnant about the risks of mercury in fish. The FDA cautions young children and women of childbearing age to avoid four types of fish — tilefish, swordfish, shark, and king mackerel — and to limit consumption of all other fish to 12 ounces per week. Although the major toxic effect of concern for methylmercury is neurotoxicity in the unborn or young child, concerns have also been raised about its association with coronary heart disease in adults^{19,20}.

Although issues with methylmercury and other contaminants, and potential risks from carcinogens as a result of food preparation methods, are important to decision making about the benefits and risks of fish consumption, they are beyond the scope of this report. Readers are advised to learn more about these issues at the FDA and EPA websites

(<http://vm.cfsan.fda.gov/~dms/admehg.html>,

<http://www.fda.gov/fdac/reprints/mercury.html>, <http://www.epa.gov/ost/fish/>,

<http://www.epa.gov/mercury/fish.htm>), and to read an EPA funded report on balancing the risk and benefits of fish consumption (<http://www.tera.org/pubs/cdrpage.htm>).

Chapter 2. Methods

Overview

This evidence report on omega-3 fatty acids and cardiovascular disease (CVD) outcomes is based on a systematic review of the literature. To identify the specific issues central to this report, the Tufts-New England Medical Center (NEMC) Evidence-based Practice Center (EPC) held meetings and teleconferences with a Technical Expert Panel (TEP). A comprehensive search of the medical literature was conducted to identify studies addressing key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality and applicability of the studies were appraised. Study results were summarized with qualitative reviews of the evidence, summary tables, and quantitative meta-analyses, as appropriate.

Several individuals and groups collaborated with the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. The EPC engaged technical experts and representatives from the Agency for Healthcare Research and Quality (AHRQ) and the National Heart, Lung, and Blood Institute (NHLBI) to help refine key questions, identify important issues, and define parameters to the report. The Tufts-NEMC EPC also worked in conjunction with the EPCs at the University of Ottawa (UO) and Southern California-RAND (SC-RAND). Together, the 3 EPCs will produce evidence reports on 10 topics related to omega-3 fatty acids over a 2-year period. The 3 EPCs coordinated activities with the goal of producing evidence reports of uniform format. Through frequent teleconferences and email contact, approaches toward data presentation, summary and evidence table layout, and study quality and applicability assessment were standardized, whenever feasible. In addition, the primary literature searches for all evidence reports were performed by the UO EPC, using identical search terms for studies of omega-3 fatty acids. However, each EPC developed its own eligibility criteria to identify relevant studies as appropriate for its topic.

Analytic Framework

To guide our assessment of studies that examine the association between omega-3 fatty acids and cardiovascular outcomes, we developed an analytic framework that maps the specific linkages associating the populations of interest, the exposures, modifying factors, and outcomes of interest (Figure 2.1)²¹. The framework graphically presents the key components of well-formulated study questions:

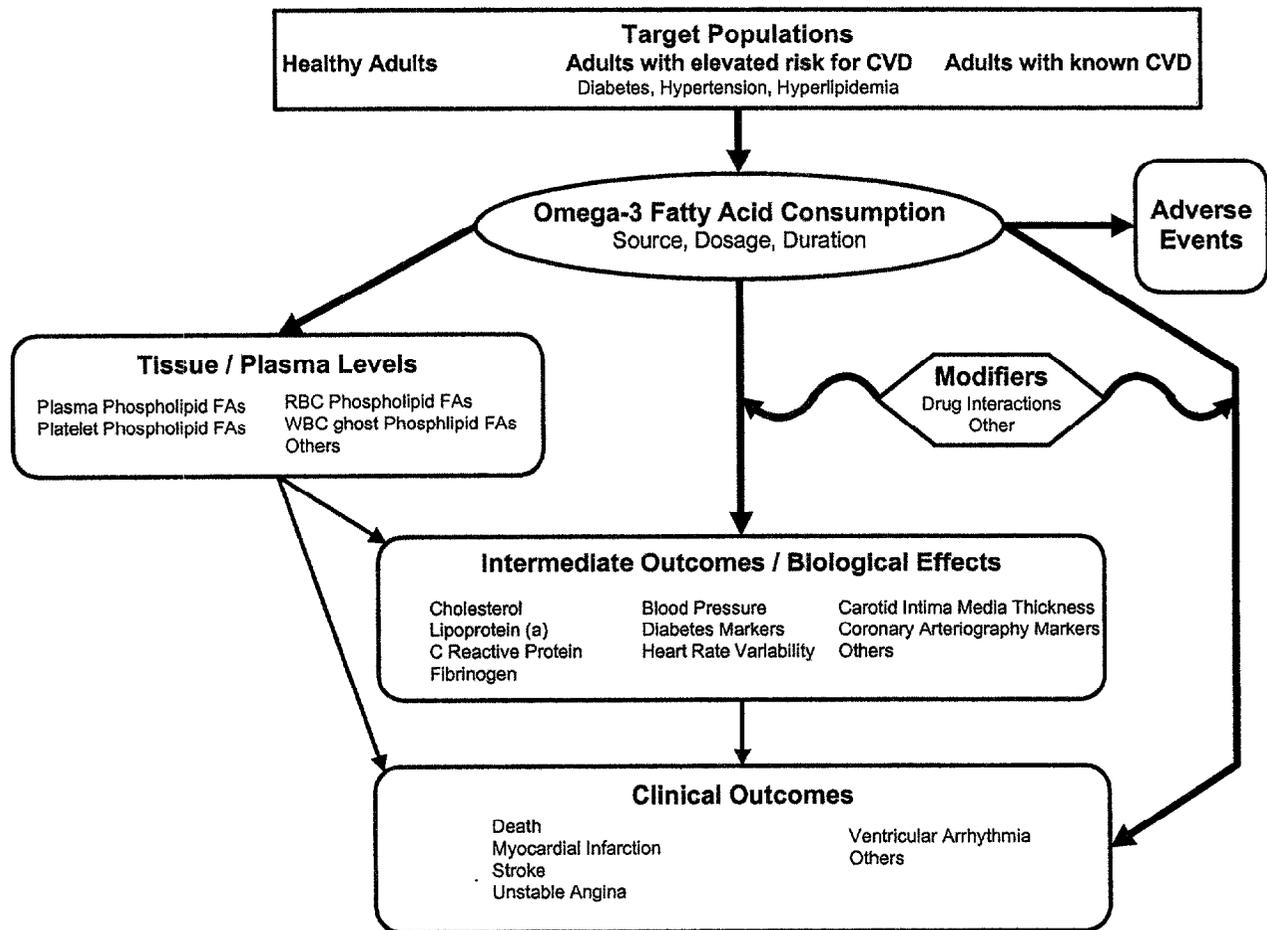
- 1) Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
- 2) What are the interventions?
- 3) What are the outcomes of interest (intermediate and health outcomes)?

Appendixes and Evidence Tables are provided electronically
at <http://www.ahrq.gov/clinic/epcindex.htm>

4) What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to omega-3 fatty acids) to improved health outcomes.

Figure 2.1 Analytic framework for omega-3 fatty acid exposure and cardiovascular disease. This framework concerns the effect of omega-3 fatty acid exposure (as a supplement or from food sources) on cardiovascular disease. Populations of interest are noted in the top rectangle, exposure in the oval, outcomes in the rounded rectangles, and effect modifiers in the hexagon. Thick connecting lines indicate associations and effects reviewed in this and the accompanying report. Lists noted in a smaller font indicate the specific factors reviewed. CVD indicates cardiovascular disease; FA, fatty acid; RBC, red blood cell (erythrocyte); WBC, white blood cell (leukocyte).



This report and the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*, review the evidence addressing the associations or effects of omega-3 fatty acids in humans. Specifically, this report examines evidence addressing the association between omega-3 fatty acids and clinical cardiovascular outcomes, their efficacy in improving CVD outcomes, and potential adverse effects of omega-3 fatty acid intake in humans. The accompanying report examines evidence addressing both the association in humans between omega-3 fatty acids and cardiovascular

intermediate outcomes or risk factors and the association between omega-3 fatty acids and tissue or plasma levels of omega-3 fatty acids.

In both reports, the 3 specific populations of interest are: (1) healthy adults with no known CVD or risk factors; (2) adults at increased risk of CVD due specifically to diabetes, hypertension, or hyperlipidemia; and (3) adults with known CVD. The exposure of interest is omega-3 fatty acids. Unlike medications, there are numerous possible sources, types, and possible dosages for omega-3 fatty acids. Thus, questions of interest include how different sources, dosages, and relative proportions of the fatty acids differ in their effects on the outcomes of interest. Included are questions addressing possible differences between the effects of supplements (e.g., fish oil capsules) and dietary sources (e.g., fatty fish), the effect of duration of intervention or exposure, and whether any effect is sustained after stopping treatment.

The analytic framework does not directly address the level of evidence that is necessary to evaluate each of the effects. Large randomized controlled trials that are adequately blinded and otherwise free of substantial bias provide the best evidence to prove causation between intervention and outcome. However, this study design is not always available (or possible). Observational studies provide lesser degrees of evidence that are usually hypothesis-generating regarding causation. The current analysis relies as much as possible on high quality, randomized controlled trials, using evidence from observational studies when data are relatively sparse.

Key Questions Addressed in this Report

The purpose of this evidence report is to summarize information from studies that address specific key questions. One general question concerns the intake of omega-3 fatty acids in the US population, and 3 additional questions address the relationship between omega-3 fatty acids and CVD. CVD question 1 pertains to the clinical effects of omega-3 fatty acids on clinical CVD outcomes; CVD question 2 evaluates the relative effects of the numerous sources, compositions, dosages, and uses of omega-3 fatty acids and related factors; and CVD question 3 pertains primarily to the association between omega-3 fatty acids and adverse events and drug interactions. The key questions and their related sub-questions are outlined in detail below.

General Question

What are the mean and median intakes of eicosapentaenoic acid (EPA, 20:5 n-3), docosahexaenoic acid (DHA, 22:6 n-3), alpha linolenic acid (ALA, 18:3 n-3), fish, fish oil, and omega-6 fatty acids, and what is the mean and median omega-6 to omega-3 fatty acid ratio, in the US population?

- *Do consumption levels differ among subpopulations?*

CVD Questions

What is the efficacy or association of omega-3 fatty acids (DHA, EPA or ALA supplements, and fish consumption) in reducing CVD events (including all-cause mortality, CVD mortality, non-fatal CVD events, and new diagnosis of CVD)?

- *What is the efficacy or association of omega-3 fatty acids in preventing incident CVD outcomes in people without known CVD (primary prevention) and with known CVD (secondary prevention)?*
- *How does the efficacy or association of omega-3 fatty acids in preventing incident CVD outcomes differ in sub-populations, including men, pre-menopausal women, post-menopausal women, and different age groups?*
- *What are the effects of potential confounders — such as lipid levels, body mass index (BMI), blood pressure, diabetes, aspirin use, hormone replacement therapy, and cardiovascular drugs — on associations found in prospective cohort studies?*
- *What is the relative efficacy of omega-3 fatty acids on different CVD outcomes? Can the CVD outcomes be ordered by strength of treatment effect of omega-3 fatty acids?*

Omega-3 fatty acid variables and modifiers:

- *What is the efficacy or association of specific omega-3 fatty acids (DHA, EPA, ALA), and different ratios of omega-3 fatty acid components in dietary supplements, on CVD outcomes?*
- *Does the ratio of omega-6 to omega-3 fatty acid intake affect the efficacy or association of omega-3 fatty acid intake on CVD outcomes?*
- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)?*
- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by different ratios of DHA, EPA, and ALA?*
- *Is there a threshold or dose-response relationship between omega-3 fatty acids and CVD outcomes?*
- *How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on CVD outcomes?*
- *Are treatment effects or the association of omega-3 fatty acids on CVD events sustained after the intervention or exposure stops?*
- *What is the effect or association of baseline dietary intake of omega-3 fatty acids on the efficacy of omega-3 fatty acid supplements on CVD outcomes?*
- *Does the use of medications for CVD and/or CVD risk factors (including lipid lowering agents and diabetes medications) affect the efficacy or association of omega-3 fatty acids?*

Adverse events and drug interactions:

- *What adverse events related to omega-3 fatty acid dietary supplements are reported in studies of CVD outcomes and markers?*
- *What adverse events related to omega-3 fatty acid dietary supplements are reported specifically among diabetics and people with CVD in studies of CVD outcomes and markers?*
- *What interactions between omega-3 fatty acid dietary supplements and medications are reported in studies of CVD outcomes and markers?*
- *What interactions between omega-3 fatty acid dietary supplements and medications are reported specifically among diabetics and people with CVD in studies of CVD outcomes and markers?*

Method to Assess the Dietary Intake of Omega-3 Fatty Acids in the US population

Two major sources of dietary intake data in the US population are the Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the US Department of Agriculture (USDA) and the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics (NCHS). The USDA's most recent survey, the CSFII 1994-96, popularly known as the *What We Eat in America* survey, addressed the requirements of the National Nutrition Monitoring and Related Research Act of 1990 (Public Law [P.L.] 101-445) for continuous monitoring of the dietary status of the American population²². In CSFII 1994-96, improved data collection methods (i.e., the multiple-pass approach for the 24-hour recall) were used. Given the normal, large day-to-day variation in dietary intake, multiple 24-hour recalls are considered to be best suited for most nutrition monitoring⁹ and produce stable estimates of mean nutrient intakes from groups of individuals.

The NHANES is designed to collect periodic information on the dietary, nutritional, and health status of the civilian, non-institutional US population. Since 1970, 3 NHANES have been completed: NHANES I, 1971-74; NHANES II, 1976-80; and NHANES III, 1988-94. NHANES is unique in that it combines a home interview with health tests that are done in a Mobile Examination Center (MEC). The Third National Health and Nutrition Examination Survey (NHANES III, 1988-94) was conducted at 89 locations in the US. Data obtained through the survey include dietary intake (one 24-hour recall and food frequency questionnaire), socioeconomic and demographic information, biochemical analyses of blood and urine, physical health behaviors, and health conditions. Although multiple 24-hour recalls are considered the "gold standard" for nutrition monitoring (e.g., the dietary assessment method used in CSFII, 1994-96), single 24-hour recalls will also produce reasonably accurate estimates of mean nutrient intakes if the sample size is large²³. By combining dietary data from NHANES III with its unique MEC health test results, we were able to analyze the mean intake of omega-3 fatty acids among

people with and without cardiovascular diseases, an analysis that could not be performed if we used CSFII data.

The 3rd National Health and Nutrition Survey (NHANES III) Database

The NHANES III, 1988-94 database was used to examine the population intake of omega-3 fatty acids in the US (General Question). NHANES III was designed to collect information on the US population aged ≥ 2 months. Mexican Americans and non-Hispanic African Americans, children ≤ 5 years old, and adults ≥ 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall.

Definitions of Key Variables

The population means and standard errors of the mean (SEM) of total polyunsaturated fatty acids (PUFAs), ALA, EPA, and DHA by sex, age, and/or income levels have been presented in a report by the National Center for Health Statistics². However, the sub-population grouping system is different from the system that is used in Institute of Medicine (IOM) reports. In order to provide the most parsimonious interpretation of IOM reports and this evidence report, we have decided to adopt the approach used in *Dietary References Intakes* (DRIs) published by the IOM². The main variables in this evidence report are defined as follows:

- **Age groups:** Subjects' age in months was used to form ten age groups: 2-6 months, 7-12 months, 1-3 years, 4-8 years, 9-13 years, 14-18 years, 19-30 years, 31-50 years, 51-70 years, and 71+ years. Age in months was calculated by computing the number of months between the screener questionnaire date and each subject's date of birth. Two additional age groups were created for the adult sub-population: less than 45 years old, and 45 years old and older.
- **Race/ethnicity groups:** Four ethnicity groups were used in this report: non-Hispanic white, non-Hispanic black, Mexican American, and others. The groups were defined by the race or ethnicity reported by respondents. Respondents were asked to identify themselves as: black; Mexican or Mexican American; white, non-Hispanic; Asian or Pacific Islander; Aleut, Eskimo, or American Indian; or other Latin American or other Spanish.
- **Poverty:** Two poverty income ratio (PIR) groups were created for use in analyses: $PIR \leq 1.3$ and poverty income ratio > 1.3 . The numerator of the ratio was the midpoint of the respondent's family income category. The denominator was based on the poverty threshold, the respondent's age, and the calendar year of the interview.
- **Urbanization:** Metropolitan or non-metropolitan areas were based on the USDA's rural-urban codes that categorize counties by degree of urbanization and nearness to a metropolitan area.
- **People with a history of CVD:** Respondents defined in this report as having a history of CVD were those who responded "yes" to one of the following interview questions: (1) Has a

doctor ever told you that you had congestive heart failure? (2) Has a doctor ever told you that you had a stroke? (3) Has a doctor ever told you that you had a heart attack? Respondents whose electrocardiography results showed a probable or possible myocardial infarction (MI), or probable or possible left-ventricular hypertrophy (LVH), by the Minnesota Code (Appendix C) were also defined as having CVD.

- **Polyunsaturated fatty acids:** ALA, EPA, DHA, docosapentaenoic acid (DPA, 22:5 n-3), and linoleic acid (LA, 18:2 n-6) data, estimated from a single 24-hour dietary recall, were used.

Analyses of NHANES III Data

The data were analyzed using SAS-callable SUDAAN, version 7.5.6 (Research Triangle Institute, Research Triangle Park, NC), which is a statistical analytic software program that adjusts for the complex NHANES III sample design. All analyses incorporated sampling weights that adjusted for unequal sampling probabilities. Variance estimations were made with the WR method (sampling With Replacement). Each denominator has 49 degrees of freedom. The design effect (deff4) was defined as the ratio of the properly computed actual variance of an estimated parameter to the variance based on a simple random sample of the same size.

We used simple linear regression to test the significance of the differences in daily intake of PUFAs between groups. The adjusted means for categorical covariates in the regression model were calculated with the least squares method. Statistical significance of the correlation between the dependent variables (e.g., intake of ALA) and independent variables (e.g., sex groups, age groups, CVD groups) were calculated with the Wald chi-square statistics. The details of these statistical methods are described in the SUDAAN user's manual. Since the amount of dietary PUFAs may be associated with the amount of dietary total fat, results expressed as grams per day can be misleading. Thus, all PUFAs used in the tests of significant differences between groups were measured as percent of total energy intake per day (% kcal/day).

All analyses assume a normal distribution of the nutrient intake. However, data related to EPA and DHA are very skewed. As a result, the mean and SEM estimates for these nutrients should be used and interpreted with caution. The reliability of an estimated mean or median also depends on the coefficient of variation or relative standard error (RSE), defined as the ratio between the standard error of the estimate and the estimate, multiplied by 100. Estimates with an RSE greater than 20 percent are deemed unreliable in this report.

Literature Search Strategy

A comprehensive literature search was conducted to address the 3 key questions related to CVD. Relevant studies were identified primarily through search strategies conducted in collaboration with the UO EPC. The Tufts-NEMC EPC, using the Ovid search engine, conducted preliminary searches on the Medline database. The final searches used six databases including Medline from 1966 to week 2 of February 2003, PreMedline February 7, 2003, Embase from 1980 to week 6 of 2003, Cochrane Central Register of Controlled Trials 4th quarter of 2002, Biological Abstracts 1990 - December 2002, and Commonwealth Agricultural Bureau (CAB) Health from 1973 to December 2002. Subject headings and text words were selected so that the

same set could be applied to each of the different databases with their varying attributes. Supplemental search strategies were conducted as needed. Additional publications were referred to us by the TEP and the other 2 EPCs. Details about selected terms used in the search strategy are discussed below.

Omega-3 Fatty Acids Search Strategy

A wide variety of search terms were used to capture the many potential sources of omega-3 fatty acids. Search terms used include the specific fatty acids, fish and other marine oils, and specific plant oils (flaxseed, linseed, rapeseed, canola, soy, walnut, mustard seed, butternut, and pumpkin seed). These terms were used in all search strategies. Because some studies evaluated the effect of nuts on CVD outcomes without specifying in the abstract the type of nuts used in the study, we performed a supplemental Medline search using the term “nut” as a text word for studies of CVD.

Cardiovascular Search Strategy

The primary search strategy was designed to address both the clinical and intermediate outcomes of CVD in humans (Appendix A). In order to identify CVD outcomes in human studies, the search was divided into 3 categories consisting of controlled trials, other studies, and reviews. These 3 categories were further divided into English and non-English subsets. To address the questions regarding stroke, the Tufts-NEMC EPC performed a separate search on the Medline database. This search yielded no additional relevant publications.

Diabetes

Because specific terms referring to diabetes had been omitted from the primary search strategy, a supplemental search strategy was conducted on March 29, 2003. The diabetes supplemental search strategy included relevant search terms for diabetes. This search strategy resulted in an additional 410 citations for screening.

Overall

The final number of citations identified by the database searches is approximate. Because the 5 main databases used in the search employ different citation formats, duplicate publications were encountered. The UO EPC eliminated most of the duplicate publications; however, because of many different permutations, it was impossible to identify all of them. We eliminated additional duplicate publications as we encountered them.

Ongoing automatic updates of Medline searches were conducted using the CVD search strategy. The last automatic update was on April 19, 2003. The UO EPC conducted a final update search of the other databases on April 10, 2003.

Study Selection

Abstract Screening

All abstracts identified through the literature search were screened using eligibility criteria developed in conjunction with the TEP. These criteria were designed to minimize incorrect exclusion of relevant studies. We included all English language original, experimental, or observational studies that evaluated any potential source of omega-3 fatty acids in at least 5 human subjects, regardless of the study outcomes reported in the abstract. In addition, we excluded abstracts that clearly included only subjects who had a non-CVD-related condition (e.g., cancer, schizophrenia, or organ transplant). Reports published only as letters or as abstracts in proceedings were also excluded. All abstracts were categorized to 1 or more of the key questions or as rejects.

Full Article Inclusion Criteria

Articles that passed the abstract screening process were retrieved, and the full articles were screened for eligibility. The following types of articles were rejected during this round: review articles, inappropriate human population, pediatric studies and studies conducted on subjects less than 19 years old, no mention of omega-3 fatty acid intake, dietary supplements, or fish consumption, daily dose of omega-3 fatty acid greater than 6 g, fewer than 5 subjects in omega-3 fatty acid arm(s), prospective interventional studies of less than 4 weeks duration, and no appropriate outcome of interest reported. Studies that reported only the tissue level of omega-3 fatty acid without explicitly reporting the amount of omega-3 fatty acid consumed were also excluded. However, we included studies of Mediterranean diets and studies that reported fish servings. Specific sources of omega-3 fatty acid considered acceptable included fish oils, dietary fish, canola (rapeseed) oil, soybean oil, flaxseed or linseed oil, walnuts or walnut oil, and mustard seed oil. Other sources were eligible if omega-3 fatty acid levels were reported to be greater than control. For each study that was rejected, the reason(s) for rejection was noted. For analyses of adverse events and drug interactions, all studies were included regardless of omega-3 fatty acid dose or study duration (including washout period).

Inclusion and exclusion criteria for maximal omega-3 fatty acid intake were based on discussions with the TEP, in which it was agreed that omega-3 fatty acid intake above 6 g per day is impractical and has little relevance for health care recommendations. Therefore, with the exception of studies of adverse events, the inclusion criterion for maximum daily intake was set at 6 g per day and studies of higher daily intake were excluded. The definition of omega-3 fatty acid dose varied greatly across studies. Thus, the maximal allowable dose may have applied to total daily omega-3 fatty acid, total EPA+DHA, or a total of other combinations of omega-3 fatty acids. The total did not refer to total fish oil.

In this report, we accepted randomized controlled trials (RCTs) or prospective cohort studies with a minimum of 1-year follow-up to address CVD outcome questions. We also accepted case-control studies and cross-sectional studies that assessed the prevalence of CVD in populations with varying levels of omega-3 fatty acid consumption. In some cases, a study was reported in multiple publications (e.g., interim results might have been reported in 1 publication and various outcomes in others). For these studies, we identified and grouped articles belonging to the same

overall study and used data from the latest publication, supplemented by data from earlier publications, as appropriate.

Selection of Studies for Adverse Events and Drug Interactions

Human studies that were analyzed for clinical outcomes (for this report) or for risk factors (for the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease Risk Factors*) were reviewed for data on adverse events and drug interactions. The eligibility criteria for these analyses were broader than for analyses of CVD outcomes, as described above.

The Food and Drug Administration's (FDA) definition of adverse events was used [FDA]. This definition includes morbidity, mortality, and evidence of organ damage. Because fishy after-taste is almost universally reported in subjects taking fish oil supplements²⁴ it was explicitly excluded as an adverse event in this report.

Analyses of data on adverse events were limited to fish oils or omega-3 fatty acid supplements. Food-related illnesses and toxicities due to marine food sources, cooking oils, and cooking methods are beyond the purview of this report. Thus, data on mercury toxicity and carcinogenic hydrocarbons from grilling were not reviewed.

We looked for studies that evaluated potential interactions between omega-3 fatty acid supplements and commonly used drugs including, but not limited to, hormone replacement therapy, diabetes medications, aspirin, and anticoagulants. In the studies that reported serious adverse events such as clinical bleeding, we note the concurrent medications that the subjects were taking.

Data Extraction Process

We developed an electronic data form to collect the data extracted from studies for this report. In an iterative process, the data form underwent modifications and data extractors underwent training and consensus building. Consensus was reached on definitions, and issues specific to omega-3 fatty acid studies were addressed. After this process, each study was screened for eligibility criteria and for outcomes using the electronic form. Each eligible study was then fully extracted by a single reviewer. Data extraction problems were addressed during weekly meetings. Occasional sections were re-extracted to ensure that uniform definitions were applied across extracted studies. Problems and corrections were noted through spot checks of extracted data and during the creation of summary and evidence tables. A second reviewer independently verified the data in the summary tables using the original article.

Items extracted included: factors related to study design (randomization method, allocation concealment method, blinding, study duration, and funding source), population characteristics (country, eligibility criteria, demographics, comorbid conditions, concomitant medications, and baseline diet), interventions and comparison groups (description of omega-3 fatty acid and control interventions or diets, including amount of specific fatty acids), outcomes of interest (number enrolled and analyzed, intermediate and clinical outcomes, adverse events, reasons for withdrawals, results [including baseline value, final value, within-treatment change or between-treatment difference, and variance, as reported]), and whether each study addressed each of the

key questions. In addition, each study was categorized based on applicability and study quality as described below.

Grading Evidence

Studies accepted in evidence reports have been designed, conducted, analyzed, and reported with various degrees of methodological rigor and completeness. Deficiencies in any of these processes may lead to biased reporting or interpretation of the results. While it is desirable to grade individual studies so that readers of evidence reports are informed about the degree of potential bias, grading the quality of evidence is not a straightforward process even for a single type of study design. For example, despite many attempts, most factors commonly used in the quality assessment of RCTs have not been found to be consistently related to the direction or magnitude of the reported effect size²⁵. There is still no uniform approach to reliably grade published studies based on the information reported in the literature. As a result, different EPCs have used a variety of approaches to grade study quality in past evidence reports.

To evaluate the quality of studies included in this report, we first assessed each study against criteria specific to its study design (RCT, prospective cohort study, case control study). Based on this assessment, we then assigned a summary quality grade that grades each study within its particular study design strata.

In this section, we discuss quality rating criteria for each type of study design and our summary quality rating system. We also discuss how we assessed a study's applicability, sample size, and results.

Quality Rating Criteria for Randomized Controlled Trials

As part of the overall omega-3 fatty acid project, the 3 collaborating EPCs agreed to use the Jadad Score and adequacy of random allocation concealment as elements to grade individual randomized controlled trials^{26,27}. We also agreed that individual EPCs might add other elements to this core set, as we deemed appropriate. All EPCs agreed that studies should not be graded using a single numerical quality score, as this has been found to be unreliable and arbitrary²⁸.

The Jadad Score assesses the quality of RCTs using 3 criteria: adequacy of randomization, double blinding, and dropouts²⁶. A study that meets all 3 criteria gets a maximum score of 5 points. Adequacy of random allocation concealment was assessed as adequate, inadequate, or unclear using criteria described by Schultz et al²⁷.

The Jadad and Schulz scores address only some aspects of the methodological quality of RCTs. In particular, items in the core set ignore potential biases due to analytic and reporting problems in a study. To rectify this, we also assessed each RCT for the following:

- Validity of methods used to assess diet
- Errors or discrepancies in reporting results

Quality Rating Criteria for Prospective Cohort Studies

Unlike RCTs, where there is at least some empirical evidence to support the use of the core set of quality rating items, there is no empirical data to support the use of elements that should comprise a core set for non-randomized studies such as cohort and case-control studies. Because prospective cohort and case control studies do not have randomization, allocation concealment, and blinding, a core set different from that used for RCTs must be defined for these types of studies. In addition, because this report focuses on the effect of omega-3 fatty acids on CVD, the studies must estimate the amount of omega-3 fatty acid consumed by the study population as accurately as possible. We used the following criteria to assess the quality of prospective cohort studies:

- Unbiased selection of the cohort (prospective recruitment of subjects)
- Sufficiently large sample size (>1,000 subjects)
- Adequate description of the cohort
- Use of validated dietary assessment method
- Quantification of the type and amount of fish/estimates of omega-3 fatty acid intake
- Use of validated method for ascertaining clinical outcomes
- Adequate follow-up period (at least 5 years)
- Completeness of follow-up
- Analysis (multivariate adjustments) and reporting of results

Quality Rating Criteria for Case Control Studies

Criteria used to assess the quality of case control studies include:

- Valid ascertainment of cases
- Unbiased selection of cases
- Appropriateness of the control population
- Verification that the control is free of CVD
- Comparability of cases and controls with respect to potential confounders
- Validated dietary assessment method
- Appropriateness of statistical analyses

Generic Summary Quality Grade for All Studies

After evaluating each study against its design-specific quality criteria, we applied a 3 category (A, B, C) summary quality grading system that we have used in most of our previous EPC evidence reports, as well as in several evidence-based clinical practice²⁹. This scheme defines a generic grading system for study quality that is applicable to each type of study design (i.e., RCT, cohort study, case-control study). The categories are defined as follows:

- A Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal

randomized study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.

- B Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category A. It has some deficiencies but none likely to cause major bias. Study may be missing information making assessment of the limitations and potential problems difficult.
- C Significant bias that may invalidate the results. A study with serious errors in design, analysis, or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

The summary quality grading system evaluates and grades the studies within each of the study design strata. By design, it does not attempt to assess the comparative validity of studies across different design strata. Thus, in interpreting the methodological quality of a study, one should note the study design *and* the quality grade that it received. For RCTs, in addition to the summary quality grade, we also indicate the Jadad score and the rating of the adequacy of allocation concealment.

While it might be desirable to rank the quality of all studies on the same scale regardless of study design, experience with this approach is limited and has never been validated. In fact, using a single rating scale for all studies creates potential problems. For example, a hierarchy of study design that places RCTs above cohort studies in terms of methodological rigor is commonly accepted. However, if an RCT is seriously flawed, the results may be more biased than a well-done cohort study.

Applicability

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, sex). Some may be implicit or due to unintentional biases, such as those related to study country, location (e.g., community vs. specialty clinic), or factors resulting in study withdrawals. The question of whether a study is applicable to a population of interest (such as Americans) is distinct from the question of the study's methodological quality. For example, due to differences in the background diets, an excellent study of Japanese men may be very applicable to people in Japan, but less applicable to Japanese American men, and even less applicable to African American men. The applicability of a study is thus dictated by the questions and populations that are of interest to those analyzing the studies.

In this report, the focus is on the US population and on specific subgroups within that population (i.e., healthy Americans, Americans with CVD, and Americans with diabetes or dyslipidemia), as specified in the scope of work for this series of evidence reports. To capture the

potential applicability of studies to the different populations of interest as defined in the scope of work, we define the following target population categories:

- GEN General population. Typical healthy people similar to Americans without known CVD.
CVD Cardiovascular disease population. Subjects with a history of, or currently with, 1 of the following: stroke, myocardial infarction, angina, ischemic peripheral vascular disease, or other condition as defined by the author.

We planned to include categories for diabetic and dyslipidemic populations but found no relevant studies within these categories.

Even though a study may focus on a specific target population, limited study size, eligibility criteria, and the patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To address this issue, we categorized studies within a target population into 1 of 3 levels (I, II, III) of applicability that are defined as follows:

- I Sample is representative of the target population. It should be sufficiently large to cover both sexes, a wide age range, and other important features of the target population (e.g., diet).
- II Sample is representative of a relevant sub-group of the target population, but not the entire population. For example, while the Nurses Health Study is the largest such study and the results are highly applicable to women, it is nonetheless representative only of women. A fish oil study in Japan, where the background diet is very different from that of the US, also falls into this category.
- III Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups. For example, a study of the oldest-old men or a study of a population on a highly controlled diet.

In the summary tables, each study receives a combined applicability grade comprised of the target population (GEN or CVD) and the 3-level grade (I, II, III). For example, GEN-I represents a study of subjects representative of the general population in the US, such as a study of the NHANES population. Studies such as the Nurses Health Study and the Health Professionals Study are graded GEN-II because of each study's focus on a single sex. If several studies of complementary populations (e.g., the Nurses Health Study and the Health Professionals Study) were viewed together, they would offer highly applicable evidence for the general population and receive a grade of GEN-I.

Sample Size

The study sample size provides a quantitative measure of the weight of the evidence. In general, large studies provide more precise estimates of efficacy and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee broad applicability.

Results of Randomized Clinical Trials

RCTs typically report a relative risk or the number of events for the outcome of interest. When relative risk was reported, we calculated it along with the confidence interval to verify the accuracy of the reporting. We also calculated it when only the number of events was reported. We present the adjusted relative risks when these were reported.

Results of Observational Studies

Prospective cohort studies typically categorize subjects into different quantiles (e.g., tertiles, quartiles, quintiles) of omega-3 fatty acid or fish intake and report the associated relative risk for the outcome of interest. For studies that report both unadjusted and multivariate adjusted results, we report the adjusted results in the evidence and summary tables.

Due to the heterogeneous nature of the studies (e.g., different population, background diet, dietary assessment method, and methods used to report estimates of fish or omega-3 fatty acid intake), meta-analyses were not feasible for this group of studies. To succinctly report each study's results and to help readers interpret them, we created a qualitative score or "overall effect" metric to supplement the main quantitative results in the summary tables. The overall effect metric is defined as follows:

- ++ Clinically meaningful benefit demonstrated. Study reported on the clinical outcome of interest in 1 or both of the following ways:
 - statistically significant trend of benefit for the quantile estimates of fish/omega-3 fatty acid intake
 - at least one-half of the quantile estimates of fish/omega-3 fatty acid intake reported statistically significant beneficial effects of at least a 10% relative risk (RR) reduction (i.e., $RR < 0.9$), and no quantile reported a statistically significant adverse outcome
- + A clinically meaningful beneficial trend exists but is not conclusive. Study reported on the clinical outcome of interest in 1 or both of the following ways:
 - a borderline significant ($0.10 > P > 0.05$) trend of benefit for the quantile estimates of fish/omega-3 fatty acid intake
 - non-significant but potentially clinically meaningful effect ($RR < 0.9$) in at least one-half of the quantile estimates, and no quantile reported a statistically significant adverse outcome
- 0 Clinically meaningful effect not demonstrated or is unlikely. Study reported clinically unimportant differences between low/no fish intake with various higher levels of fish intake. The majority of the quantiles of estimates of fish/omega-3 fatty acid intake reported less than 10% relative difference compared with the reference (i.e., $1.1 > RR > 0.9$)

- Harmful effect demonstrated or is likely. Study reported on the clinical outcome of interest in one or both of the following ways:
 - a positive association ($P < .10$) between quantile estimates of fish/omega-3 fatty acid intake and increased risk
 - several quantile estimates reported RR > 1.1

Evidence Reporting Format

Evidence and Summary Tables

We report the evidence in 3 complementary forms:

- 1) *Evidence tables* offer a detailed description of the studies we identified that address each of the key questions. These tables provide detailed information about the study design, patient characteristics, inclusion and exclusion criteria, interventions and comparators evaluated, and outcomes. A study, regardless of how many interventions or outcomes were reported, appears once in the evidence tables. Evidence tables are grouped into RCTs and observational studies (cohorts, case-control, cross-sectional). Within each group, the studies are ordered alphabetically by the first author's last name to allow for easy searching within the tables.
- 2) *Summary tables* succinctly report on each study using summary measures of the main outcomes. These tables were developed by condensing information from the evidence tables and are designed to facilitate comparisons and synthesis across studies. Summary tables include important concise information regarding study size, intervention and control, study population (e.g., general population or CVD), outcome measures, methodological quality, and applicability. A study with multiple populations, methods of reporting estimates of omega-3 fatty acid intake, or clinical outcomes may appear multiple times in different summary tables. Because there were few RCTs and almost as many outcomes to report, we organized the RCTs into 2 groups (trials of omega-3 fatty acid supplements and trials of diet or dietary advice) to reduce the number of tables and minimize redundant information.

Summary tables for prospective cohort and case-control studies were organized based on clinical outcomes. For each of the clinical outcomes is a table for estimates of omega-3 fatty acid consumption and a table for estimates of fish consumption. Within each table, cohort studies preceded case-control studies and studies are ordered by the number of study subjects.

- 3) *Summary matrices* provide an alternative to meta-analysis (when meta-analysis is not feasible) to facilitate the synthesis of a body of evidence. A summary matrix organizes potentially disparate studies into more homogeneous subgroups by their methodological

quality and applicability grades. This allows the reader to appreciate the number of studies available and the effect size of these studies. Because there were too few RCTs and too few cohort studies of the CVD population, summary matrices were created only for prospective cohort studies for the general population in this report. Each summary matrix has applicability grades as row headings and methodological quality grades as column headings. Thus, 3 applicability grades and 3 methodological quality grades create a matrix with 9 cells. Studies assessed with a specific combination of methodological and applicability grades are displayed in their respective cells. Information displayed includes study name, study size, a measure of the effect size, and other information that may help to interpret the results.

Adverse Events Reporting

Separate adverse events evidence tables were not created. Most of these studies were included in the evidence tables of RCTs in this report or in the accompanying risk factor report. In this report, we produced summary tables on adverse events for two categories of studies: RCTs or crossover studies that compared an omega-3 fatty acid supplement with a control, and single arm cohort studies. For RCTs, we report the number and percentage of adverse events for both the omega-3 fatty acid arm and control arms for the following categories: clinical bleeding (nasal, hematuria, gastrointestinal, and other bleeding), gastrointestinal complaints, diarrhea, headaches, and withdrawals due to adverse events. We noted the dosages of omega-3 fatty acid and the control, as well as the study duration and the number of study subjects. For single arm studies, similar information was summarized. For studies that simply reported that they observed no adverse events, we created a simpler summary table listing only the information about the dosage, study size, and duration.

Chapter 3. Results

In this chapter, we present the results of our review of the effects of omega-3 fatty acids on cardiovascular disease (CVD) outcomes. The chapter is divided into 3 major sections. The first section reports on the dietary intake of omega-3 fatty acids in the US population. The second section reports on the effect of omega-3 fatty acid supplements or fish consumption on all cause mortality and CVD outcomes. The last section describes adverse events and drug interactions in human clinical studies of omega-3 fatty acids. Relevant tables are embedded within, or appear at the end, of each section.

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

A total of 33,994 persons were interviewed between 1988 and 1994 in the third National Health and Nutrition Examination Survey (NHANES III). The sociodemographic characteristics of the NHANES III sample population are shown in Table 3.1. Because a large number of participants (6%) refused to report their income or income category during the interview, all the analyses on the poverty income ratio (PIR) should be used carefully. In Tables 3.2 to 3.9, results of the mean daily intakes with a standard error of the mean (SEM) are tabulated for linoleic acid (LA, 18:2 n-6), alpha linolenic acid (ALA, 18:3 n-3), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3) by gender, race/ethnicity, and age groups. Two tables were created for each fatty acid. The first table presents the means and SEMs for the fatty acid from the NHANES III (1988-94) database and the Continuing Survey of Food Intakes by Individuals (CSFII, 1994-96, 1998) database. No statistical test was performed to compare the NHANES III (1988-94) and CSFII (1994-96, 1998) data due to the differences in the dietary survey designs. The second table for each fatty acid shows the means and SEMs for the fatty acid by race/ethnicity groups using NHANES

Table 3.1. The Sociodemographic Characteristics of the Participants in the Third National Health and Nutrition Survey, 1988-94

Sub-populations	Number of participants	Percent
Gender		
- Male	16,295	48%
- Female	17,699	52%
Race/ethnicity		
- Non-Hispanic white	13,085	38%
- Non-Hispanic black	9,627	28%
- Mexican-American	9,751	29%
- Other	1,531	5%
Age groups *		
- 2-6 months	1,076	3%
- 7-12 months	1,129	3%
- 1-3 years	3,189	9%
- 4-8 years	4,271	13%
- 9-13 years	2,744	8%
- 14-18 years	2,183	6%
- 19-30 years	4,550	13%
- 31-50 years	6,307	19%
- 51-70 years	4,678	14%
- 71+ years	3,848	11%
Urbanization of living areas		
- Metro areas	17,183	51%
- Non-metro areas	16,811	49%
Poverty Income Ratio †		
- ≤ 1.3	13,335	39%
- > 1.3	18,509	54%

* Contain small number of missing data.

† 6% (2,150) participants refused to report their income or income category.

III, 1988-94 data only. Additional summary tables present the means and SEMs of LA, ALA, EPA, and DHA by adults vs youths less than 18 years old (Table 3.10), males vs females (Table 3.11), race/ethnicity groups (Table 3.12), urbanization of living area (Table 3.13), and PIR \leq 1.3 or $>$ 1.3 (Table 3.14).

Average Intake Estimates of ALA, EPA, DHA, and LA in the US Population (Tables 3.2-3.9)

Analyses of intake estimates of ALA, EPA, DHA, and LA in the US population are based on the 29,000+ NHANES III respondents who had a complete and reliable 24-hour dietary recall. This sample is representative of about 200,000,000 non-institutionalized civilians in the United States. The mean intake \pm SEM of ALA, EPA, DHA, and LA were 1.33 ± 0.02 , 0.04 ± 0.003 , 0.07 ± 0.004 , and 14.13 ± 0.20 grams per day, respectively. These estimates were equivalent to 0.55 ± 0.004 , 0.02 ± 0.001 , 0.03 ± 0.002 , and 5.79 ± 0.05 percent of total energy intake per day, respectively. The distributions of EPA and DHA intake estimates were very skewed. More than 50% of subjects had less than 0.0001 or zero grams per day of EPA or DHA intake. Therefore, the means and SEMs for EPA and DHA should be used and interpreted with caution.

Consumption Levels of US Subpopulations: Age, Gender, Ethnicity, Socio-economic Status, Urban vs Rural (Tables 3.10-3.14)

In general, the mean intake of ALA and that of LA were highest among adults between age 18 and age 50. The intakes were higher in non-Hispanic blacks and whites than in Mexican Americans and other races/ethnicities. Males consumed more grams per day of ALA and LA than did females. However, an inverse pattern was observed for both ALA and LA when expressed as percent of the total energy intake per day: at the same energy intake level, males consumed less ALA and LA than did females. Results from each table are summarized below.

- **Adults vs Youths:** Adults consumed significantly more ALA ($+0.05 \pm 0.01$ %kcal/day) and LA ($+0.59 \pm 0.07$ %kcal/day) than did youths (see Table 3.10).
- **Males vs Females:** Males had a significantly lower intake of ALA (-0.02 ± 0.01 %kcal/day) and LA (-0.28 ± 0.07 %kcal/day) than did females (see Table 3.11).
- **Race/Ethnicity Groups:** Compared to the reference group, non-Hispanic whites, non-Hispanic blacks, and Mexican Americans all had a significantly higher intake of both ALA and LA on average. The intakes of omega-3 fatty acids among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans were similar. The mean difference \pm SED (standard error of the difference) ranged from 0.04 ± 0.01 to 0.09 ± 0.01 (%kcal/day) for ALA, and from 0.43 ± 0.14 to 0.61 ± 0.15 (%kcal/day) for LA (see Table 3.12).
- **Urban vs Rural Living Area:** No significant differences in the average intake of ALA and LA were found when people living in metro areas were compared to those living in non-metro areas (see Table 3.13).

- Poverty Index Ratio (PIR): People who had a PIR ≤ 1.3 consumed significantly less ALA (-0.04 ± 0.01 %kcal/day) and LA (-0.28 ± 0.06 %kcal/day) than people who had a PIR > 1.3 (see Table 3.14)

Average Intake Estimates of ALA, EPA, DHA, and LA in Individuals with and without Cardiovascular Disease (Tables 3.15-3.19)

A sub-population of NHANES III participants aged 18 and older was used for the analyses of the estimated mean intakes of ALA, EPA, DHA, and LA among individuals with and without a history of CVD (see definition for CVD in Chapter 2). Of the 16,683 adults in NHANES III, 12.7% (2,121) had CVD, while 87.3% (14,562) had no CVD (Table 3.15).

There was no significant difference in the mean intake of LA (%kcal/day) between people with and without CVD (Table 3.16). However, people with CVD consumed significantly less ALA than those without CVD (-0.02 ± 0.01 %kcal/day, $P = .04$) (Table 3.17). The means \pm SEMs of EPA and DHA for people with CVD and those without CVD are shown in Table 3.18 and Table 3.19, respectively. The distributions of EPA and DHA intake estimates were very skewed, so the means and SEMs for EPA and DHA should be used and interpreted with caution. For the same reason, no statistical tests for the differences between people with CVD and those without CVD were performed.

The crude means \pm SEMs for people with CVD and those without CVD could be misleading because significant differences in the mean intake of ALA and LA were found among gender, age, and race/ethnicity groups. After adjusting for sex, age, and race/ethnicity, people with CVD still had a significantly lower intake of ALA compared to people without CVD (0.54 ± 0.01 vs 0.57 ± 0.01 %kcal/day, respectively, $P = .02$). Based on a typical total energy intake of 2,000 kilocalories per day, our results show that people with CVD consumed 0.67g per day less ALA than people without CVD. We found no significant difference in the mean intake of LA between the 2 groups after adjusting for sex, age, and race/ethnicity. In both ALA and LA models, gender and races were strong predictors of CVD. The regression and least-square results are shown in detail in Appendix D.

Estimates of Average Omega-3 Fatty Acid or Fish Intake in Countries Outside the US

We found no population-based dietary surveys based on single or multiple 24-hour dietary recalls for countries other than the US. However, reports of average fish consumption from the European Investigation into Cancer and Nutrition (EPIC) study provide good estimates for fish intake among the European population³⁰. The EPIC study was a cohort study (rather than a population-based survey) on diet and cancer that included more than 480,000 men and women from 10 European countries. The consumption (in grams/day) of total fish and fish products and at least 10 classifications of fish sub-groups was estimated for each country and different geographical areas by gender. The main results demonstrated that fish intake varies greatly throughout Europe, with the highest consumption in centers in Spain (51-120 g/d) and the lowest in centers in Germany (16-24 g/d). The mean daily intake of total fatty fish, which is usually high in omega-3 fatty acids, was the highest in centers in Spain (18-42 g/d) and the lowest in

centers in the Netherlands (6-8 g/d)³¹. We found no report on the estimated amount of omega-3 fatty acids consumed by EPIC study participants.

A few other cross-cultural studies and a household budget survey in Spain estimate per capita intakes of major food groups per day. These studies observed large differences in fish consumption across the 21 countries. Japan was found to have a high per capita fish consumption of about 100 g/capita/day³². An increased trend in per capita fish and shellfish consumption (62-88 g/capita/day) was found in Spain between 1964 and 1991³³.

Table 3.2. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data[§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake		Sample Size	Mean Intake (g/day)
			(g/day)	(%kcal/day)		
Both sexes, 0-6 months ¶	793	1,323,807	6.90	8.32	596	6.70
SEM			0.15	0.14		0.10
Both sexes, 7-12 months	915	1,625,559	5.91	5.28	530	6.90
SEM			0.14	0.12		0.20
Both sexes, 1-3 y	2,734	8,724,437	7.27	4.69	3,949	7.30
SEM			0.14	0.07		0.10
Both sexes, 4-8 y	3,673	17,409,438	10.31	5.16	3,935	10.10
SEM			0.28	0.11		0.10
M, 9-13 y	1,251	9,113,670	13.79	5.09	595	13.40
SEM			0.48	0.11		0.40
M, 14-18 y	925	8,908,287	18.12	5.37	474	16.60
SEM			0.92	0.17		0.50
M, 19-30 y	1,902	21,918,936	19.34	5.60	920	17.60
SEM			0.59	0.13		0.50
M, 31-50 y	2,579	35,368,777	18.90	5.95	1,806	17.00
SEM			0.50	0.09		0.30
M, 51-70 y	1,934	18,623,500	15.37	5.86	1,680	15.30
SEM			0.34	0.09		0.30
M, 71+ y	1,296	6,723,233	12.42	5.69	722	12.20
SEM			0.29	0.09		0.40
F, 9-13 y	1,261	8,888,987	12.23	5.56	606	11.00
SEM			0.41	0.14		0.30
F, 14-18 y	1,062	8,962,331	13.61	5.98	449	11.70
SEM			0.54	0.19		0.50
F, 19-30 y	2,181	22,809,351	13.59	6.13	808	11.80
SEM			0.36	0.11		0.30
F, 31-50 y	3,097	37,172,408	13.44	6.24	1,690	11.70
SEM			0.26	0.10		0.20
F, 51-70 y	2,075	20,961,630	10.62	5.82	1,605	11.00
SEM			0.29	0.13		0.20
F, 71+ y	1,421	9,687,597	9.54	5.92	670	9.30
SEM			0.21	0.10		0.30
All individuals	29,099	238,221,947	14.13	5.79	21,159	13.00
SEM			0.20	0.05		0.10

[§] All NHANES III variance estimates were based on Taylor Series (WR) method.

[¶] NHANES III data consisted of individuals ≥ 2 months and excluded nursing infants and children.

Table 3.3. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	10,634	14.27	0.24	8,510	14.23	0.20	8,626	14.07	0.20	1,329	12.77	0.48
Both sexes, 2-6 months	444	6.45	0.18	156	7.50	0.40	124	8.03	0.44	69	8.03	0.44
Both sexes, 7-12 months	488	5.36	0.14	156	7.53	0.47	181	6.58	0.38	90	6.58	0.38
Both sexes, 1-3 y	854	7.08	0.20	784	8.78	0.19	962	7.78	0.18	134	7.78	0.18
Both sexes, 4-8 y	989	10.19	0.45	1,179	11.54	0.25	1,322	10.38	0.29	183	10.38	0.29
Both sexes, 9-13 y	646	13.14	0.40	886	13.23	0.39	881	13.21	0.55	99	13.21	0.55
Both sexes, 14-18 y	517	15.58	0.81	714	17.07	0.54	646	14.87	0.56	110	14.87	0.56
Both sexes, 19-30 y	1,065	16.31	0.47	1,314	17.68	0.44	1,533	16.75	0.34	171	16.75	0.34
Both sexes, 31-50 y	1,894	16.45	0.39	1,869	15.54	0.32	1,669	16.07	0.32	244	16.07	0.32
Both sexes, 51-70 y	1,836	13.19	0.29	1,024	11.05	0.35	985	12.18	0.39	164	12.18	0.39
Both sexes, 71+ y	1,901	10.91	0.21	428	9.44	0.51	323	9.79	0.55	65	9.79	0.55
M, Total	5,028	16.70	0.34	4,001	15.87	0.25	4,264	15.84	0.25	628	14.40	0.66
M, 2-6 months	229	6.52	0.23	81	7.57	0.41	66	8.64	0.55	32	8.64	0.55
M, 7-12 months	239	5.38	0.19	78	7.55	0.71	96	6.09	0.44	37	6.09	0.44
M, 1-3 y	421	7.55	0.25	396	9.23	0.27	478	8.04	0.29	81	8.04	0.29
M, 4-8 y	491	11.10	0.72	580	11.71	0.36	627	10.78	0.45	102	10.78	0.45
M, 9-13 y	320	14.07	0.64	440	13.08	0.49	440	13.11	0.65	51	13.11	0.65
M, 14-18 y	228	18.14	1.13	333	18.82	0.74	320	16.13	0.74	44	16.13	0.74
M, 19-30 y	460	19.85	0.76	583	20.33	0.73	776	19.27	0.55	83	19.27	0.55
M, 31-50 y	853	19.22	0.61	826	18.14	0.49	800	18.57	0.38	100	18.57	0.38
M, 51-70 y	895	15.70	0.41	483	12.46	0.61	488	14.72	0.51	68	14.72	0.51
M, 71+	892	12.75	0.29	201	10.35	0.69	173	10.99	0.84	30	10.99	0.84
F, Total	5,606	11.96	0.19	4,509	12.82	0.21	4,362	12.20	0.21	701	11.23	0.61
F, 2-6 months	215	6.37	0.27	75	7.41	0.52	58	7.28	0.46	37	7.28	0.46
F, 7-12 months	249	5.33	0.24	78	7.52	0.42	85	7.16	0.60	53	7.16	0.60
F, 1-3 y	433	6.60	0.25	388	8.34	0.27	484	7.50	0.23	53	7.50	0.23
F, 4-8 y	498	9.15	0.32	599	11.36	0.35	695	10.01	0.37	81	10.01	0.37
F, 9-13 y	326	12.17	0.55	446	13.39	0.55	441	13.32	0.72	48	13.32	0.72
F, 14-18 y	289	12.88	0.70	381	15.32	0.67	326	13.58	0.74	66	13.58	0.74
F, 19-30 y	605	13.03	0.43	731	15.48	0.51	757	13.63	0.35	88	13.63	0.35
F, 31-50 y	1,041	13.71	0.30	1,043	13.38	0.35	869	13.50	0.38	144	13.50	0.38
F, 51-70 y	941	10.93	0.37	541	10.00	0.38	497	9.99	0.51	96	9.99	0.51
F, 71+	1,009	9.65	0.22	227	8.84	0.66	150	8.61	0.75	35	8.61	0.75

Table 3.4. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Alpha Linolenic Acid (ALA, 18:3 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data[§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake		Sample Size	Mean Intake (g/day)
			(g/day)	(%kcal/day)		
Both sexes, 0-6 months [¶]	793	1,323,807	0.62	0.74	596	0.72
SEM			0.02	0.021		0.02
Both sexes, 7-12 months	915	1,625,559	0.60	0.54	530	0.77
SEM			0.02	0.013		0.02
Both sexes, 1-3 y	2,734	8,724,437	0.73	0.48	3,949	0.77
SEM			0.01	0.005		0.01
Both sexes, 4-8 y	3,673	17,409,438	0.98	0.49	3,935	0.97
SEM			0.03	0.010		0.01
M, 9-13 y	1,251	9,113,670	1.29	0.49	595	1.26
SEM			0.05	0.009		0.04
M, 14-18 y	925	8,908,287	1.73	0.52	474	1.65
SEM			0.08	0.018		0.05
M, 19-30 y	1,902	21,918,936	1.80	0.52	920	1.66
SEM			0.05	0.011		0.05
M, 31-50 y	2,579	35,368,777	1.76	0.57	1,806	1.73
SEM			0.04	0.009		0.04
M, 51-70 y	1,934	18,623,500	1.46	0.57	1,680	1.55
SEM			0.03	0.010		0.03
M, 71+y	1,296	6,723,233	1.18	0.55	722	1.26
SEM			0.03	0.011		0.04
F, 9-13 y	1,261	8,888,987	1.18	0.54	606	1.03
SEM			0.04	0.014		0.02
F, 14-18 y	1,062	8,962,331	1.21	0.53	449	1.13
SEM			0.05	0.016		0.05
F, 19-30 y	2,181	22,809,351	1.25	0.56	808	1.18
SEM			0.04	0.012		0.03
F, 31-50 y	3,097	37,172,408	1.25	0.58	1,690	1.19
SEM			0.03	0.009		0.02
F, 51-70 y	2,075	20,961,630	1.04	0.57	1,605	1.13
SEM			0.03	0.013		0.02
F, 71+y	1,421	9,687,597	0.92	0.58	670	0.97
SEM			0.02	0.011		0.03
All individuals	29,099	238,221,947	1.33	0.55	21,159	1.30
SEM			0.02	0.004		0.01

[§] All NHANES III variance estimates were based on Taylor Series (WR) method.

[¶] NHANES III data consisted of individuals \geq 2 months and excluded nursing infants and children.

Table 3.5. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Alpha Linolenic Acid (ALA, 18:3 n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	10,634	1.37	0.02	8,510	1.27	0.02	8,626	1.20	0.02	1,329	1.12	0.04
Both sexes, 2-6 months	444	0.55	0.02	156	0.71	0.06	124	0.81	0.07	69	0.76	0.08
Both sexes, 7-12 months	488	0.54	0.02	156	0.76	0.04	181	0.65	0.05	90	0.60	0.04
Both sexes, 1-3 y	854	0.73	0.02	784	0.82	0.02	962	0.73	0.01	134	0.64	0.03
Both sexes, 4-8 y	989	0.98	0.04	1,179	1.04	0.02	1,322	0.97	0.03	183	0.87	0.04
Both sexes, 9-13 y	646	1.28	0.05	886	1.18	0.03	881	1.19	0.04	99	1.06	0.08
Both sexes, 14-18 y	517	1.48	0.07	714	1.53	0.06	646	1.30	0.06	110	1.42	0.19
Both sexes, 19-30 y	1,065	1.56	0.04	1,314	1.56	0.04	1,533	1.41	0.03	171	1.27	0.08
Both sexes, 31-50 y	1,894	1.57	0.04	1,869	1.38	0.03	1,669	1.30	0.03	244	1.17	0.08
Both sexes, 51-70 y	1,836	1.28	0.03	1,024	1.02	0.03	985	1.06	0.04	164	1.06	0.08
Both sexes, 71+ y	1,901	1.05	0.02	428	0.87	0.05	323	0.83	0.04	65	0.88	0.15
M, Total	5,028	1.60	0.03	4,001	1.43	0.02	4,264	1.36	0.02	628	1.29	0.06
M, 2-6 months	229	0.56	0.03	81	0.73	0.02	66	0.91	0.08	32	0.77	0.09
M, 7-12 months	239	0.55	0.02	78	0.79	0.06	96	0.63	0.06	37	0.66	0.06
M, 1-3 y	421	0.75	0.02	396	0.85	0.07	478	0.74	0.02	81	0.69	0.03
M, 4-8 y	491	1.08	0.07	580	1.08	0.02	627	0.98	0.03	102	0.87	0.06
M, 9-13 y	320	1.35	0.07	440	1.21	0.03	440	1.21	0.07	51	1.12	0.08
M, 14-18 y	228	1.73	0.09	333	1.70	0.04	320	1.50	0.07	44	2.00	0.46
M, 19-30 y	460	1.89	0.07	583	1.80	0.07	776	1.62	0.06	83	1.35	0.09
M, 31-50 y	853	1.84	0.05	826	1.63	0.06	800	1.49	0.04	100	1.38	0.15
M, 51-70 y	895	1.51	0.04	483	1.11	0.05	488	1.26	0.04	68	1.34	0.11
M, 71+	892	1.22	0.04	201	0.97	0.07	173	0.92	0.07	30	0.94	0.23
F, Total	5,606	1.15	0.02	4,509	1.14	0.02	4,326	1.05	0.02	701	0.97	0.04
F, 2-6 months	215	0.54	0.03	75	0.69	0.08	58	0.68	0.07	37	0.75	0.10
F, 7-12 months	249	0.54	0.03	78	0.72	0.05	85	0.68	0.05	53	0.56	0.05
F, 1-3 y	433	0.71	0.02	388	0.78	0.03	484	0.72	0.02	53	0.58	0.05
F, 4-8 y	498	0.86	0.02	599	1.00	0.02	695	0.96	0.04	81	0.87	0.07
F, 9-13 y	326	1.22	0.06	446	1.15	0.04	441	1.16	0.05	48	0.99	0.17
F, 14-18 y	289	1.22	0.07	381	1.36	0.08	326	1.10	0.05	66	1.03	0.09
F, 19-30 y	605	1.25	0.04	731	1.35	0.05	757	1.15	0.03	88	1.16	0.16
F, 31-50 y	1,041	1.30	0.03	1,043	1.18	0.03	869	1.10	0.03	144	1.01	0.08
F, 51-70 y	941	1.07	0.04	541	0.95	0.03	497	0.90	0.04	96	0.79	0.08
F, 71+	1,009	0.94	0.02	227	0.80	0.05	150	0.75	0.06	35	0.81	0.12

Table 3.6. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Eicosapentaenoic Acid (EPA, 20:5 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998) [‡]	
	Sample Size	Population Size	Mean intake		Sample Size	Mean Intake (g/day)
			(g/day)	(%kcal/day)		
Both sexes, 0-6 months [¶] SEM	793	1,323,807	-	-	578	<0.0005
Both sexes, 7-12 months SEM	915	1,625,559	†	†	487	0.002
Both sexes, 1-3 y SEM	2,734	8,724,437	†	†	3,777	0.008
Both sexes, 4-8 y SEM	3,673	17,409,438	0.010	0.010	3,769	0.012
M, 9-13 y SEM	1,251	9,113,670	†	†	569	0.016
M, 14-18 y SEM	925	8,908,287	†	†	446	0.018
M, 19-30 y SEM	1,902	21,918,936	0.040	†	854	0.030
M, 31-50 y SEM	2,579	35,368,777	0.060	0.02	1,684	0.038
M, 51-70 y SEM	1,934	18,623,500	0.050	0.02	1,606	0.046
M, 71+y SEM	1,296	6,723,233	0.050	0.02	674	0.049
F, 9-13 y SEM	1,261	8,888,987	†	†	580	0.012
F, 14-18 y SEM	1,062	8,962,331	0.020	†	436	0.016
F, 19-30 y SEM	2,181	22,809,351	0.030	0.01	760	0.024
F, 31-50 y SEM	3,097	37,172,408	0.040	0.01	1,614	0.027
F, 51-70 y SEM	2,075	20,961,630	0.040	0.03	1,539	0.035
F, 71+y SEM	1,421	9,687,597	0.030	†	623	0.029
All individuals SEM	29,099	238,221,947	0.040	0.02	20,108	0.03
			0.003	0.001		

[§] All NHANES III variance estimates were based on Taylor Series (WR) method.

[‡] EPA estimates of CSFII (1994-96, 98) in the IOM report were calculated using SAS PROC UNIVERIATE, not via JACKKNIFE replication method. SEM data was not available in IOM report.

[¶] NHANES III data consisted of individuals ≥ 2 months and excluded nursing infants and children. Distribution of EPA is very skewed; means and standard errors of the means should be used and interpreted with caution.

- estimate = 0; † Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.7. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Eicosapentaenoic Acid (EPA, 20:5 n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	10,634	0.03	0.003	8,510	0.05	0.002	8,626	0.02	0.003	1,329	0.06	0.012
Both sexes, 2-6 months	444	-		156	-		124	-		69	†	
Both sexes, 7-12 months	488	†		156	†	0.001	181	†		90	†	
Both sexes, 1-3 y	854	0.01	0.001	784	0.01	0.001	962	†		134	†	
Both sexes, 4-8 y	989	†		1,179	0.01	0.002	1,322	0.01	0.002	183	†	
Both sexes, 9-13 y	646	†		886	0.02	0.004	881	†		99	†	
Both sexes, 14-18 years	517	†		714	†		646	†		110	†	
Both sexes, 19-30 y	1,065	0.03	0.005	1,314	0.05	0.004	1,533	0.03	0.004	171	†	
Both sexes, 31-50 y	1,894	0.04	0.005	1,869	0.07	0.008	1,669	0.04	0.007	244	†	
Both sexes, 51-70 y	1,836	0.04	0.004	1,024	0.06	0.006	985	0.03	0.004	164	†	
Both sexes, 71+ y	1,901	0.03	0.003	428	†		323	†		65	†	
M, Total	5,028	0.04	0.004	4,001	0.05	0.005	4,264	0.03	0.004	628	0.06	0.010
M, 2-6 months	229	-		81	-		66	-		32	†	
M, 7-12 months	239	†		78	†		96	†		37	†	
M, 1-3 y	421	0.01	0.002	396	0.01	0.001	478	†	0.001	81	†	
M, 4-8 y	491	†		580	0.02	0.003	627	0.01	0.002	102	†	
M, 9-13 y	320	†		440	0.02	0.004	440	†		51	†	
M, 14-18 y	228	†		333	†		320	†		44	†	
M, 19-30 y	460	0.04	0.008	583	0.05	0.008	776	0.03	0.006	83	0.06	0.011
M, 31-50 y	853	0.06	0.009	826	0.09	0.015	800	†		100	†	
M, 51-70 y	895	0.05	0.006	483	0.07	0.013	488	†		68	†	
M, 71+	892	0.05	0.006	201	†		173	†		30	†	
F, Total	5,606	0.03	0.003	4,509	0.04	0.002	4,362	0.02	0.003	701	†	
F, 2-6 months	215	-		75	-		58	-		37	-	
F, 7-12 months	249	†		78	-		85	-		53	†	
F, 1-3 y	433	†		388	†		484	†		53	†	
F, 4-8 y	498	†		599	†		695	†		81	†	
F, 9-13 y	326	†		446	†		441	†		48	†	
F, 14-18 y	289	†		381	†		326	†		66	†	
F, 19-30 y	605	0.03	0.005	731	0.04	0.005	757	†		88	†	
F, 31-50 y	1,041	0.03	0.004	1,043	0.06	0.006	869	†		144	†	
F, 51-70 y	941	0.04	0.005	541	0.05	0.007	497	†		96	†	
F, 71+	1,009	0.02	0.003	227	†		150	†		35	†	

- estimate = 0; † Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.8. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Docosahexaenoic Acid (DHA, 22:6 n-3), United States, NHANES III (1988-94) and CSFII (1994-1996, 1998) Data [§]

Age/Gender Groups	NHANES III (1988-94)				CSFII (1994-1996, 1998)	
	Sample Size	Population Size	Mean Intake		Sample Size	Mean Intake (g/day)
			(g/day)	(%kcal/day)		
Both sexes, 0-6 months ¶ SEM	793	1,323,807	-	†	596	<0.0005 0.001
Both sexes, 7-12 months SEM	915	1,625,559	†	†	530	0.030 0.008
Both sexes, 1-3 y SEM	2,734	8,724,437	0.020 0.002	0.01 0.001	3,949	0.032 0.001
Both sexes, 4-8 y SEM	3,673	17,409,438	0.030 0.003	0.01 0.002	3,935	0.050 0.005
M, 9-13 y SEM	1,251	9,113,670	0.030 0.005	0.01 0.002	595	0.063 0.010
M, 14-18 y SEM	925	8,908,287	†	†	474	0.072 0.012
M, 19-30 y SEM	1,902	21,918,936	0.090 0.008	0.03 0.004	920	0.079 0.006
M, 31-50 y SEM	2,579	35,368,777	0.120 0.012	0.04 0.005	1,806	0.094 0.006
M, 51-70 y SEM	1,934	18,623,500	0.100 0.008	0.04 0.003	1,680	0.111 0.007
M, 71+ y SEM	1,296	6,723,233	0.080 0.008	0.04 0.004	722	0.128 0.019
F, 9-13 y SEM	1,261	8,888,987	0.030 0.006	0.02 0.003	606	0.055 0.009
F, 14-18 y SEM	1,062	8,962,331	0.030 0.004	0.02 0.002	449	0.062 0.009
F, 19-30 y SEM	2,181	22,809,351	0.060 0.010	0.03 0.003	808	0.067 0.006
F, 31-50 y SEM	3,097	37,172,408	0.080 0.009	0.03 0.004	1,690	0.071 0.009
F, 51-70 y SEM	2,075	20,961,630	0.080 0.007	0.04 0.004	1,605	0.089 0.006
F, 71+ y SEM	1,421	9,687,597	0.050 0.008	0.03 0.005	670	0.077 0.010
All individuals SEM	29,099	238,221,947	0.070 0.004	0.03 0.002	21,159	0.057 0.018

[§] All NHANES III variance estimates were based on Taylor Series (WR) method.

[¶] NHANES III data consisted of individuals ≥ 2 months and excluded nursing infants and children. Distribution of EPA is very skewed; means and standard errors of the means should be used and interpreted with caution.

- estimate = 0

† Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

‡ EPA estimates of CSFII (1994-96, 98) in the IOM report were calculated using SAS PROC UNIVERIATE, not via JACKKNIFE replication method. SEM data was not available in IOM report.

Table 3.9. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Docosahexaenoic Acid (DHA, 22:6n-3) (g/d), United States, NHANES III (1988-94) by Race/Ethnicity Groups

Age/Gender Groups	Non-Hispanic White			Non-Hispanic Black			Mexican-American			Other		
	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM	Sample Size	Mean	SEM
Both Sexes, Total	10,634	0.07	0.005	8,510	0.09	0.004	8,626	0.05	0.003	1,329	0.10	0.015
Both sexes, 2-6 months	444	†		156	-		124	-		69	-	
Both sexes, 7-12 months	488	†		156	*	0.002	181	*	0.002	90	†	
Both sexes, 1-3 y	854	†		784	0.02	0.004	962	0.01	0.002	134	†	
Both sexes, 4-8 y	989	0.02	0.004	1,179	0.03	0.003	1,322	0.03	0.004	183	†	
Both sexes, 9-13 y	646	0.03	0.004	886	0.04	0.005	881	0.03	0.003	99	†	
Both sexes, 14-18 years	517	†		714	0.07	0.012	646	0.03	0.004	110	†	
Both sexes, 19-30 y	1,065	0.07	0.010	1,314	0.10	0.007	1,533	0.06	0.006	171	†	
Both sexes, 31-50 y	1,894	0.09	0.009	1,869	0.13	0.013	1,669	0.07	0.010	244	†	
Both sexes, 51-70 y	1,836	0.08	0.006	1,024	0.10	0.008	985	0.06	0.007	164	0.13	0.024
Both sexes, 71+ y	1,901	0.06	0.004	428	†		323	0.04	0.008	65	†	
M, Total	5,028	0.08	0.006	4,001	0.11	0.008	4,264	0.06	0.004	628	0.10	0.012
M, 2-6 months	229	†		81	-		66	-		32	-	
M, 7-12 months	239	†		78	†		96	*	0.003	37	†	
M, 1-3 y	421	0.02	0.004	396	0.02	0.003	478	0.01	0.002	81	†	
M, 4-8 y	491	0.02	0.004	580	0.03	0.004	627	0.03	0.002	102	†	
M, 9-13 y	320	0.03	0.006	440	0.05	0.006	440	0.03	0.005	51	†	
M, 14-18 y	228	†		333	0.08	0.017	320	0.03	0.004	44	†	
M, 19-30 y	460	0.08	0.012	583	0.13	0.014	776	0.07	0.007	83	0.10	0.011
M, 31-50 y	853	0.11	0.013	826	0.18	0.025	800	0.08	0.015	100	0.14	0.028
M, 51-70 y	895	0.09	0.010	483	0.12	0.015	488	0.08	0.013	68	†	
M, 71+	892	0.08	0.009	201	†		173	0.06	0.016	30	†	
F, Total	5,606	0.05	0.005	4,509	0.07	0.003	4,326	0.04	0.004	701	†	
F, 2-6 months	215	-		75	-		58	-		37	-	
F, 7-12 months	249	†		78	*	0.001	85	*	0.002	53	†	
F, 1-3 y	433	†		388	†		484	†		53	†	
F, 4-8 y	498	0.03	0.006	599	0.03	0.005	695	†		81	†	
F, 9-13 y	326	0.03	0.006	446	0.04	0.007	441	†		48	†	
F, 14-18 y	289	0.03	0.005	381	0.06	0.011	326	0.03	0.005	66	†	
F, 19-30 y	605	0.06	0.012	731	0.08	0.007	757	0.04	0.006	88	†	
F, 31-50 y	1,041	0.07	0.009	1,043	0.09	0.008	869	0.06	0.009	144	†	
F, 51-70 y	941	0.07	0.008	541	0.08	0.011	497	0.04	0.006	96	†	
F, 71+	1,009	0.04	0.006	227	†		150	†	0.010	35	†	

- estimate = 0; * Value < 0.001 but greater than 0.

† Indicates a statistic that is potentially unreliable because the ratio of the SEM to the estimate times 100 > 20%.

Table 3.10. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) and Omega-3 PUFAs, United States, NHANES III (1988-94), Adults vs. Youths (Age < 18 y)

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d) †					
Total	29,099	238,221,947	14.13	0.1962	9.48
Adults	16,683	175,098,828	14.94	0.2298	7.02
Youths	12,416	63,123,119	11.88	0.2215	6.65
ALA (18:3 n-3) (g/d) †					
Total	29,099	238,221,947	1.33	0.0154	6.81
Adults	16,683	175,098,828	1.40	0.0191	5.59
Youths	12,416	63,123,119	1.13	0.0191	5.97
‡EPA (20:5 n-3) (g/d)					
Total	29,099	238,221,947	0.04	0.0026	8.57
Adults	16,683	175,098,828	0.04	0.0035	6.99
Youths	12,416	63,123,119	0.01	0.0014	3.90
‡DHA (22:6 n-3) (g/d)					
Total	29,099	238,221,947	0.07	0.0044	8.69
Adults	16,683	175,098,828	0.08	0.0058	7.40
Youths	12,416	63,123,119	0.03	0.0031	4.18
LA (18:2 n-6) (%kcal/d) †					
Total	29,097	238,218,723	5.79	0.0458	7.29
Adults	16,683	175,098,828	5.95	0.0512	5.06
Youths	12,414	63,119,895	5.36	0.0603	6.19
ALA (18:3 n-3) (%kcal/d) †					
Total	29,097	238,218,723	0.55	0.0041	5.78
Adults	16,683	175,098,828	0.56	0.0049	4.33
Youths	12,414	63,119,895	0.51	0.0047	4.12
‡EPA (20:5 n-3) (%kcal/d)					
Total	29,097	238,218,723	0.02	0.0011	8.47
Adults	16,683	175,098,828	0.02	0.0014	6.89
Youths	12,414	63,119,895	0.01	0.0006	3.56
‡DHA (22:6 n-3) (%kcal/d)					
Total	29,097	238,218,723	0.03	0.0019	10.67
Adults	16,683	175,098,828	0.04	0.0025	8.52
Youths	12,414	63,119,895	0.01	0.0010	3.97

† $P < .001$ between groups

‡ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.11. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94), Males vs. Females

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d) †					
Total	29,105	238,245,897	14.13	0.1962	9.48
Male	13,923	115,778,180	16.36	0.2841	7.48
Female	15,182	122,467,717	12.02	0.1618	5.04
ALA (18:3 n-3) (g/d) †					
Total	29,105	238,245,897	1.33	0.0154	6.81
Male	13,923	115,778,180	1.54	0.0233	6.05
Female	15,182	122,467,717	1.13	0.0134	3.84
‡EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.57
Male	13,923	115,778,180	0.04	0.0032	4.89
Female	15,182	122,467,717	0.03	0.0031	8.34
‡DHA (22:6 n-3) (g/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Male	13,923	115,778,180	0.08	0.0050	4.36
Female	15,182	122,467,717	0.06	0.0051	8.11
LA (18:2 n-6) (%kcal/d) †					
Total	29,103	238,242,673	5.79	0.0458	7.29
Male	13,922	115,776,672	5.65	0.0526	5.02
Female	15,181	122,466,001	5.93	0.0606	6.22
ALA (18:3 n-3) (%kcal/d) †					
Total	29,103	238,242,673	0.55	0.0041	5.78
Male	13,922	115,776,672	0.54	0.0047	4.05
Female	15,181	122,466,001	0.56	0.0054	4.81
‡EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.02	0.0011	8.47
Male	13,922	115,776,672	0.02	0.0011	4.67
Female	15,181	122,466,001	0.02	0.0014	7.40
‡DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.03	0.0019	10.67
Male	13,922	115,776,672	0.03	0.0020	5.19
Female	15,181	122,466,001	0.03	0.0023	9.00

† $P < .001$ between groups

‡ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.12. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94), by Race/Ethnicity groups

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d)					
Total	29,105	238,245,897	14.13	0.1962	9.48
* Non-Hispanic white	10,634	174,119,805	14.27	0.2354	5.05
* Non-Hispanic black	8,513	29,355,656	14.23	0.1956	2.55
* Mexican-American	8,627	14,878,866	14.07	0.2025	2.82
Other	1,331	19,891,569	12.77	0.4797	2.78
ALA (18:3 n-3) (g/d)					
Total	29,105	238,245,897	1.33	0.0154	6.81
† Non-Hispanic white	10,634	174,119,805	1.37	0.0192	3.78
* Non-Hispanic black	8,513	29,355,656	1.27	0.0166	2.16
* Mexican-American	8,627	14,878,866	1.20	0.0168	3.04
Other	1,331	19,891,569	1.12	0.0379	2.32
‡EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.56
Non-Hispanic white	10,634	174,119,805	0.03	0.0026	3.79
Non-Hispanic black	8,513	29,355,656	0.05	0.0024	1.37
Mexican-American	8,627	14,878,866	0.02	0.0026	4.35
Other	1,331	19,891,569	0.06	0.0120	4.60
‡DHA (22:6 n-3) (%kcal/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Non-Hispanic white	10,634	174,119,805	0.07	0.0048	3.93
Non-Hispanic black	8,513	29,355,656	0.09	0.0040	1.58
Mexican-American	8,627	14,878,866	0.05	0.0033	4.27
Other	1,331	19,891,569	0.10	0.0153	4.21

(continued to the next page)

PUFAs	Sample Size	Population Size	Mean	SEM	Design Effect	
LA (18:2 n-6) (%kcal/d)						
Total	29,103	238,242,673		5.79	0.0458	7.29
* Non-Hispanic white	10,634	174,119,805		5.79	0.0579	4.38
† Non-Hispanic black	8,512	29,353,940		5.98	0.0592	3.42
† Mexican-American	8,626	14,877,359		5.93	0.0476	2.11
Other	1,331	19,891,569		5.37	0.1279	2.48
ALA (18:3 n-3) (%kcal/d)						
Total	29,103	238,242,673		0.55	0.0041	5.78
† Non-Hispanic white	10,634	174,119,805		0.56	0.0054	3.55
† Non-Hispanic black	8,512	29,353,940		0.54	0.0051	2.77
† Mexican-American	8,626	14,877,359		0.52	0.0063	5.20
Other	1,331	19,891,569		0.48	0.0106	2.23
‡ EPA (20:5 n-3) (%kcal/d)						
Total	29,103	238,242,673		0.02	0.0011	8.47
Non-Hispanic white	10,634	174,119,805		0.01	0.0010	3.26
Non-Hispanic black	8,512	29,353,940		0.02	0.0009	1.18
Mexican-American	8,626	14,877,359		0.01	0.0009	3.39
Other	1,331	19,891,569		0.03	0.0057	4.72
‡ DHA (22:6 n-3) (%kcal/d)						
Total	29,103	238,242,673		0.03	0.0019	10.67
Non-Hispanic white	10,634	174,119,805		0.03	0.0019	4.20
Non-Hispanic black	8,512	29,353,940		0.04	0.0016	1.63
Mexican-American	8,626	14,877,359		0.02	0.0013	3.60
Other	1,331	19,891,569		0.05	0.0079	4.67

Other race/ethnicity group was the reference group.

* $P < .05$ compared to the reference group.

† $P < .001$ compared to the reference group.

‡ Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.13. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) and Omega-3 PUFAs, United States, NHANES III (1988-94), Metro vs. Non-metro Areas

PUFAs	Sample Size	Population Size	Mean	Design SEM	Effect
LA (18:2 n-6) (g/d)					
Total	29,105	238,245,897	14.13	0.1962	9.48
Metro	14,374	114,581,912	14.28	0.2701	8.23
Non-metro	14,731	123,663,985	13.99	0.2479	8.25
ALA (18:3 n-3) (g/d)					
Total	29,105	238,245,897	1.33	0.0154	6.81
Metro	14,374	114,581,912	1.34	0.0250	8.28
Non-metro	14,731	123,663,985	1.32	0.0203	6.39
EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897	0.04	0.0026	8.56
Metro	14,374	114,581,912	0.04	0.0032	6.45
Non-metro	14,731	123,663,985	0.03	0.0040	10.49
DHA (22:6 n-3) (g/d)					
Total	29,105	238,245,897	0.07	0.0044	8.69
Metro	14,374	114,581,912	0.08	0.0056	5.81
Non-metro	14,731	123,663,985	0.06	0.0069	13.43
LA (18:2 n-6) (%kcal/d)					
Total	29,103	238,242,673	5.79	0.0458	7.29
Metro	14,373	114,580,196	5.79	0.0554	5.06
Non-metro	14,730	123,662,477	5.79	0.0629	7.28
ALA (18:3 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.55	0.0041	5.78
Metro	14,373	114,580,196	0.55	0.0066	6.97
Non-metro	14,730	123,662,477	0.55	0.0059	6.29
†EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.02	0.0011	8.47
Metro	14,373	114,580,196	0.02	0.0014	6.39
Non-metro	14,730	123,662,477	0.01	0.0017	10.44
†DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673	0.03	0.0019	10.67
Metro	14,373	114,580,196	0.03	0.0021	5.95
Non-metro	14,730	123,662,477	0.03	0.0032	16.57

†Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.14. Means and the Standard Error of the Mean (SEMs) for Usual Daily Intake of Linoleic Acid (LA, 18:2 n-6) & Omega-3 PUFAs, United States, NHANES III (1988-94)^{*}, PIR ≤ 1.3 vs. PIR > 1.3

Poverty Index Ratio (PIR)	Sample Size	Population Size	Mean	SEM	Design Effect
LA (18:2 n-6) (g/d)					
Total	27,482	226,488,050	14.15	0.2015	9.48
PIR ≤ 1.3	11,711	53,365,381	12.85	0.2258	5.50
PIR > 1.3	15,771	173,122,669	14.55	0.2289	6.89
ALA (18:3 n-3) (g/d)					
Total	27,482	226,488,050	1.33	0.0160	6.88
PIR ≤ 1.3	11,711	53,365,381	1.19	0.0191	4.67
PIR > 1.3	15,771	173,122,669	1.38	0.0186	5.22
†EPA (20:5 n-3) (g/d)					
Total	27,482	226,488,050	0.04	0.0026	8.03
PIR ≤ 1.3	11,711	53,365,381	0.03	0.0027	4.67
PIR > 1.3	15,771	173,122,669	0.04	0.0031	6.45
†DHA (22:6 n-3) (g/d)					
Total	27,482	226,488,050	0.07	0.0042	7.77
PIR ≤ 1.3	11,711	53,365,381	0.06	0.0056	5.65
PIR > 1.3	15,771	173,122,669	0.07	0.0050	6.15
LA (18:2 n-6) (%kcal/d)					
Total	27,480	226,484,827	5.79	0.0470	7.27
PIR ≤ 1.3	11,710	53,363,665	5.58	0.0562	4.35
PIR > 1.3	15,770	173,121,162	5.86	0.0527	5.27
ALA (18:3 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.55	0.0042	5.83
PIR ≤ 1.3	11,710	53,363,665	0.52	0.0056	4.83
PIR > 1.3	15,770	173,121,162	0.56	0.0047	4.00
†EPA (20:5 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.01	0.0011	7.98
PIR ≤ 1.3	11,710	53,363,665	0.01	0.0009	3.09
PIR > 1.3	15,770	173,121,162	0.02	0.0013	6.68
†DHA (22:6 n-3) (%kcal/d)					
Total	27,480	226,484,827	0.03	0.0019	9.97
PIR ≤ 1.3	11,710	53,363,665	0.02	0.0015	3.41
PIR > 1.3	15,770	173,121,162	0.03	0.0023	7.97

^{*} 6% participants refused to report their income or income category.

[†] Distribution of EPA and DHA were very skewed; means and standard errors of the means should be used and interpreted with caution. No test of differences in the mean intakes of EPA, DPA, and DHA between groups was performed.

Table 3.15. The Demographic Characteristics of Adult Participants With and Without a History of Cardiovascular Diseases, United States, NHANES III (1988-94)[§]

Gender and Race/Ethnicity Groups	People With a History of CVD		People Without a History of CVD	
	Sample Size	Population Size	Sample Size	Population Size
Total	2,121	14,964,332	14,562	160,134,496
Male	1,136	8,036,546	6,664	75,438,001
Female	985	6,927,787	7,898	84,696,495
Non-Hispanic White				
Total	973	10,966,582	5,771	121,941,462
Male	554	6,165,912	2,567	57,378,183
Female	419	4,800,670	3,204	64,563,276
Non-Hispanic Black				
Total	686	2,445,381	4,033	17,057,068
Male	353	1,175,699	1,777	7,493,735
Female	333	1,269,682	2,256	9,563,333
Mexican-American				
Total	391	502,292	4,176	8,673,940
Male	205	261,129	2,060	4,507,199
Female	186	241,163	2,116	4,166,741
Other				
Total	71	1,050,078	582	12,462,026
Male	24	433,807	260	6,058,884
Female	47	616,271	322	6,403,141

[§] All NHANES III variance estimates were based on Taylor Series (WR) method.

Table 3.16. The Mean Intakes \pm SEMs of Linoleic Acid (LA, 18:2n-6), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94)

	Linoleic acid (LA, 18:2n-6)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	12.58	0.4753	15.16	0.2355	5.80	0.0954	5.96	0.0536
Male	15.12	0.8243	17.96	0.3390	5.87	0.1263	5.80	0.0598
Female	9.64	0.2815	12.67	0.1980	5.73	0.1343	6.10	0.0729
Non-Hispanic White								
Total	13.06	0.6196	15.20	0.2798	5.98	0.1178	5.96	0.0663
Male	15.62	1.0596	18.17	0.4158	6.06	0.1699	5.82	0.0739
Female	9.76	0.3733	12.57	0.2245	5.88	0.1803	6.08	0.0844
Non-Hispanic Black								
Total	11.71	0.5201	15.42	0.2521	5.60	0.1378	6.09	0.0687
Male	13.96	0.7583	17.85	0.3712	5.62	0.1692	5.79	0.0613
Female	9.62	0.4955	13.52	0.2714	5.57	0.1811	6.33	0.0999
Mexican-American								
Total	11.36	0.4970	15.92	0.2814	5.79	0.1469	6.16	0.0706
Male	11.28	0.6263	18.57	0.3443	5.17	0.2655	6.06	0.0874
Female	11.44	0.7056	13.05	0.3075	6.46	0.2943	6.26	0.0819
Other								
Total	10.27	1.3049	13.88	0.5446	4.43	0.4121	5.67	0.1486
Male	13.47	2.9402	15.65	0.6688	4.16	0.7905	5.44	0.2131
Female	8.02	0.7190	12.21	0.7737	4.62	0.4265	5.88	0.2396

Table 3.17. The Mean Intakes \pm SEMs of Alpha Linolenic Acid (ALA, 18:3 n-3), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94)

	Alpha Linolenic Acid (ALA, 18:3 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	1.16	0.0349	1.42	0.0201	0.55 *†	0.0093	0.57 *†	0.0051
Male	1.38	0.0600	1.69	0.0298	0.55	0.0132	0.55	0.0059
Female	0.90	0.0238	1.19	0.0181	0.54	0.0108	0.58	0.0066
Non-Hispanic White								
Total	1.20	0.0399	1.46	0.0253	0.56	0.0105	0.58	0.0069
Male	1.40	0.0651	1.75	0.0368	0.57	0.0148	0.57	0.0075
Female	0.93	0.0305	1.21	0.0224	0.56	0.0132	0.59	0.0089
Non-Hispanic Black								
Total	1.08	0.0456	1.37	0.0222	0.52	0.0115	0.54	0.0057
Male	1.25	0.0684	1.60	0.0389	0.51	0.0141	0.52	0.0067
Female	0.92	0.0552	1.19	0.0224	0.54	0.0192	0.56	0.0079
Mexican-American								
Total	0.96	0.0453	1.32	0.0221	0.49	0.0161	0.52	0.0078
Male	1.04	0.0600	1.53	0.0332	0.47	0.0252	0.50	0.0099
Female	0.87	0.0627	1.09	0.0248	0.52	0.0234	0.53	0.0095
Other								
Total	1.07	0.1754	1.18	0.0453	0.44	0.0370	0.48	0.0167
Male	1.57	0.3688	1.13	0.0701	0.46	0.0820	0.46	0.0244
Female	0.72	0.0584	1.03	0.0724	0.42	0.0314	0.50	0.0233

* Univariate analysis showed significant differences between the CVD groups ($P=.04$)

† Multivariate analysis (adjusted for sex, age, and race/ethnicity) showed significant differences between the CVD groups. The results are shown in Appendix C in detail.

Table 3.18. The Mean Intakes \pm SEMs of Eicosapentaenoic Acid (EPA, 20:5 n-3), Respondents with a History of CVD Compared to Those Without CVD, NHANES III (1988-94) §

	Eicosapentaenoic acid (EPA, 20:5 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	0.04	0.0042	0.04	0.0037	0.02	0.0023	0.02	0.0015
Male	0.05	0.0071	0.05	0.0045	0.02	0.0034	0.02	0.0017
Female	0.04	0.0061	0.04	0.0041	0.03	0.0043	0.02	0.0019
Non-Hispanic White								
Total	0.04	0.0044	0.04	0.0036	0.02	0.0028	0.02	0.0013
Male	0.04	0.0067	0.05	0.0056	0.02	0.0033	0.02	0.0018
Female	0.04	0.0082	0.03	0.0034	0.03	0.0061	0.02	0.0014
Non-Hispanic Black								
Total	0.07	0.0131	0.06	0.0039	0.03	0.0057	0.02	0.0013
Male	0.09	0.0261	0.07	0.0082	0.04	0.0103	0.02	0.0025
Female	0.05	0.0113	0.05	0.0027	0.03	0.0061	0.02	0.0013
Mexican-American								
Total	0.02	0.0064	0.03	0.0039	0.01	0.0030	0.01	0.0014
Male	0.04	0.0117	0.04	0.0058	0.02	0.0053	0.01	0.0019
Female	0.01	0.0040	0.02	0.0039	0.00	0.0014	0.01	0.0017
Other								
Total	0.07	0.0240	0.08	0.0188	0.03	0.0110	0.04	0.0088
Male	0.11	0.0530	0.07	0.0138	0.05	0.0224	0.03	0.0066
Female	0.04	0.0184	0.09	0.0290	0.02	0.0097	0.04	0.0137

§ Distribution of this nutrient is very skewed; means and standard errors of the means should be used and interpreted with caution.

Table 3.19. The Mean Intakes \pm SEMs of Docosahexaenoic Acid (DHA, 22:6 n-3), Respondents With a History of CVD Compared to Those Without CVD, NHANES III (1988-94) [§]

	Docosahexaenoic acid (DHA, 22:6 n-3)							
	CVD		Non-CVD		CVD		Non-CVD	
	Mean (g/d)	SEM	Mean (g/d)	SEM	Mean (%kcal/d)	SEM	Mean (%kcal/d)	SEM
Total	0.08	0.0050	0.09	0.0062	0.04	0.0032	0.04	0.0026
Male	0.08	0.0085	0.10	0.0074	0.04	0.0042	0.04	0.0031
Female	0.07	0.0103	0.07	0.0067	0.04	0.0066	0.03	0.0029
Non-Hispanic White								
Total	0.07	0.0060	0.08	0.0066	0.04	0.0040	0.03	0.0025
Male	0.07	0.0096	0.10	0.0088	0.03	0.0045	0.03	0.0033
Female	0.06	0.0132	0.06	0.0065	0.04	0.0091	0.03	0.0024
Non-Hispanic Black								
Total	0.12	0.0167	0.12	0.0063	0.06	0.0078	0.05	0.0023
Male	0.14	0.0280	0.15	0.0129	0.06	0.0104	0.05	0.0040
Female	0.09	0.0205	0.09	0.0041	0.06	0.0104	0.04	0.0020
Mexican-American								
Total	0.05	0.0093	0.06	0.0049	0.03	0.0047	0.03	0.0018
Male	0.08	0.0158	0.08	0.0069	0.04	0.0082	0.03	0.0023
Female	0.03	0.0053	0.05	0.0051	0.02	0.0025	0.03	0.0023
Other								
Total	0.11	0.0300	0.13	0.0234	0.05	0.0138	0.06	0.0119
Male	0.14	0.0580	0.13	0.0142	0.06	0.0249	0.05	0.0086
Female	0.08	0.0358	0.14	0.0385	0.04	0.0151	0.07	0.0194

[§] Distribution of this nutrient is very skewed; means and standard errors of the means should be used and interpreted with caution.

Effects of Consumption of Omega-3 Fatty Acid from Fish or Overall Diet, or from Supplements of Fish Oil or ALA, on Cardiovascular Disease Outcomes

In this section, we present results from our review of studies that examined the effect of omega-3 fatty acid supplements or fish consumption on all-cause mortality and CVD outcomes. An overview of our literature search is presented first, followed by findings from secondary and primary prevention studies. Specific key questions relating to the efficacy of omega-3 fatty acids on CVD outcomes are also discussed. Relevant summary tables appear at the end of this section.

Summary of Studies Analyzed

We screened over 7,464 abstracts that were indexed as English language articles concerning humans. Based on this initial review, we retrieved and screened 768 full text articles for potentially relevant human data. We subsequently examined 118 articles that passed a screen for studies that might have CVD clinical outcome data. We rejected 80 articles. Thirty of the rejected articles were reviews or commentaries that did not provide primary data. The reasons for rejecting the remaining 50 articles are listed in the section, Excluded Studies.

Thirty-nine unique studies fulfilled our inclusion criteria for reporting mortality or CVD clinical outcomes with a follow-up duration of 1 year or longer (interim reports or articles reporting different outcomes from the same overall study were counted as a single study). The 39

studies included: 12 randomized controlled trials (RCTs), 22 unique prospective cohort studies (including 4 studies that each contributed 2 separate articles on different analyses), 4 case-control studies, and 1 cross-sectional study. We created evidence and summary tables for these studies and included the studies in our analyses. Evidence Table 1 provides detailed information about the RCTs, and Evidence Table 2 describes prospective cohort, case-control, and cross-sectional studies. The summary tables present information about the study population, study design and duration, the frequency or amount of omega-3 fatty acid supplements or fish or fish oil consumed, dietary assessment method, main results, study quality, and study applicability. Studies are ordered by study size in each summary table.

For all practical purposes, CVD populations were studied with RCTs and the general population was studied with prospective cohort and case-control studies. Thus, in this section we first discuss results of the secondary prevention studies (i.e., studies of the CVD population), which are comprised of 11 RCTs and 1 cohort study. This is followed by a discussion of the primary prevention studies (or studies of the general population), which are comprised mostly of prospective cohort studies and 1 RCT.

For the non-randomized studies, data on each outcome are presented in 2 tables. One table presents outcomes based on estimates of omega-3 fatty acid or fish oil consumption, the other presents outcomes based on estimates of fish consumption. Because of the large amount of outcomes data reported in the prospective cohort studies, we created an “overall effect” metric to reduce this volume of information and to help interpret the results of these studies (see Chapter 2, Methods). This metric is used in the summary matrices (Tables 3.40-3.51).

In discussing results for the CVD and general populations, evidence for the following CVD clinical outcomes is presented: all-cause mortality, CVD deaths (deaths due to strokes, cardiac and peripheral vascular diseases), cardiac deaths, sudden death, myocardial infarction (MI), stroke, and all CVD events. It should be noted that different studies reported different combinations of these outcomes, and that the definitions for some of the outcomes varied across studies. For example, coronary deaths, ischemic deaths, cardiac deaths, and fatal myocardial infarction have largely overlapping but not identical meanings, as defined by individual studies. We placed the outcome reported by a study under the most similar common definition, as judged by a clinician-methodologist member of the EPC.

Tables 3.20-3.23 and 3.25 summarize the 12 RCTs. Six of the RCTs were trials of omega-3 fatty acid supplements, and 6 were trials of diets or dietary advice. Only 1 of the 12 trials, a large study that compared linseed oil (ALA) with sunflower oil, was a primary prevention study conducted in the general population. The remaining 11 trials were secondary prevention studies conducted in patients with known CVD. This profile was reversed among the 22 prospective cohort studies (which included 26 separate papers), as all but 1 of the cohort studies were conducted in the general population.

Tables 3.24-3.39 summarize the results of the prospective cohort, case-control, and cross-sectional studies. Studies are ordered by study size in each table. Data on each outcome are presented in 2 tables: 1 table presents outcomes based on estimates of omega-3 fatty acid or fish oil consumption, the other presents outcomes based on estimates of fish consumption. Because of the large amount of data reported in the prospective cohort studies, we created an “overall effect” metric to help in interpreting the results of these studies (see Chapter 2, Methods). This metric is reported by outcome in Tables 3.40-3.51.

Information about omega-3 fatty acid consumption varied across studies. In the RCTs of omega-3 fatty acid supplements, the amount and composition of omega-3 fatty acid is known

and reported, whereas in the diet/dietary advice trials, estimates of the average amount of omega-3 fatty acids consumed by subjects are reported. In the prospective cohort studies, the amount of omega-3 fatty acid was not prescribed. As a result, omega-3 fatty acid intake and the amount or frequency of fish intake were estimated and reported as different quantiles corresponding to the observed relative risk of the outcomes.

Secondary Prevention Studies (Tables 3.20-3.24)

Evidence for the effects of the consumption of omega-3 fatty acids, omega-3 fatty acid supplements, or fish on CVD outcomes in populations known to have CVD was derived from 11 RCTs and 1 prospective cohort study. The 11 RCTs include 5 trials of omega-3 fatty acid supplements and 6 diet or dietary advice trials.

Characteristics of the omega-3 fatty acids supplements trials (Table 3.20-3.21). Of the 5 RCTs of omega-3 fatty acid supplements, 4 examined EPA+DHA supplements. The methodological quality of all 4 RCTs of EPA+DHA supplements was generally good (grade A or B)³⁴⁻³⁷. Data on women are limited. The fifth is the single RCT with both an ALA arm and an EPA+DHA arm and the methodological quality was poor (grade C)³⁸.

The study populations of these 5 trials were rated as CVD-I (highly applicable) to CVD-II (relevant subgroups). One of the trials, the GISSI-Prevenzione trial, is the largest secondary prevention study with over 11,000 patients randomized^{35,39}. The other 3 EPA+DHA trials, combined, contributed fewer than 1,000 patients. The study subjects in these 3 smaller trials were MI survivors, patients with other vascular diseases, or patients with significant CVD risks. Most of the omega-3 fatty acid arms used a combination of EPA+DHA, although the dosages vary from 0.27 g/d to 4.8 g/d. The types of control also varied across the studies. The GISSI study used vitamin E or no vitamin E in a factorial design. Three of the studies used an equivalent amount of non-omega-3 oil as a control. The duration of the trials ranged from 2 to 3.5 years, and most were conducted outside the US.

The ALA trial was conducted in India and had a duration of 1 year. This trial compared 2.9 g/d of ALA in the form of mustard oil in 1 treatment arm and a combination of EPA+DHA in another treatment arm with a non-oil placebo³⁸. The methodological quality of this study was poor (grade C).

Table 3.20 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (secondary prevention)

Author Year Country	Omega-3 fatty acid		Control		Duration (year)	All cause mortality		CVD death		Cardiac death		Sudden death		Quality			Applicability
	N	Type Dose	N	Type Dose		Control Group Event Rate (%)	RR 95% CI	Control Group Event Rate (%)	RR 95% CI	Control Group Event Rate	RR 95% CI	Control Group Event Rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA + DHA																	
2002 Marchioli Italy	5665	EPA + DHA (1:2) 0.85 g/d±Vit E	5658	Control ±Vit E	3.5	9.8	0.79 ¹ 0.66-0.93	6.5	0.70 ¹ 0.56-0.86	5.4	0.65 ¹ 0.51-0.82	2.7	0.55 ¹ 0.39-0.77	B	3	A	CVD I
Nilsen Norway	2001 150	EPA + DHA (1:2) 1.7 g/d	150	Corn oil 1.7 g/d	1.5	7.3	1.0 0.45-2.2	-	nd	5.3	1.0 0.39-2.6	-	nd.	B	4	U	CVD II
Singh 1997 India	122	EPA + DHA (1:1) 1.8 g/d	118	Non-oil placebo	1	-	nd	-	nd	22	0.52 0.29-0.95	6.6	0.24 0.05-1.1	C	4	I	CVD II
Leng 1998 Scotland	60	EPA 0.27g/d	60	Sun flower seed oil 3 g/d	2	5.0	1.0 0.21-4.8	3.3	1.0 0.15-6.9	-	nd	-	nd.	A	5	A	CVD II
Sacks 1995 US	31	EPA + DHA (3:2) 4.8 g/d	28	Olive Oil	2.4	3.6	0.3 0.01-7.1	3.6	0.3 0.01-7.1	3.6	0.3 0.01-7.1	0	nd	B	3	U	CVD II
ALA																	
Singh 1997 India	120	Mustard Oil ALA 2.9 g/d	118	Non-oil placebo	1	-	nd	-	nd	22	0.61 0.34-1.1	6.6	0.25 0.05-1.1	C	4	I	CVD II

¹ RR adjusted for main confounders as reported in article.

Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Applicability is derived from a combination of the target population (GEN or CVD) and the three-level grades (I, II, III). CVD-II represents a relevant subgroup of US subjects with history or risk of CVD. Most studies in this table are graded CVD-II because they are foreign mixed-gender populations with different background diets at risk for CVD.

Table 3.21 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (secondary prevention)

Author Year Country	Omega-3 Fatty acid		Control		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jaded score	Alloc. conceal.	
EPA + DHA																	
Marchioli 2002 Italy	5665	EPA + DHA (1:2) 0.85 g/d±Vit E	5658	Control Or Vit E	3.5	4.6	0.68 ¹ 0.53-0.88	4.1	0.91 ¹ 0.70-1.2	1.4	1.2 ¹ 0.81-1.9	11	0.80 ¹ 0.68-0.94	B	3	A	CVD I
Nilsen 2001 Norway	150	EPA + DHA (1:2) 1.7 g/d	150	Corn oil 1.7 g/d	1.5	-	nd	10	1.4 0.75-2.6	-	nd	47	1.1 0.84-1.3	B	4	U	CVD II
Singh 1997 India	122	EPA + DHA (1:1) 1.8 g/d	118	Non-oil placebo	1	-	nd	25	0.52 0.3-0.9	-	nd	35	0.71 0.48-1.1	C	4	I	CVD II
Leng 1998 Scotland	60	EPA 0.27g/d	60	Sunflower seed oil 3 g/d	2	-	nd	6.7	0.75 0.18-3.2	1.7	Non-fatal stroke 3.0 0.32-28	23	0.86 ² 0.43-1.7	A	5	A	CVD II
Sacks 1995 US	31	EPA + DHA (3:2) 4.8 g/d	28	Olive Oil	2.4	3.6	0.3 0.01-7.1	7.1	0.45 0.04-4.7	0	2.7 0.12-64	-	nd	B	3	U	CVD II
ALA																	
Singh 1997 India	120	Mustard Oil ALA 2.9 g/d	118	Non-oil placebo	1	-	nd	25	0.59 0.35-1.0	-	nd	35	0.82 0.56-1.2	C	4	I	CVD II

¹ RR adjusted for main confounders as reported in article. ² Includes critical ischemia/amputation, angioplasty and bypass surgery.

Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Applicability is derived from a combination of the target population (GEN or CVD) and the three-level grades (I, II, III). CVD-II represents a relevant subgroup of US subjects with history or risk of CVD. Most studies in this table are graded CVD-II because they are foreign mixed-gender populations with different background diets at risk for CVD

Table 3.22 Randomized controlled trials of omega-3 fatty acid diet or dietary advice on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (secondary prevention)

Author Year Country	Diet / Fish advice		No Diet / No fish advice		Duration (Year)	All cause mortality			CVD death		Cardiac death		Sudden death		Quality			Applicability	
	N	Estimated omega-3 fatty acid intake	N	Estimated omega-3 fatty acid intake		Control group event rate (%)	RR	95% CI	Control group event rate (%)	RR	95% CI	Control group event rate (%)	RR	95% CI	Control group event rate (%)	RR	95% CI		Summary
EPA estimate																			
Burr 2003 UK	1571	EPA 2.11-2.65 g/wk	1543	EPA 0.12-0.17 g/wk	5	16	HR 1.15 0.86-1.36	-	-	9	HR 1.26 (1.00-1.58)	3	HR 1.54 (1.06-2.23)	C	2	A	CVD II		
Burr 1989 UK	1015	EPA 2.4 g/wk (SD 1.4)	1018	EPA 0.06 g/wk (SD 0.7)	2	13	0.73 0.56-0.93	-	nd	11	0.67 0.51-0.89	-	nd	C	1	U	CVD II		
ALA estimate																			
Singh 2002 India	499	Indo Mediterranean diet ALA 1.8 g/d	501	ALA 0.8 g/d	2	8	0.63 0.38-1.04	-	nd	-	nd	3.2	0.38 0.15-0.95	C	3	U	CVD III		
Leren 1966 Norway	406	Cholesterol-lowering diet ¹ ALA 1-1.9 g/d (soybean oil)	406	Usual diet	5	27	0.75 0.52-1.06	25	0.73 0.50-1.06	-	nd	13	1.00 0.61-1.64	C	2	I	CVD II		
DeLorgeril 1999 France	302	Cretan Mediterranean diet ¹ ALA 1.9 g/d	303	Prudent diet ² ALA 0.67 g/d	2.3	7.9	0.44 ³ 0.21-0.94	-	nd	6.3	0.35 ³ 0.15-0.83	2.6	0.06 0.003-1.02	C	4	A	CVD II		
Bemelmans 2002 Netherlands	109	ALA 6.3 g/d	157	ALA 1.0 g/d	2	0.6	4.3 0.46-41	0.6	1.44 0.09-23	-	nd	-	nd	B	3	A	CVD I		

¹ ALA=0.84 % energy = calculated from daily nutrient recorded on the final visit in 144 unselected consecutive experimental patients

² ALA=0.29% energy = calculated from daily nutrient recorded on the final visit in 83 unselected consecutive control patients

³ RR adjusted for main confounders as reported in article.

Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Table 3.23 Randomized controlled trials of omega-3 fatty acid diet or dietary advice on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (secondary prevention)

Author Year Country	Diet / Fish advice		No Diet / No fish advice		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Estimated omega-3 fatty acid intake	N	Estimated omega-3 fatty acid intake		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
EPA estimate																	
Burr 2003 UK	1571	EPA 2.11-2.65 g/wk	1543	EPA 0.12-0.17 g/wk	5	-	nd	-	nd	-	nd	-	nd	C	1	U	CVD II
Burr 1989 UK	1015	EPA 2.4 g/wk	1018	EPA 0.6g/wk (SD 0.7)	2	-	0.7 0.5-0.9	3.2	1.5 0.97-2.3	-	nd	-	nd	C	1	U	CVD II
ALA estimate																	
Singh 2002 India	499	Indo Mediterranean diet ALA 1.8 g/d	501	ALA 0.8 g/d	2	3.4	0.71 0.34-1.5	8.6	0.49 0.30-0.81	2.6	0.54 0.22- 1.3	-	nd	C	3	U	CVD III
Leren 1966 Norway	406	Cholesterol- lowering diet ALA 1-1.9 g/d (soybean oil)	406	Usual diet	5	11	0.43 0.21- 0.89	15	0.77 0.47-1.27	-	nd	-	nd	C	2	I	CVD II
DeLorgeril 1999 France	302	Cretan Mediterranean diet ¹ ALA 1.9 g/d	303	Prudent diet ² ALA 0.67 g/d	2.3	-	nd	8.3	0.32 0.15- 0.70	1.3	0.11 0.01-2.1	59	0.53 ³ 0.38-0.74	C	4	A	CVD II
Bemelmans 2002 Netherlands	109	ALA 6.3 g/d	157	ALA 1.0 g/d	2	-	nd	2.5	0.16 0.01- 2.9	1.3	0.29 0.01-5.9	5.7	0.16 0.02-1.3	B	3	A	CVD I

¹ALA = 0.84% daily energy = calculated from daily nutrient recorded on the final visit in 144 unselected consecutive experimental patients

²ALA = 0.29% daily energy = calculated from daily nutrient recorded on the final visit in 83 unselected consecutive control patients

³Total major and minor endpoints.

Alloc. conceal. – allocation concealment; g/d – grams per day; nd – no data

Characteristics of the diet and dietary advice trials. (Tables 3.22-3.23) Evidence for the effects of diet or dietary advice on CVD outcomes in populations known to have CVD was derived from 6 RCTs. About 4,000 patients were studied in the trials, and trial duration ranged from 2 to 5 years.

Two of the trials of diet and dietary advice were conducted among males from the ^{40,41}. The amount of omega-3 fatty acid consumption in these 2 trials can only be estimated. The methodological quality of the trials was poor (grade C) and the study populations were rated as CVD-II (relevant subgroups). Two other trials reported estimates of EPA intake. The weekly EPA consumption in the first of these trials was 0.6 g in the control group and 2.4 g in the intervention group. Weekly EPA consumption in the second trial was 0.12g in the control group and 2.7 g in the intervention group.

Four trials provided estimates of daily ALA consumption. In the control groups of these trials, estimated ALA consumption ranged from 0.67 g/d to 1 g/d. Estimated ALA intake of the intervention groups was at least double that of the control groups (range 1.8 g/d to 6.3 g/d^{42 43-45}. The methodological quality of 3 of the 4 trials was poor (Grade C). The applicability of the trials ranged from CVD-I (highly applicable) to CVD-III (limited applicability). The subjects were mostly MI survivors or those at significant CVD risk. The study by Bemelmans et al. randomized patients in a factorial design to consume a margarine rich in ALA or LA, and to receive nutritional education or not ⁴⁵. The amount of margarine prescribed was not fixed, but instead was based on the participants' usual consumption patterns. The study by ⁴⁴ was conducted among patients in India. Two-thirds of the participants were vegetarians, which limits the applicability of the study results to the US population.

Table 3.24 Association of estimates of fish consumption with all cause mortality, cardiovascular death, and myocardial infarction in prospective cohort studies (secondary prevention)

Author Year Location	N	Duration (year)	Dietary Assessment	Results			Trend P-value	Overall effect	Quality	Applicability	
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)							
Erkkila 2003 Finland	415	5	4-day food record	0	1-57	>57 g/d	0.06 NS NS	+ + 0	B	CVD II	
				All cause mortality	1.0	0.50					0.37*
				CV Death	1.0	0.64					0.45
				CAD death or MI	1.0	1.0	0.49				

There was 1 prospective cohort study⁴⁶ (Table 3.24) in a CVD population that associated estimates of daily fish consumption with CVD outcomes. The methodological quality of this study was good (grade B). The study populations were rated as CVD-II (relevant subgroups). This study lasted 5 years and included 415 subjects with known coronary artery disease. A 4-day food record was used to assess the daily fish intake. Fish intake was divided into 3 categories: no intake, below medium consumption (57 g/d), and above medium consumption.

CVD Outcomes of Secondary Prevention Studies

Results from the secondary prevention studies are summarized by outcome, below.

All-cause mortality. Ten RCTs reported all-cause mortality (Tables 3.20-3.23). Of these, 4³⁴⁻³⁷ used omega-3 fatty acid supplements. The quality of the 4 studies was generally good (grade A or B).

The all-cause mortality rate for control groups in the 10 RCTs ranged from 3.6% to 9.8% over a period of 1 to 3.5 years of follow-up. The largest study³⁵ found significant reduction of all-cause mortality with a relative risk reduction of 21% over 2 to 3.5 years. The amount of omega-3 fatty acid used in the intervention arms of this study was 0.85 g/d of EPA+DHA.

The 2 largest diet/dietary advice trials^{41,47} were both of poor quality (Grade C). In the first trial⁴⁷, the amount of omega-3 fatty acid in the diet in the intervention arms was 2.4g/week of EPA. This trial found a significant reduction of all-cause mortality with a relative risk of 27%⁴⁷. However, the 10 year follow-up to this trial found no long-term benefit of fish advice in the same group of patients taking a similar amount of EPA⁴⁸.

Of the 4 diet/dietary advice trials that provided estimates of ALA consumption^{42,43,44,45}, 3 found significant or near-significant reduction of all-cause mortality with a relative risk reduction of 25% to 56% over 2 to 5 years. The quality of these studies were fair to poor (grade B or C). The amount of omega-3 fatty acid in the diet in the intervention arms data ranged from about 1 to 6.3 g/d of ALA. Because these trials were interventions based on diet, the daily variations in the amount of omega-3 fatty acids would make the interpretations of their results difficult.

The single prospective cohort study (Table 3.24) compared subjects who consumed fish to those who did not and reported an at least 50% relative risk reduction in all-cause mortality and CVD death with any amount of fish intake⁴⁶.

Sudden death. (Tables 3.20, 3.22, 3.25). Six RCTs reported data on sudden deaths Four studies^{35 38,43,44} Singh reported a significant or near-significant large reduction of this outcome (relative risk [RR] 0.06 to 0.55). The reduction of sudden deaths in these studies was observed in both the fish oil group and the ALA oil group. However, of the 4 studies, 3 (a Mediterranean diet study⁴³ and 2 Indian studies^{38,44}) were poorly designed (grade C).

An early trial by Leren⁴² randomized 206 men 1-to-2-years post-MI to a cholesterol lowering diet and followed them for 5 years. There were no differences between subjects on the diet and those in the control group. However, a new report by Burr et al⁴¹ found that persons taking fish oil supplements have an increased risk of sudden death risk, although this study is also of poor quality (grade C).

Stroke. (Tables 3.21, 3.23, 3.26). Six trials reported data on stroke Strokes occurred in 0% to 3% of subjects in control groups. Three of the trials^{34,35,37} were of fish oil supplements; the methodological quality of these trials was generally good (2 studies of grade B and 1 study of grade A) and each reported trends of increased strokes. However, the 3 diet/dietary advice trials^{43 44,45} (which were of poor quality 2 studies of grade C and of 1 grade B) reported trends of fewer strokes. None of the results from the 6 studies were statistically significant.

Other CVD outcomes. One study consistently reported no beneficial effect of omega-3 fatty acids on any CVD outcomes (Tables 3.20 and 3.22)³⁶. This study randomized 300 patients to 1.7 g/d of EPA+DHA or an equivalent amount of corn oil and followed subjects for 1.5 years. Of

note, 15% of the study subjects died during the study, and about 40% of the subjects had been taking fish oil before the trial.

Three of the RCTs were too small, with 59 and 120 subjects each^{34,37}, or had too few CVD events⁴⁵ to provide meaningful results.

Reports of other outcomes, such as CVD deaths, cardiac deaths, sudden death, fatal and non-fatal MI, were inconsistently reported. The overall beneficial results were similar across studies.

Table 3.25 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: all cause mortality, CVD death, cardiac death, sudden death (Primary intervention)

Author Year Country	Omega -3 Fatty acid		Control		Duration (year)	All cause mortality		CVD death		Cardiac death		Sudden death		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
ALA																	
Natvig 1968 Norway	6716	Linseed oil ALA 5.5 g/d	6690	Sunflower seed oil ALA 0.14 g/d	1	0.6	1.1 0.7-1.6	-	nd	0.4	1.0 0.58-1.7	-	nd	C	4	A	GEN II

Table 3.26 Randomized controlled trials of omega-3 fatty acid supplements on cardiovascular disease outcomes: myocardial infarction, stroke, all CVD events (Primary intervention)

Author Year Country	Omega -3 Fatty acid		Control		Duration (year)	Fatal MI		Non-fatal MI		All strokes		All CVD events		Quality			Applicability
	N	Type Dose	N	Type Dose		Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Control group event rate (%)	RR 95% CI	Summary	Jadad score	Alloc. conceal.	
ALA																	
Natvig 1968 Norway	6716	Linseed oil ALA 5.5 g/d	6690	Sunflower seed oil ALA 0.14 g/d	1	All MI 0.8		All MI 1.2 (0.84-1.7)		0.13	1.4 0.62-3.4	-	nd	C	4	A	GEN II

Table 3.27 Association of estimates of omega-3 fatty acid consumption with all cause mortality in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results ¹					Trend P-value ²	Overall effect	Quality	Applicability	
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)									
Nagata 2002 Japan	29079	7	FFQ	EPA+DHA					NS 0.01	++	A	GEN II	
				Men	0.41	0.6	0.79	1.1					1.6 g/d
				Hazard ratio	1.0	0.82*	0.87	0.88					0.87
				Women	0.33	0.49	0.64	0.83					1.3 g/d
				Hazard ratio	1.0	0.92	0.84	0.90	0.77*				
Yuan 2001 China	18244	12	FFQ	EPA+DHA					0.01	++	A	GEN II	
					0.15	0.38	0.65	0.91					1.7 g/wk
					1.0	0.79*	0.76*	0.86*	0.79*				
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA					0.014 0.01	++	A	GEN II	
					0.87	1.3	1.6	1.9					2.8 g/d
					1.0	0.96	0.69	0.89					0.69
				EPA+DHA									
					0.0	0.009	0.046	0.15	0.66 g/d				
					1.0	1.1	1.0	0.85	0.76				

The footnotes and abbreviations below apply to summary tables 3.27– 3.39 in this section.

¹ Adjusted results are presented here when reported in original study. See evidence tables for details.

² Trend for inverse association. Up arrow indicates a statistically significant positive association (worse outcome).

* Statistically significant p<0.05; numerical p-value reported for p<0.1.

Study acronyms:

ABCC = Alpha-Tocopherol Beta-Carotene Cancer Prevention

ADVENTIST = Adventist Health Study

CHS = Cardiovascular Health Study

HPS = Health Professionals Study

MRFIT = Multiple Risk Factor Intervention Study

NHANES = National Health and Nutrition Examination Study

NHS = Nurses' Health Study

PHS = Physicians' Health Study

WES = Western Electric Company Study

Table 3.28 Association of estimates of fish consumption with all cause mortality in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability			
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)											
Nagata 2002 Japan	29079	7	FFQ	Men Hazard ratio	46 1.0	68 0.92	87 0.91	112 0.90	158 0.94	g/d	NS	0	A	GEN II	
				Women Hazard ratio	37 1.0	54 0.93	69 0.96	88 0.93	122 0.86	g/d					
Albert 1998 US PHS	20551	12	FFQ	<1/mo	1-3/mo	1-<2/wk	2-<5/wk	≥5/wk			0.045	++	A	GEN II	
				1.0	0.79	0.71*	0.70*	0.73*							
Yuan 2001 China	18244	12	FFQ	<50	50-100	100-150	150-200	≥200	g/wk	0.01	++	A	GEN II		
				1.0	0.79*	0.76*	0.86*	0.79*							
Mann 1997 UK	10802	13.3	FFQ	0	<1	≥1/wk				NS	0	B	GEN II		
				Death rate ratio	100	97	96								
Gillum 2000 US NHANES	8825	18.8	FFQ + 24-hr recall	White Men	Black Men	White Women	Black Women	Never	<1	1	>1/wk	0.01	+	B	GEN I
				1.0	1.0	1.0	1.0	1.0	0.88	1.0	0.85	NS			
				1.0	1.0	1.0	1.0	0.77	0.79	0.82	nd				
Osler 2003 Denmark	8497	18	FFQ	Hazard ratio	≤1/mo	2/mo	1/wk	>2/wk			0.02↑	-	B	GEN I	
				0.88	0.84*	1.0 (ref)	1.1								
Daviglus 1997 US WES	1822	30	FFQ	0	1-17	18-34	≥35	g/d			NS	0	A	GEN II	
				1.0	1.02	0.98	0.85								
Fraser 1997 US Adventist	603	12	FFQ	>84 years old subset of Adventist Health Study	<1/wk	>1/wk					NS	0	B	GEN III	
				Hazard ratio	1.0	0.98									
Kromhout 1995 Holland	272	17	CCD	Non-fish eaters	Fish Eaters (24 g/d)						NS	0	C	GEN II	
				1.0	0.96										

Table 3.29 Association of estimates of omega-3 fatty acid consumption with cardiovascular death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results			Trend P-value	Overall effect	Quality	Applicability				
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)										
Nagata 2002 Japan	29079	7	FFQ	Quintiles (amount not reported)			NS	+	A	GEN II				
				Men	1.0	0.74	0.71	0.82	0.76	Hazard ratio				
				Women	1.0	0.82	0.79	0.86	0.77*		NS			
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA	0.87	1.3	1.6	1.9	2.8	g/d	0.067	++	A	GEN II
				EPA+DHA	0.0	0.009	0.046	0.15	0.66	g/d	0.004			
					1.0	1.06	0.92	0.92	0.59					

Table 3.30 Association of estimates of fish consumption with cardiovascular death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability	
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)									
Albert 1998 US PHS	20551	11	FFQ	<1/mo	1-3/mo	1-<2/wk	2-<5/wk	≥5/wk		NS	+	A	GEN II
				1.0	0.96	0.79	0.84	0.81					
Gillum 2000 US NHANES	8825	18.8	FFQ + 24-hr recall	Never <1 1 >1 /wk					NS	0	B	GEN II	
				White men	1.0	0.98	0.87	0.95		NS			
				Black men	1.0	0.96	0.99	1.1		NS			
				White women	1.0	1.1	1.1	1.1		nd			
				Black women	1.0	0.85	0.94	0.99		nd			
Daviglus 1997 US WES	1822	30	FFQ	0	1-17	18-34	≥35	g/d		0.01	++	A	GEN II
				1.0	0.94	0.89	0.74						

Table 3.31 Association of estimates of omega-3 fatty acids with cardiac death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability	
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)									
Pietinen 1997 Finland ABCC	21930	6.1	FFQ	ALA	0.9	1.2	1.5	1.9	2.5	NS	0	A	GEN II
					1.0	0.94	0.98	1.03	0.99				
				EPA+DHA	0.2	0.3	0.4	0.5	0.8	0.01	++	A	GEN II
					1.0	0.94	1.0	1.1	1.3				
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA	0.87	1.3	1.6	1.9	2.8	NS	++	A	GEN II
					1.0	0.98	0.57	0.98	0.68				
				EPA+DHA	0	0.009	0.046	0.15	0.66	0.01	++	A	GEN II
					1.0	1.1	0.91	0.88	0.60				

Table 3.32 Association of estimates of fish consumption with cardiac death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results	Trend P-value	Overall effect	Quality	Applicability																								
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)																												
Hu 2002, US NHS	84688	16	FFQ	<table border="0"> <tr> <td><1/mo</td> <td>1-3/mo</td> <td>1/wk</td> <td>2-4/wk</td> <td>>5/wk</td> </tr> <tr> <td>1.0</td> <td>0.80</td> <td>0.65*</td> <td>0.72</td> <td>0.55*</td> </tr> </table>	<1/mo	1-3/mo	1/wk	2-4/wk	>5/wk	1.0	0.80	0.65*	0.72	0.55*	0.01	++	A	GEN II														
<1/mo	1-3/mo	1/wk	2-4/wk	>5/wk																												
1.0	0.80	0.65*	0.72	0.55*																												
Ascherio 1995, US HPS	44895	6	FFQ	<table border="0"> <tr> <td>1-3/mo</td> <td>1/wk</td> <td>2-3/wk</td> <td>4-5/wk</td> <td>>6/wk</td> </tr> <tr> <td>0.74</td> <td>0.86</td> <td>0.71</td> <td>0.54*</td> <td>0.77</td> </tr> </table>	1-3/mo	1/wk	2-3/wk	4-5/wk	>6/wk	0.74	0.86	0.71	0.54*	0.77	NS	+	A	GEN II														
1-3/mo	1/wk	2-3/wk	4-5/wk	>6/wk																												
0.74	0.86	0.71	0.54*	0.77																												
Egeland 2001 Norway	42612	7	Dietary questionnaire	<table border="0"> <tr> <td></td> <td></td> <td>None</td> <td>Cod liver oil</td> </tr> <tr> <td>Never smoker</td> <td>Hazard ratio</td> <td>1.0</td> <td>0.7</td> </tr> <tr> <td>Current smoker</td> <td></td> <td>1.0</td> <td>0.8</td> </tr> </table>			None	Cod liver oil	Never smoker	Hazard ratio	1.0	0.7	Current smoker		1.0	0.8	NS	+	C	GEN II												
		None	Cod liver oil																													
Never smoker	Hazard ratio	1.0	0.7																													
Current smoker		1.0	0.8																													
Fraser 1997, US Adventist	26743	6	FFQ	<table border="0"> <tr> <td></td> <td>0</td> <td><1/wk</td> <td>>1/wk</td> </tr> <tr> <td>Hazard ratio</td> <td>1.0</td> <td>1.1</td> <td>0.74</td> </tr> </table>		0	<1/wk	>1/wk	Hazard ratio	1.0	1.1	0.74	nd	0	B	GEN II																
	0	<1/wk	>1/wk																													
Hazard ratio	1.0	1.1	0.74																													
Albert 1998, US PHS	20551	11	FFQ	<table border="0"> <tr> <td><1/mo</td> <td>1-3/mo</td> <td>1-2/wk</td> <td>2-5/wk</td> <td>≥5/wk</td> </tr> <tr> <td>1.0</td> <td>1.18</td> <td>0.82</td> <td>0.91</td> <td>0.81</td> </tr> </table>	<1/mo	1-3/mo	1-2/wk	2-5/wk	≥5/wk	1.0	1.18	0.82	0.91	0.81	NS	+	A	GEN II														
<1/mo	1-3/mo	1-2/wk	2-5/wk	≥5/wk																												
1.0	1.18	0.82	0.91	0.81																												
Mann 1997 UK	10802	13.3	FFQ	<table border="0"> <tr> <td></td> <td>0</td> <td><1</td> <td>≥1 /wk</td> </tr> <tr> <td>Death Rate Ratio</td> <td>100</td> <td>121</td> <td>123</td> </tr> </table>		0	<1	≥1 /wk	Death Rate Ratio	100	121	123	NS	-	B	GEN II																
	0	<1	≥1 /wk																													
Death Rate Ratio	100	121	123																													
Rodriguez 1996 US Honolulu	8006	23	Dietary questionnaire	<table border="0"> <tr> <td>Cigarettes/d</td> <td><2/wk</td> <td>≥2/wk</td> <td>Fish consumption</td> </tr> <tr> <td><20</td> <td>0.30</td> <td>0.42</td> <td></td> </tr> <tr> <td>20-30</td> <td>0.38</td> <td>0.45</td> <td></td> </tr> <tr> <td>>30</td> <td>1.0</td> <td>0.50*</td> <td></td> </tr> </table>	Cigarettes/d	<2/wk	≥2/wk	Fish consumption	<20	0.30	0.42		20-30	0.38	0.45		>30	1.0	0.50*		NS NS nd	+	C	GEN II								
Cigarettes/d	<2/wk	≥2/wk	Fish consumption																													
<20	0.30	0.42																														
20-30	0.38	0.45																														
>30	1.0	0.50*																														
Osler 2003 Denmark	8497	18	FFQ	<table border="0"> <tr> <td></td> <td>≤1/mo</td> <td>2/mo</td> <td>1/wk</td> <td>>2/wk</td> </tr> <tr> <td>Hazard ratio</td> <td>1.1</td> <td>0.98</td> <td>1.0 (ref)</td> <td>0.98</td> </tr> </table>		≤1/mo	2/mo	1/wk	>2/wk	Hazard ratio	1.1	0.98	1.0 (ref)	0.98	NS	0	B	GEN I														
	≤1/mo	2/mo	1/wk	>2/wk																												
Hazard ratio	1.1	0.98	1.0 (ref)	0.98																												
Mozaffarian 2003 US CHS	3910	9.3	FFQ	<table border="0"> <tr> <td>Tuna/other fish</td> <td><1/mo</td> <td>1-3/mo</td> <td>1/wk</td> <td>2/wk</td> <td>>3/wk</td> </tr> <tr> <td>Total IHD death</td> <td>1.0</td> <td>0.78</td> <td>0.77</td> <td>0.53*</td> <td>0.47*</td> </tr> <tr> <td>Fried fish/sand.</td> <td><1/mo</td> <td>1-3/mo</td> <td>1/wk</td> <td>2/wk</td> <td>>3/wk</td> </tr> <tr> <td>Total IHD death</td> <td>1.0</td> <td>1.2</td> <td>1.6</td> <td>1.1</td> <td>1.4</td> </tr> </table> <p style="text-align: center;">Hazard ratios</p>	Tuna/other fish	<1/mo	1-3/mo	1/wk	2/wk	>3/wk	Total IHD death	1.0	0.78	0.77	0.53*	0.47*	Fried fish/sand.	<1/mo	1-3/mo	1/wk	2/wk	>3/wk	Total IHD death	1.0	1.2	1.6	1.1	1.4	0.002 NS	++ -	A	GEN II
Tuna/other fish	<1/mo	1-3/mo	1/wk	2/wk	>3/wk																											
Total IHD death	1.0	0.78	0.77	0.53*	0.47*																											
Fried fish/sand.	<1/mo	1-3/mo	1/wk	2/wk	>3/wk																											
Total IHD death	1.0	1.2	1.6	1.1	1.4																											
Oomen 2000 Finland Italy Holland	2738	20	CCD	<table border="0"> <tr> <td></td> <td>1-19</td> <td>20-39</td> <td>>40 g/d</td> </tr> <tr> <td>Total fish</td> <td>0.93</td> <td>0.95</td> <td>1.1</td> </tr> <tr> <td>Fatty fish</td> <td>0.57*</td> <td>0.87(≥20 g/d)</td> <td></td> </tr> </table>		1-19	20-39	>40 g/d	Total fish	0.93	0.95	1.1	Fatty fish	0.57*	0.87(≥20 g/d)		NS	+	A	GEN II												
	1-19	20-39	>40 g/d																													
Total fish	0.93	0.95	1.1																													
Fatty fish	0.57*	0.87(≥20 g/d)																														
Daviglus 1997, US WES	1822	30	FFQ	<table border="0"> <tr> <td></td> <td>0</td> <td>1-17</td> <td>18-34</td> <td>≥35 g/d</td> </tr> <tr> <td></td> <td>1.0</td> <td>0.88</td> <td>0.84</td> <td>0.62*</td> </tr> </table>		0	1-17	18-34	≥35 g/d		1.0	0.88	0.84	0.62*	0.04	++	A	GEN II														
	0	1-17	18-34	≥35 g/d																												
	1.0	0.88	0.84	0.62*																												
Kromhout 1985 Holland	852	20	CCD	<table border="0"> <tr> <td></td> <td>0</td> <td>1-14</td> <td>5-29</td> <td>30-44</td> <td>45 g/d</td> </tr> <tr> <td></td> <td>1.0</td> <td>0.64</td> <td>0.56</td> <td>0.36*</td> <td>0.39</td> </tr> </table>		0	1-14	5-29	30-44	45 g/d		1.0	0.64	0.56	0.36*	0.39	nd	+	B	GEN II												
	0	1-14	5-29	30-44	45 g/d																											
	1.0	0.64	0.56	0.36*	0.39																											
Kromhout 1995 Holland	272	17	CCD	<table border="0"> <tr> <td>No fish</td> <td>Fish eater</td> </tr> <tr> <td>1.0</td> <td>0.51*</td> </tr> </table>	No fish	Fish eater	1.0	0.51*	nd	+	C	GEN I																				
No fish	Fish eater																															
1.0	0.51*																															

Table 3.33 Association of estimates of omega-3 fatty acids with sudden death in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability	
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)									
Prospective cohort													
Albert 1998 US PHS	20551	12	FFQ	EPA+DHA	<0.3	0.3-2.7	2.7-4.9	4.9-7.4	>7.4 g/mo	NS	++	A	GEN II
					1.0	0.58	0.34*	0.60	0.43*				
Case control													
Siscovick 1995 US	827	na	FFQ	EPA+DHA	0	0.96	2.9	5.5	13.7 g/mo	ND	++	A	GEN I
				Odds ratio	1.0	0.9*	0.7*	0.5*	0.4*				

Table 3.34 Association of estimates of fish consumption with sudden death in prospective cohort studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability
				Fish consumption (amount or frequency) Relative risk								
Albert 1998 US PHS	20551	12	FFQ	<1/mo	1-3/mo	1-2/wk	2-5/wk	≥5/wk	NS	++	A	GEN II
				1.0	0.64	0.47*	0.51	0.39*				
Daviglus 1997 US WES	1822	30	FFQ	0	1-17	18-34	≥35 g/d		NS	+	A	GEN II
				1.0	0.78	0.80	0.68					

Table 3.35 Association of estimates of omega-3 fatty acids consumption with myocardial infarction in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability
				Estimated omega-3 fatty acid consumption								
Relative risk (unless stated otherwise)												
Prospective cohort												
Hu 2002	84688	16	FFQ	EPA+DHA					<0.001	++	A	GEN II
Hu 1999 US NHS		10		Median intake (% energy) <u>0.03 0.05 0.08 0.14 0.24</u> Nonfatal MI 1.0 0.92 0.83 0.75* 0.69*								
Ascherio 1995 US HPS	44895	6	FFQ	EPA+DHA <0.11 0.12-0.19 0.20-0.28 0.29-0.41 >0.42 g/d Total MI 1.0 1.0 0.92 0.86 1.1 Nonfatal MI 1.0 0.93 0.89 0.78 1.1					NS NS	+	A	GEN II
Morris 1995 US PHS	21185	4	FFQ	EPA+DHA <0.05 0.5-<1.0 1.0-<1.7 1.7-<2.3 >2.3 g/wk Total MI 1.0 1.6 1.4 1.2 1.2 Nonfatal MI 1.0 1.5 1.3 1.2 1.1					NS	-	A	GEN II
Yuan 2001 China	18244	12	FFQ	EPA+DHA <0.27 0.27-0.43 0.44-0.72 0.73-1.1 >1.1 g/wk Fatal MI 1.0 0.39* 0.67 0.53* 0.43*					0.02	++	A	GEN II
Oomen 2001 Holland	67	0	CD	ALA (% energy) <0.45 0.45-0.58 >0.58 Fatal and nonfatal CAD 1.0 1.5 1.7 Fatal CAD 1.0 0.99 1.6					NS NS	-	B	GEN III
Case control												
Tavani 2001 Italy	975	na	FFQ	EPA+DHA <0.81 0.81-1.28 >1.28 g/wk Nonfatal MI odds ratio 1.0 0.71* 0.67*					0.03	++	B	GEN II

Table 3.36 Association of estimates of fish consumption with myocardial Infarction in prospective cohort and case control studies

Author Year Location	N	Duration (year)	Dietary Assessment	Results				Trend P-value	Overall effect	Quality	Applicability																														
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)																																					
Prospective cohort																																									
Hu 2002 NHS	84688	16	FFQ	<table border="0"> <tr> <td></td> <td>1-3/mo</td> <td>1/wk</td> <td>2-4/wk</td> <td colspan="2">>5/wk</td> </tr> <tr> <td>Nonfatal MI</td> <td>0.78*</td> <td>0.74*</td> <td>0.68*</td> <td colspan="2">0.73</td> </tr> </table>					1-3/mo	1/wk	2-4/wk	>5/wk		Nonfatal MI	0.78*	0.74*	0.68*	0.73		0.03	++	A	GEN II																		
	1-3/mo	1/wk	2-4/wk	>5/wk																																					
Nonfatal MI	0.78*	0.74*	0.68*	0.73																																					
Ascherio 1995 US HPS	44895	6	FFQ	<table border="0"> <tr> <td></td> <td><1/mo</td> <td>1-3/mo</td> <td>1/wk</td> <td>2-3/wk</td> <td>4-5/wk</td> <td>>6/wk</td> </tr> <tr> <td></td> <td>0</td> <td>7</td> <td>18</td> <td>37</td> <td>69</td> <td>119 g/d</td> </tr> <tr> <td>MI</td> <td>1.0</td> <td>0.66*</td> <td>0.82</td> <td>0.69*</td> <td>0.65*</td> <td>0.90</td> </tr> <tr> <td>Nonfatal MI</td> <td>1.0</td> <td>0.62*</td> <td>0.80</td> <td>0.67*</td> <td>0.69</td> <td>0.96</td> </tr> </table>							<1/mo	1-3/mo	1/wk	2-3/wk	4-5/wk	>6/wk		0	7	18	37	69	119 g/d	MI	1.0	0.66*	0.82	0.69*	0.65*	0.90	Nonfatal MI	1.0	0.62*	0.80	0.67*	0.69	0.96	NS NS	++	A	GEN II
	<1/mo	1-3/mo	1/wk	2-3/wk	4-5/wk	>6/wk																																			
	0	7	18	37	69	119 g/d																																			
MI	1.0	0.66*	0.82	0.69*	0.65*	0.90																																			
Nonfatal MI	1.0	0.62*	0.80	0.67*	0.69	0.96																																			
Fraser 1992a US Adventist	26743	6	FFQ	<table border="0"> <tr> <td></td> <td>0</td> <td><1</td> <td>>1/wk</td> </tr> <tr> <td>Nonfatal MI</td> <td>1.0</td> <td>1.0</td> <td>1.04</td> </tr> </table>				0	<1	>1/wk	Nonfatal MI	1.0	1.0	1.04	NS	0	B	GEN II																							
	0	<1	>1/wk																																						
Nonfatal MI	1.0	1.0	1.04																																						
Albert 1998 US PHS	20551	11	FFQ	<table border="0"> <tr> <td></td> <td><1/mo</td> <td>1-3/mo</td> <td>1-2/wk</td> <td>2-5/wk</td> <td>>5/wk</td> </tr> <tr> <td>All MI</td> <td>1.0</td> <td>0.91</td> <td>0.99</td> <td>1.0</td> <td>1.0</td> </tr> </table>						<1/mo	1-3/mo	1-2/wk	2-5/wk	>5/wk	All MI	1.0	0.91	0.99	1.0	1.0	NS	0	A	GEN II																	
	<1/mo	1-3/mo	1-2/wk	2-5/wk	>5/wk																																				
All MI	1.0	0.91	0.99	1.0	1.0																																				
Yuan 2001 China	18244	12	FFQ	<table border="0"> <tr> <td></td> <td><50</td> <td>50-100</td> <td>100-150</td> <td>150-200</td> <td>≥200 g/wk</td> </tr> <tr> <td>Fatal MI</td> <td>1.0</td> <td>0.55*</td> <td>0.65</td> <td>0.66</td> <td>0.41*</td> </tr> </table>						<50	50-100	100-150	150-200	≥200 g/wk	Fatal MI	1.0	0.55*	0.65	0.66	0.41*	0.03	++	A	GEN II																	
	<50	50-100	100-150	150-200	≥200 g/wk																																				
Fatal MI	1.0	0.55*	0.65	0.66	0.41*																																				
Mozaffarian 2003 US CHS	3910	9.3	FFQ	<table border="0"> <tr> <td>Tuna/other fish</td> <td>1-3/m</td> <td>1/wk</td> <td>2/wk</td> <td colspan="2">>3/wk</td> </tr> <tr> <td>Nonfatal MI</td> <td>0.81</td> <td>0.71</td> <td>0.75</td> <td colspan="2">0.67</td> </tr> <tr> <td>Fried fish/sandwich</td> <td>1-3/m</td> <td>1/wk</td> <td>2/wk</td> <td colspan="2">>3/wk</td> </tr> <tr> <td>Nonfatal MI</td> <td>1.3</td> <td>1.6</td> <td>1.2</td> <td colspan="2">1.9</td> </tr> </table>				Tuna/other fish	1-3/m	1/wk	2/wk	>3/wk		Nonfatal MI	0.81	0.71	0.75	0.67		Fried fish/sandwich	1-3/m	1/wk	2/wk	>3/wk		Nonfatal MI	1.3	1.6	1.2	1.9		0.10 NS	+ -	A	GEN II						
Tuna/other fish	1-3/m	1/wk	2/wk	>3/wk																																					
Nonfatal MI	0.81	0.71	0.75	0.67																																					
Fried fish/sandwich	1-3/m	1/wk	2/wk	>3/wk																																					
Nonfatal MI	1.3	1.6	1.2	1.9																																					
Daviglus 1997 US WES	1822	30	FFQ	<table border="0"> <tr> <td></td> <td>0</td> <td>1-17</td> <td>18-34</td> <td colspan="2">≥35 g/d</td> </tr> <tr> <td>All MI</td> <td>1.0</td> <td>0.88</td> <td>0.76</td> <td colspan="2">0.56*</td> </tr> </table>					0	1-17	18-34	≥35 g/d		All MI	1.0	0.88	0.76	0.56*		0.017	++	A	GEN II																		
	0	1-17	18-34	≥35 g/d																																					
All MI	1.0	0.88	0.76	0.56*																																					
Case control																																									
Tavani, 2001 Italy	975	na	FFQ	<table border="0"> <tr> <td></td> <td><1</td> <td>1-2</td> <td>≥2 /wk</td> </tr> <tr> <td>Nonfatal MI odds ratio</td> <td>1.0</td> <td>0.79</td> <td>0.67*</td> </tr> </table>				<1	1-2	≥2 /wk	Nonfatal MI odds ratio	1.0	0.79	0.67*	0.02	++	B	GEN II																							
	<1	1-2	≥2 /wk																																						
Nonfatal MI odds ratio	1.0	0.79	0.67*																																						
Sasazuki 2001 Japan	1846	na	FFQ	<table border="0"> <tr> <td></td> <td><2</td> <td>2-3</td> <td>>4 /wk</td> </tr> <tr> <td>Nonfatal MI odds ratio</td> <td>Men 1.0</td> <td>0.6*</td> <td>0.7*</td> </tr> <tr> <td></td> <td>Women 1.0</td> <td>0.8</td> <td>1.3</td> </tr> </table>				<2	2-3	>4 /wk	Nonfatal MI odds ratio	Men 1.0	0.6*	0.7*		Women 1.0	0.8	1.3	NS 0.09	+	B	GEN II																			
	<2	2-3	>4 /wk																																						
Nonfatal MI odds ratio	Men 1.0	0.6*	0.7*																																						
	Women 1.0	0.8	1.3																																						

Table 3.37 Association of estimates of omega-3 fatty acid consumption with stroke in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Assessment	Results					Trend P-value	Overall effect	Quality	Applicability		
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)										
Prospective cohort														
Iso 2001 US NHS	79839	14	FQ	EPA+DHA	0.077	0.12	0.17	0.22	0.48	g/d	NS	+	A	GEN II
				Ischemic	1.0	0.83	0.67*	0.82	0.71		NS			
				Hemorrhagic	1.0	0.94	0.66	0.93	0.76					
He 2002 US HPS	43671	12	FQ	EPA+DHA	<0.05	0.05-0.2	0.2-0.4	0.4-0.6	>0.6	g/d	NS	++	A	GEN II
				Ischemic	1.0	0.56*	0.63*	0.54*	0.73		NS			
				Hemorrhagic	1.0	1.3	1.0	0.89	1.1					
Morris 1995 US PHS	21185	4	FQ	EPA+DHA	<0.5	0.5-1.0	1.0-1.7	1.7-2.3	>2.3	g/wk	NS	0	A	GEN II
				All strokes	1.0	0.9	1.1	0.7	1.0					
Yuan 2001 China	18244	9	FFQ	EPA+DHA	<0.26	0.27-0.43	0.44-0.72	0.73-1.1	≥1.1	g/wk	NS	+	A	GEN II
				Fatal strokes	1.0	0.76	0.76*	0.93	1.0					
Seino 1997 Japan	2283	15.5	FFQ	n-3 fatty acid	1.8	2.3	2.7	3.2		g/d	NS	-	B	GEN II
				Ischemic stroke	1.0	0.99	1.6	1.4						
Case control														
Caicoya 2002 Spain	913	na	FQ	EPA+DHA	<0.12	0.12-0.32	0.32-0.66	>0.66		g/d	0.01↑	-	A	GEN II
				All strokes odds ratio	1.0	1.1	1.4	1.8						

Table 3.38 Association of estimates of fish consumption with stroke in prospective cohort and case-control studies

Author Year Location	N	Duration (year)	Literary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability	
				Fish consumption (amount or frequency) Relative risk (unless stated otherwise)									
Prospective cohort													
Kinjo 1999 Japan	223170	15	1-page quest- ionnaire	Ischemic deaths	>1	1-3	≥4	/wk	nd	0	C	GEN II	
				Hemorrhagic deaths	1.0	1.05	0.99		nd				
Iso 2001 US NHS	79839	14	FQ	Ischemic	<1/m	1-3/m	1/wk	2-4/wk	>5/wk	0.09	+	A	GEN II
				Hemorrhagic	1.0	0.83	0.69	0.63	0.38	NS			
He 2002 US HPS	43671	12	FQ	Ischemic	<1/mo	1-3/mo	1/wk	2-4/wk	>5/wk	NS	++	A	GEN II
				Hemorrhagic	1.0	0.57*	0.56*	0.55*	0.54*	NS			
Morris 1995 US PHS	21185	4	FFQ	Non-fatal strokes	<1	1	2-4	>5 /wk	NS	-	A	GEN II	
					1.0	1.3*	1.1	0.9					
Yuan 2001 China	18244	9	FQ	Fatal strokes	<50	50-100	100-150	150-200	≥200 g/wk	NS	0	A	GEN II
					1.0	0.93	0.79	1.01	1.11				
Gillum 1996 US NHANES	5192	12	FFQ	Ischemic stroke	0	<1	1	>1 /wk	nd	+	B	GEN I	
				Women aged 45-74	1.0	0.78	0.77	0.55*					
				Men aged 45-74	1.0	1.3	1.2	0.85					
				Black men+women	Never fish		some fish						
				Stroke incidence	1.0		0.51*		na				
				Stroke death	1.0		0.26*						
Orencia 1996 USA WES	1847	30	FFQ / 24-hr recall	All strokes	0	1-17	18-34	>35 g/d	NS	0	A	GEN II	
					1.0	0.94	0.89	1.3	Hazard ratio				
Keli 1994 Holland	872	15	CCD	All strokes	6.3 (<20)	35.4 (≥20)	g/d		0.06	+	B	GEN II	
					1.0	0.49	Hazard ratio						
Case control													
Caicoya 2002 Spain	913	na	FFQ	Total	0	1-22.5	23-45	46-90	>91 g/d	nd	+	A	GEN II
				Odds ratio	1.0	0.30*	0.44	0.59	0.76				
				Ischemic	0-11.2	11.3-28.7	28.8-46.5	>46.5 g/d					
				Odds ratio	1.0	1.1	0.90	2.0		0.08↑	-		

Table 3.39 Association of estimates of omega-3 fatty acid consumption with all CVD events in cross-sectional study

Author Year Location	N	Duration (year)	Dietary Assessment	Results					Trend P-value	Overall effect	Quality	Applicability		
				Estimated omega-3 fatty acid consumption Prevalence odds ratio for all CVD events										
Djousse 2001 US	40 6	n.a	FQ	ALA	0.53	0.67	0.78	0.90	1.1	g/d	0.012	++	B	GEN I
				men	1.0	0.77	0.61*	0.58*	0.60*					
				ALA	0.46	0.58	0.65	0.76	0.96	g/d	0.014			
				women	1.0	0.57	0.52	0.30*	0.42*					

Primary Prevention Studies (Tables 3.25-3.39)

Evidence for the effects of the consumption of omega-3 fatty acids, omega-3 fatty acid supplements, or fish on CVD outcomes in the general population is derived from 22 prospective cohort studies, 4 case-control studies, 1 cross-sectional study, and 1 RCT. The methodological quality of most of the studies within their study design category was good (grades A or B); 4 prospective cohort studies were graded as poor (grade C).

We found only 1 RCT that examined omega-3 fatty acid supplements in the general population. (Tables 3.25-3.26) The methodological quality of this study was poor (grade C). The study, which compares linseed oil (5.5 g/d of ALA) with sunflower seed oil (0.14 g/d ALA), was conducted in Norway more than 30 years ago⁴⁹ and lasted 1 year. It is the largest of all ALA supplement trials, with over 13,000 subjects. Presumably, subjects had high background omega-3 fatty acid levels because of characteristically large consumption of fish. There were too few all-cause mortality or CVD events in the control group, and it reported no benefit on any of the CVD outcomes. This trial does not contribute substantively to the assessment of the effect of omega-3 fatty acid supplements on CVD outcomes. The major conclusion one can draw from this study is that ALA, given at a dose of 0.14 g/d for 1 year, has no effect on CVD outcomes in the general population with a high fish consumption background diet.

The 22 prospective cohort studies were conducted in many parts of the world, including the US, China, Japan, and countries in the Mediterranean and Northern Europe. Most of the cohorts had several thousand subjects. The majority of the studies received an applicability grade of GEN-II, reflecting either relevant subgroups or differences in the background diet of the study population when compared with the US population. Several of the large population studies conducted in the US were graded as GEN-II because of single sex (male or female) cohorts. If viewed together, however, these studies would provide evidence that is highly applicable to the US population (GEN-I). Study duration in the cohort studies ranged from 4 to 30 years. The number of subjects followed in the cohorts ranged from 272 to as many as 223,170; many of the cohorts had tens of thousands of study subjects.

Most of the studies used the food frequency questionnaire to estimate the dietary fish intake. Most studies provided quantitative estimates of the amount of fish consumed (many also quantified the amount of EPA+DHA intake) and categorized them into various quantiles (e.g.,

tertiles, quartiles, quintiles), although some studies reported only the frequency of fish consumption or simply whether fish was consumed.

CVD Outcomes of Primary Prevention Studies

Results from the primary prevention studies are summarized by outcome, below.

All-cause mortality. Ten studies that followed a total of about 100,000 subjects for an average of over 10 years provided data on all-cause mortality. (Tables 3.27-3.28) Three of the 10 studies provided estimates of fish oil intake, and 9 provided estimates of fish consumption. The studies were conducted in the US, China, Japan, Denmark, Holland, and the UK. All 3 studies that provided estimates of fish oil intake reported a significant reduction (++ overall effect) of all-cause mortality⁵⁰⁻⁵². The results of studies reporting estimates of fish intake were heterogeneous — 1 study⁵³ reported a small but significant increase of all-cause mortality with increasing fish intake, and 5 studies found no benefit^{50,54-57}. Of the studies finding no benefit, 1 (by Nagata et al.) reported no benefit using estimates of fish consumption but observed beneficial results using estimates of fish oil. One study showed significant benefit⁵⁸, and 1 study showed a trend for benefit⁵⁹.

CVD deaths, cardiac deaths, and MI. The outcomes of CVD deaths (Tables 3.29-3.30), cardiac deaths (Tables 3.31-3.32), and MI (Tables 3.35-3.36) were similar. Most of the large cohort studies reported significant reduction of clinical events. Among the large cohort studies, only the Physicians' Health Study (PHS) failed to report a significant beneficial effect of fish consumption⁵⁸.

Sudden death. Two prospective cohort studies reported data on sudden death. (Tables 3.33-3.34). These studies provided estimates of both fish and fish oil consumption. The Physicians' Health Study, which followed 20,551 subjects for 12 years, reported an approximately 50% overall relative risk reduction even with a small amount of fish intake (>0.3 g of fish oil per month or eating fish once a month)⁵⁸. A smaller study also found a significant reduction of arrhythmic deaths at higher levels of fish intake⁶⁰. However, in the same study opposite results were seen with consumption of fried fish or fish sandwiches⁶⁰. Another smaller follow-up study of 30 years duration found a significant trend of reduction in sudden death⁵⁶. A case-control study of 827 subjects in the US also reported a significant inverse association of sudden death with increasing fish intake⁶¹.

Stroke. Nine prospective cohort studies and 1 case-control study provided data on stroke. (Tables 3.37-3.38) Five of the cohort studies estimated the amount of fish oil consumed, and 8 estimated fish intake. These studies included the large US cohorts of the Nurses' Health Study (NHS)⁶², Health Professionals Study (HPS)⁶³, and the Physicians' Health Study⁶⁴, which followed subjects for 14, 12, and 4 years, respectively. Together, these 3 studies comprised a total of about 145,000 men and women. Only the Health Professionals Study⁶³ reported a significant reduction of ischemic strokes with any level of fish consumption above the lowest quintile. In the Nurses' Health Study⁶², there was a non-significant trend of decreased strokes with increasing fish consumption. Other studies showed a weak benefit, no benefit, or an increased risk of strokes. The fish oil estimates and fish estimates yielded similar results.

Table 3.40 Association of estimates of omega-3 fatty acid consumption with all cause mortality in prospective cohort studies of general population (based on data in Table 3.27)

		Methodological Quality																			
Applicability		A	B	C																	
	I																				
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>Nagata</td> <td>2002</td> <td>29079</td> <td>++</td> </tr> <tr> <td>Yuan</td> <td>2001</td> <td>18244</td> <td>++</td> </tr> <tr> <td>MRFIT</td> <td>1992</td> <td>6250</td> <td>++</td> </tr> </tbody> </table>	Study	Year	N	Effect	Nagata	2002	29079	++	Yuan	2001	18244	++	MRFIT	1992	6250	++			
	Study	Year	N	Effect																	
Nagata	2002	29079	++																		
Yuan	2001	18244	++																		
MRFIT	1992	6250	++																		
III																					

Table 3.41 Association of estimates of fish consumption with all cause mortality in prospective cohort studies of general population (based on data in Table 3.28)

		Methodological Quality																																					
Applicability		A	B	C																																			
	I		<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>NHANES</td> <td>2000</td> <td>8825</td> <td>+</td> </tr> <tr> <td>Osler</td> <td>2003</td> <td>8487</td> <td>-</td> </tr> </tbody> </table>	Study	Year	N	Effect	NHANES	2000	8825	+	Osler	2003	8487	-																								
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Study acronyms (apply to tables 3.40-3.51):

- ABCC = Alpha-Tocopherol Beta-Carotene Cancer Prevention
- ADVENTIST = Adventist Health Study
- CHS = Cardiovascular Health Study
- HPS = Health Professionals Study
- MRFIT = Multiple Risk Factor Intervention Study
- NHANES = National Health and Nutrition Examination Study
- NHS = Nurses' Health Study
- PHS = Physicians' Health Study
- WES = Western Electric Company Study

Table 3.42 Association of estimates of omega-3 fatty acid consumption with cardiovascular death in prospective cohort studies of general population (based on data in Table 3.29)

		Methodological Quality															
Applicability		A	B	C													
	I																
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>Nagata</td> <td>2002</td> <td>29079</td> <td>+</td> </tr> <tr> <td>MRFIT</td> <td>1992</td> <td>6250</td> <td>++</td> </tr> </tbody> </table>	Study	Year	N	Effect	Nagata	2002	29079	+	MRFIT	1992	6250	++			
	Study	Year	N	Effect													
Nagata	2002	29079	+														
MRFIT	1992	6250	++														
III																	

Table 3.43 Association of estimates of fish consumption with cardiovascular death in prospective cohort studies of general population (based on data in Table 3.30)

		Methodological Quality																									
Applicability		A				B				C																	
	I																										
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>PHS</td> <td>1998</td> <td>20551</td> <td>+</td> </tr> <tr> <td>WES</td> <td>1997</td> <td>1822</td> <td>++</td> </tr> </tbody> </table>	Study	Year	N	Effect	PHS	1998	20551	+	WES	1997	1822	++	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>NHANES</td> <td>2000</td> <td>8825</td> <td>0</td> </tr> </tbody> </table>	Study	Year	N	Effect	NHANES	2000	8825	0				
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PHS	1998	20551	+																								
WES	1997	1822	++																								
Study	Year	N	Effect																								
NHANES	2000	8825	0																								
III																											

Table 3.44 Association of estimates of omega-3 fatty acid consumption with cardiac death in prospective cohort studies of general population (based on data in Table 3.31)

		Methodological Quality															
Applicability		A	B	C													
	I																
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>ABCC</td> <td>1997</td> <td>21930</td> <td>0</td> </tr> <tr> <td>MRFIT</td> <td>1992</td> <td>6250</td> <td>++</td> </tr> </tbody> </table>	Study	Year	N	Effect	ABCC	1997	21930	0	MRFIT	1992	6250	++			
	Study	Year	N	Effect													
ABCC	1997	21930	0														
MRFIT	1992	6250	++														
III																	

Table 3.45 Association of estimates of fish consumption with cardiac death in prospective cohort studies of general population (based on data in Table 3.32)

		Methodological Quality																																																									
Applicability		A	B	C																																																							
	I		<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>Osler</td> <td>2003</td> <td>8497</td> <td>0</td> </tr> </tbody> </table>	Study	Year	N	Effect	Osler	2003	8497	0	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>Kromhout</td> <td>1985</td> <td>272</td> <td>+</td> </tr> </tbody> </table>	Study	Year	N	Effect	Kromhout	1985	272	+																																							
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III																																																											

Table 3.46 Association of estimates of omega-3 fatty acid consumption with sudden death in prospective cohort studies of general population (based on data in Table 3.33)

		Methodological Quality															
Applicability		A	B	C													
	I																
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>PHS</td> <td>1998</td> <td>20551</td> <td>++</td> </tr> <tr> <td>CHS</td> <td>2003</td> <td>3910</td> <td>+</td> </tr> </tbody> </table>	Study	Year	N	Effect	PHS	1998	20551	++	CHS	2003	3910	+			
	Study	Year	N	Effect													
PHS	1998	20551	++														
CHS	2003	3910	+														
III																	

Table 3.47 Association of estimates of fish consumption with sudden death in prospective cohort studies of general population (based on data in Table 3.34)

		Methodological Quality															
Applicability		A	B	C													
	I																
	II	<table border="1"> <thead> <tr> <th>Study</th> <th>Year</th> <th>N</th> <th>Effect</th> </tr> </thead> <tbody> <tr> <td>PHS</td> <td>1998</td> <td>20551</td> <td>++</td> </tr> <tr> <td>CHS</td> <td>2003</td> <td>3910</td> <td>+</td> </tr> </tbody> </table>	Study	Year	N	Effect	PHS	1998	20551	++	CHS	2003	3910	+			
	Study	Year	N	Effect													
PHS	1998	20551	++														
CHS	2003	3910	+														
III																	

Table 3.48 Association of estimates of omega-3 fatty acid consumption with myocardial infarction in prospective cohort studies of general population (based on data in Table 3.35)

		Methodological Quality				
Applicability		A		B		C
	I					
	II	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	
		NHS ¹	2002	84688	++	
	HPS	1995	44895	+		
	PHS	1995	21185	-		
	Yuan	2001	18244	++		
III						
		<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	
		Oomen	2001	667	-	

¹ Nurses' Health Study analysis using fish oil (EPA+DHA) published in 2002 and analysis using ALA published in 1999 both reported significant beneficial effect on myocardial infarction.

Table 3.49 Association of estimates of fish consumption with myocardial infarction in prospective cohort studies of general population (based on data in Table 3.36)

		Methodological Quality				
Applicability		A		B		C
	I					
	II	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	
		NHS	2002	84688	++	
	HPS	1995	44895	++		
	PHS	1998	20551	0		
	Yuan	2001	18244	++		
	CHS	2003	3910	+		
	WES	1997	1822	++		
III						
		<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	
		Adventist	1992	26743	0	

Table 3.50 Association of estimates of omega-3 fatty acid consumption with stroke in prospective cohort studies of general population (based on data in Table 3.37)

		Methodological Quality									
		A				B				C	
Applicability	I										
	II	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>		
		NHS	2001	79839	+	Seino	1997	2283	-		
		HPS	2002	43671	++						
		PHS	1995	21185	0						
		Yuan	2001	18244	+						
III											

Table 3.51 Association of estimates of fish consumption with stroke in prospective cohort studies of general population (based on data in Table 3.38)

		Methodological Quality											
		A				B				C			
Applicability	I												
	II	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>
		NHS	2001	79839	+	NHANES	1996	5192	+	Kinjo	1999	223710	0
		HPS	2002	43671	++	Keli	1994	872	+				
		PHS	1995	21185	-								
		Yuan	2001	18244	+								
		WES	1996	1847	0								
III													

Answers to Specific Key Questions

Many of the questions noted below ask about the efficacy of omega-3 fatty acids on CVD outcomes. Efficacy has been defined in an Institute of Medicine report as “what a method can accomplish in expert hands when correctly applied to an appropriate patient.”⁶⁵. This is generally interpreted as treatment effect assessed in controlled trial settings. Comparative efficacy among different omega-3 fatty acids can only be assessed reliably within the same or across similarly designed RCTs. Similarly, the comparative effects of omega-3 fatty acids on different subpopulations or different CVD outcomes should be assessed with subgroups within the same trial or across similarly designed RCTs. However, due to the limited availability of RCTs, we

also used prospective cohort studies to answer these questions. Because of the heterogeneity of study design, populations, and settings across the RCTs, and the observational nature of prospective cohort studies, the answers presented here should be interpreted with caution.

What is the efficacy or association of omega-3 fatty acids (DHA, EPA or ALA supplements, and fish consumption) in reducing CVD events (including all-cause mortality, CVD mortality, non-fatal CVD events, and new diagnosis of CVD)?

- *What is the efficacy or association of omega-3 fatty acids in preventing incident CVD events in people without known CVD (primary prevention) and with known CVD (secondary prevention)?*

One RCT and 22 prospective cohort studies provided data on primary prevention. Among the cohort studies, there were considerable differences among the populations studied and in the estimates of fish or omega-3 fatty acids consumed. Most of the large cohort studies found fish consumption was associated with lower rates of all-cause mortality and CVD events, but several studies reported no significant or negative results for the CVD outcomes. A significant benefit for stroke was reported in 1 study. The single poor-quality RCT, which evaluated ALA in a large general population, lasted only 1 year and yielded no significant results.

Eleven RCTs and 1 prospective cohort study provided data on secondary prevention. The largest trial reported that fish oil (EPA + DHA) reduces all-cause mortality and CVD events, although it has no effect on stroke. Most other studies evaluating either fish oil or ALA supplements reported similar findings. All the ALA studies were of poor quality and provided weak conclusions.

These studies were also summarized in previous sections.

- *How does the efficacy or association of omega-3 fatty acids in preventing incident CVD events differ in sub-populations, including men, pre-menopausal women, post-menopausal women, and different age groups?*

There were no subgroup data from RCTs to address this question. In addition, the proportion of women in these RCTs was small.

Four cohort studies and 1 case-control study reported data from men and women separately. Overall, no consistent difference in the association of omega-3 fatty acids and CVD outcomes was found between men and women. A report of NHANES I that separately analyzed data for men and women found a trend of decreased stroke with increasing fish consumption for women between ages 45 and 74, but did not find a similar trend for men⁶⁶. The Adventist Health Study did not find a beneficial effect of fish intake on all-cause or coronary disease mortality after grouping subjects into those who ate fish less than once a week and those who ate fish more frequently, and the study found no differences between men and women⁶⁷. Osler et al. followed 4,007 men and 3,533 women in Denmark for 18 years. The authors did not find an inverse

association between fish consumption and all-cause mortality or the incidence of coronary heart disease, and trends observed in men and women were not consistently different⁵³. Nagata et al. followed a cohort of 13,355 men and 15,742 women in Japan for 7 years. The relationship of soy products and fish intake to all-cause mortality and CVD were evaluated⁵⁰. The association between soy intake and all-cause mortality was significant in women (trend $P = 0.04$) and marginally significant (trend $P = 0.07$) in men. The association between fish oil intake and all-cause mortality was significant for women (trend $P = 0.01$) and non-significant for men (trend $P = 0.38$). A cross-sectional study reported that ALA intake was inversely associated with the prevalence odds ratio of coronary artery disease using age and energy-adjusted quintiles of ALA⁶⁸. Significant trends were found for men and women after adjusting for multiple variables.

The Nurses' Health Study, a large prospective cohort study of women, reported no subgroup analyses based on menopausal status or age groups^{69 62}. The Adventist Health Study examined a subgroup of 603 oldest old (≥ 84 years old) subjects and found no difference in all-cause mortality between those consuming fish less than once a week and those consuming fish more than once a week⁵⁷.

- *What are the effects of potential confounders — such as lipid levels, body mass index (BMI), blood pressure, diabetes, aspirin use, hormone replacement therapy, and cardiovascular drugs — on associations found in prospective cohort studies?*

Most prospective cohort studies report multivariate adjusted results, but few studies report results adjusted for individual potential confounders. Iso et al. analyzed subgroups of women in the Nurses' Health Study who took aspirin regularly vs those who did not⁶². Stroke events were reduced in both groups at most levels of fish intake, and a statistically significant trend with increasing fish consumption was found in women who did not take aspirin regularly.

- *What is the relative efficacy of omega-3 fatty acids on different CVD outcomes? Can the CVD outcomes be ordered by strength of treatment effect of omega-3 fatty acids?*

Because of large heterogeneity across studies and inconsistent reporting of outcomes, it is difficult to compare magnitude of the outcomes across studies. Evidence from RCTs is strongest for sudden death, cardiac death (coronary or MI death), all cause mortality, and stroke. All the prospective cohort studies showed a similar order; however, the effect on total mortality (assuming benefits are restricted to CVD) was directly dependent on the proportion of all deaths due to CVD. Given the inconsistent effects in RCTs on stroke, and less consistent effects in cohort studies, the effect on stroke is uncertain.

Omega-3 fatty acid variables and modifiers

- *What is the efficacy or association of specific omega-3 fatty acids (DHA, EPA, ALA), and different ratios of omega-3 fatty acid components in dietary supplements, on CVD outcomes?*

Data on specific omega-3 fatty acids are very limited. The only RCT addressing this question³⁸ directly compared ALA 2.9 g/d with fish oil (EPA+DHA) 1.8 g/d. The study found both to be efficacious when compared with placebo, and there were no differences in CVD outcomes between the 2 supplements. The study took place in India where background diets and other environmental variables make extrapolation to the US population questionable. In addition, because the study's results contradict other good quality studies, this study is of limited use in assessing the effects of omega-3 fatty acid supplements on CVD events.

- *Does the ratio of omega-6 to omega-3 fatty acid intake affect the efficacy or association of omega-3 fatty acid intake on CVD outcomes?*

Two cohort^{52,69} and 1 cross-sectional study⁶⁸ reported associations between the omega-3/omega-6 ratio and CVD outcomes. Using data from the Multiple Risk Factor Intervention Study (MRFIT) study, Dolecek divided omega-6/omega-3 ratios into 5 quintiles and reported near significant trends ($P < .10$) for reduction of CVD and all-cause mortality. The mean omega-3/omega-6 ratio for the entire cohort was 0.133, the lowest quintile was 0.086 and the highest was 0.199⁵².

Djousse et al. analyzed the association of omega-6/omega-3 ratios with quintiles of ALA intake on the prevalence odds ratio of coronary artery disease⁶⁸. They reported a near-significant association in the lowest tertile of omega-6/omega-3 ratio (higher ALA intake) with higher levels of ALA intake (trend $P = 0.06$). Near-significant reduction of the prevalence odds ratio of coronary artery disease was also found for the combination of the highest tertile of LA and highest tertile of ALA.

Hu et al. stratified the omega-6/omega-3 ratio into 2 groups (low ratio group, median = 5.9; high ratio group, median = 9.2) and compared the effect of increasing amounts of omega-3 fatty acids (ALA, EPA, DHA). They reported that the inverse association with risk of CVD appeared to be somewhat stronger in the high-ratio group compared to the low-ratio group, but a test for interaction was not statistically significant⁶⁹.

- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)?*

Determining the comparative efficacy of different sources of omega-3 fatty acids requires direct comparisons. The available studies were too heterogeneous in terms of study design, duration, background diet, methods of assessment, and outcomes to allow even indirect comparisons that were meaningful. Overall, the evidence suggests that fish oil is efficacious, whereas the evidence for ALA is sparse and inconsistent. In the Nurses' Health Study, Hu et al. performed primary analyses of ischemic heart disease outcomes using ALA intake quantified from all sources, and repeated the same analyses using ALA from plant sources only⁷⁰. Results for fatal ischemic heart disease outcomes were similar for the 2 ALA estimates.

- *How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by different ratios of DHA, EPA, and ALA?*

Comparative efficacy of different ratios of DHA, EPA, and ALA can be reliably assessed only by concurrent multi-arm comparisons in a randomized trial setting. No data were found to answer this question.

- *Is there a threshold or dose-response relationship between omega-3 fatty acids and CVD outcomes?*

Several RCTs reported beneficial effects from fish oil at a relatively low daily dose. The GISSI trial used a fish oil (EPA+DHA) dose of 0.85 g/d and reported significant beneficial effects on CVD outcomes. Leng et al. found no beneficial effect with a daily EPA dose of 0.27 g/d in a 2-year trial involving 120 CVD patients³⁴. Nilsen et al used 1.7 g/d of EPA+DHA and showed no effects on CVD outcomes³⁶. Two diet trials^{43,44} compared the effects of diets containing ALA to the effects of control diets with lower levels of ALA. DeLorgeril et al. compared estimated ALA intakes of 1.8 g/d and 0.67 g/d, and Singh et al. compared estimated ALA intakes of 1.9 g/d and 0.8 g/d.) Both trials reported that the group with higher ALA intake experienced significant or near-significant beneficial effects on CVD outcomes compared to control.

- *How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on CVD outcomes?*

The duration of the RCTs in CVD populations ranged from 1.5 to 5 years. The largest RCT (13,000 subjects) had a duration of 1 year and was conducted in the non-CVD population. This RCT found no effect on any of the CVD outcomes⁴⁹. The duration of the prospective cohort studies ranged from 4 to 30 years. Among the cohort studies, those that followed subjects for less than 6 years demonstrated no significant benefit on clinical effects. The Physicians' Health Study reported no significant effect on CVD outcomes after 4 years of follow-up⁶⁴.

- *Are treatment effects or the association of omega-3 fatty acids on CVD events sustained after the intervention or exposure stops?*

Only 1 study⁴⁸ a 10-year follow-up to the Diet and Reinfarction Trial addressed whether treatment effects of omega-3 fatty acids on CVD events were sustained after the intervention or exposure stops. This study showed no long-term benefit from being in the fish advice group in the DART study.

- *What is the effect or association of baseline dietary intake of omega-3 fatty acids on the efficacy of omega-3 fatty acid supplements on CVD events?*

To answer this question, we need studies using the same omega-3 fatty acid treatment in 2 or more groups of subjects who have different baseline diet profiles.

We found no such trials in our search. Several dietary RCTs provide a glimpse of the benefits of adding additional omega-3 fatty acids to baseline intake in comparable populations. As noted above, 2 diet trials^{43,44} compared the effects of diets containing ALA to the effects of control diets with lower levels of ALA. Both trials were of 2 years duration, and both reported that the group with the higher ALA intake experienced significant or near significant beneficial effects on multiple CVD outcomes compared to control. In an RCT of dietary fish advice, Burr et al. estimated the amount of EPA in the control group (0.6 g/week) and the intervention group (2.4 g/week)⁴⁷ and reported a significant reduction of all cause mortality.

- *Does the use of medications for CVD and/or CVD risk factors (including lipid lowering agents and diabetes medications) affect the efficacy or association of omega-3 fatty acids?*

None of the RCTs were specifically designed to address whether the addition of CVD risk factor medications (lipid lowering agents or diabetes medications) affected the efficacy of omega-3 fatty acids. Among the cohort studies, as well, there were no studies that specifically adjusted for CVD risk factor medications.

Adverse Events Associated with Omega-3 Fatty Acid Consumption

We reviewed 395 clinical articles for potentially relevant human data on adverse events associated with omega-3 fatty acid consumption. These articles included studies of clinical outcomes and risk factors and encompassed RCTs, non-randomized comparison studies, and observational studies in the general and CVD populations.

Adverse events considered in this report are those associated with omega-3 fatty acid supplements, but not fish. As stated in Chapter 1, issues related to mercury toxicity are outside the scope of this report. We also excluded fishy aftertaste as an adverse event.

Of the 395 articles, 247 articles were rejected because they did not provide adverse event information, and 2 additional articles were rejected because of duplicate publications. Of the remaining 148 articles, a variety of adverse events were reported in 71 studies (Tables 3.52-3.53), and 77 studies reported that no adverse events occurred (Tables 3.54-3.55).

Studies that reported adverse events included 54 RCTs and 17 non-randomized comparison studies. Categorizing and reporting of adverse events varied greatly across studies. Only 1 study explicitly defined serious adverse events³⁴ based on the scale developed by the World Health Organization (WHO). Some studies combined all nausea and vomiting, while others limited reporting to “mild to severe” gastrointestinal (GI) disturbance. In 10 studies, the authors reported that “few,” “some,” or “most” subjects had symptoms, but did not provide any further description. No definitions for clinical bleeding or headache were given. In addition, adverse event rates were reported sometimes as a number and sometimes as a percent of patients with symptoms. In some studies, adverse events were reported without differentiating by treatment assignment, while others studies did not report whether patients who withdrew from the studies experienced adverse events. We grouped the different types of adverse events reported into 4

major categories: clinical bleeding (nasal, hematuria, gastro-intestinal, and other bleeding), GI complaints, withdrawal due to adverse events, and miscellaneous.

No adverse events were reported that associated omega-3 fatty acid consumption with events such as death, life-threatening illness, significant disability, or handicap. However, 4 studies reported that some important bleeding occurred among subjects on fish oil combined with aspirin or warfarin^{71, 72, 73, 74}.

Studies reporting adverse events are presented in Tables 3.52-3.53. To help readers appreciate the occurrence of adverse events in different populations, we grouped the studies into 5 different categories: general, cardiovascular disease, hyperlipidemia, diabetes, and hypertension.

Overall

We analyzed 148 articles for data on adverse events. These articles represented about 20,000 subjects. About half of these subjects were exposed to omega-3 fatty acid in different forms and dosages and for durations ranging from 1 to 364 weeks. The majority of the studies evaluated a few dozen subjects for less than 6 months. The GISSI-Prevenzione trial, with over 11,000 subjects and a follow-up duration of 182 weeks, reported the largest number of adverse events³⁹. This trial contributed about one-third of the total number of GI complaints (in both the omega-3 fatty acid arm and the control arm) from all the studies combined. It also contributed almost all the withdrawals due to adverse events (although the reasons for withdrawals were not given). This discordance suggests that many studies do not adequately report adverse event data, especially data about withdrawals due to adverse events.

GI Complaints

Among the 71 studies that reported adverse events, GI complaints were the most common. They were reported in 6.6% (584/8,805) of subjects in the omega-3 fatty acid arms and 4.3% (381/8680) of subjects in the control arms. The high percentage of GI complaints in the control arms is probably due to the equivalent amounts of non-omega-3 oil that were given to control subjects. In the GISSI study, in which the control arm received either vitamin E or no treatment, the GI complaints in the control group were half that of the fish oil arm. There appears to be more GI complaints with omega-3 fatty acids in the studies of the diabetes population^{75-78 79-81} but the total number of events and total number of subjects evaluated in these studies was too small to draw meaningful conclusions. There was no significant difference in other categories of study populations.

Clinical Bleeding

Clinical bleeding was reported almost exclusively in the CVD study populations. Overall, there was no difference in the frequency of bleeding events between the omega-3 fatty acid and control arms. Because of the lack of uniform definitions for the severity and seriousness of clinical bleeding, case descriptions from 5 RCTs^{74,82 83 84 85} that reported clinical bleeding are noteworthy. Together, the RCTs involved a total of 125 subjects (57 in omega-3 fatty acid arms, 68 in control arms). There were no significant differences between omega-3 fatty acid and control groups in the 5 studies. All of the subjects in these studies took warfarin or 200-325 mg

of aspirin daily. Severe bleeding was reported in 2 of the 5 studies. Eritsland randomized 511 patients⁸² and reported an intrathoracic postoperative bleeding event that required transfusion and re-operation; however, it was not mentioned whether this patient received fish oil. This study also reported that bleeding complications were the reason for 9 of the withdrawals (5 from the fish oil group and four from the olive oil group). Similarly, in a large study, Reis⁷⁴ compared 6g of omega-3 fatty acid daily with the same amount of olive oil and reported that important bleeding occurred in 4 patients on fish oil and none on placebo. Two of the patients had severe bleeding at the site of a femoral puncture and 1 required surgical repair. The other 2 patients experienced GI bleeding during follow-up. One of these patients required hospital admission and transfusion, and the other had a heme-positive stool. Cairns⁸⁴ found that most bleeding was mild, leading to permanent discontinuation of the study medication in only 6 patients (0.9%). No transfusions were required, and bleeding was less frequent in patients taking fish oil compared to those taking placebo. Leaf⁸³ reported that 3% of patients in each treatment group experienced bleeding episodes⁸⁵ noted 1 patient with chronic lower GI bleeding.

Studies that Reported that No Adverse Events Occurred

In addition to studies that reported adverse events, we reviewed 77 studies (51 RCTs and 26 non-randomized comparison studies) that reported there were no adverse events associated with the omega-3 fatty acid supplements used (Table 3.54-3.55). Together, these studies involved 2,325 subjects in omega-3 fatty acid arms. Study duration ranged from 1 to 364 weeks, and the EPA and DHA dosage ranged from 0.3 to 8 g/d.

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Wander 1996	24	EPA+DHA 4.3	24	Soybean oil 4 capsules	36			1	0			Post-menopausal women
Hamazaki 1996	13	DHA 1.5-1.8	11	Soybean oil ND	13			2	3			1 weight gain in each group
Kaminski 1993	7	EPA+DHA 5.8	7	ND	6			"some"				
Allard 1997	35	EPA+DHA 5.4	37	Olive oil 6.3	6			3	0	3	0	
Hawkes 2002	40	EPA+DHA 0.74	40	Placebo oil 2.0	4			4				1 skin rash in n-3 FA
	40	EPA+DHA 0.37										
Stark 2000	18	EPA+DHA 4.0	17	Primrose oil 8 capsules	4			2				Post-menopausal women
Harris 1993	4	EPA+DHA 0.64	4	Olive oil ND	4			1				1 headache in n-3 FA
Mueller 1991	6	n-3 FA 8.0 + EPA 3.5	6	Olive oil 8 capsules	3			3	3			1 constipation, 1 weight gain, 1 headache in n-3 FA 1 diarrhea in olive oil
Total	187		146					16	6	3	0	
Cardiovascular disease population												
GISSI-P 2001	5665	EPA+DHA 0.85±VitE	5658	Vit E or Control	182			179	93	215	119	
Sacks 1995	31	EPA+DHA 4.8	28	Olive oil ND	112			3		3	0	≥93% in both groups took antiplatelet agents
Von Schacky 1999	111	EPA+DHA 3.5 to 1.7	112	Blend of fish oil	104			4	3	4	3	1 rash in n-3 FA
Leng 1998	60	GLA 1.7 + EPA 0.27	60	Sunflower seed oil 3.0	104			30	19			47 vs 40% on aspirin
Kaul 1992	58	EPA+DHA 3.0	49	Calcium blocker	48	0	0	2	0			All on aspirin
Borchgrevink 1966	100	Linseed oil 10 ml	100	Corn oil 10 ml	40			7	7	3	0	All taking anticoagulants
Eritsland 1995	119	EPA+DHA ² and Aspirin	106	Aspirin	36	10	8	34		5	4	See footnote 2

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
	132	EPA+DHA ² and Warfarin	154	Warfarin		17	14					
Maresta 2002	125	EPA+DHA 5.1	132	Olive oil	26	0	0	2	2			All on aspirin
Leaf 1994	226	EPA+DHA 6.9	221	Corn oil	24	8	8	19	22	3	8	All on aspirin, 4% (11) infections in each group
Johansen 1999	196	EPA+DHA 5.1	192	Corn oil 5.1	24			3	2			71 vs 67% on Aspirin 18% vs 16 on Warfarin
Reis 1989	124	n-3 FA 6.0 + aspirin	62	Olive oil	24	4 ³	0	59	11	46		n-3 vs olive Weight gain: 6 vs 3 (5% in each group) Diarrhea: 15 vs 4
Milner 1989	95	EPA+DHA 4.5	99	Olive oil	24	14	0	24				1 insomnia, 1 headache in n-3 FA
Bairati 1992	59	EPA+DHA 4.5	60	Olive oil 15	24			29	30			All on aspirin
Bellamy 1992	60	EPA+DHA 3.0	53	ND	24			4	0			1 diarrhea with n-3 FA, 96% of all on aspirin
Dehmer 1988	43	EPA+DHA 5.4	39	ND	24	0	0	7	3			All on aspirin + dipyridamole
Cairns 1996	325	EPA+DHA 5.4	328	Corn oil	18	17	38	122	101	3	3	All on aspirin See footnote 5
Franzen 1993	92	n-3 FA 3.2	83	Olive oil 9 capsules	16	0	0	13	5	13		All on aspirin
Berrettini 1996	20	EPA+DHA 2.6	19	Corn oil 3.0	16				1	0	1	> 2/3 on aspirin
Berg 1965	42	Linseed oil 10 - 30 ml	37	Corn oil 10 - 30 ml	12			5		0	0	Diarrhea: 5 in n-3 FA, all on anticoagulants
Berg 1988	14	EPA+DHA 4.5	16	Vegetable oil 15 capsules	12			0	1	0	1	
Davidson 1989	15	EPA+DHA 3.6	15	Olive oil 20 capsules	4							1 diarrhea in olive oil
EPA+DHA 2.4												
Total	7712		7623			57	68	512	300	236	139	
Hyperlipidemia population												

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Sirtori 1997	470	EPA+DHA 2.5 to 1.7	465	Olive oil ND	24			18	21			
Harris 1997	22	EPA+DHA 3.4	20	Corn oil ND	16			4	3	0	0	
Boberg 1986	7	EPA+DHA 3.0	7	Olive oil ND	16			"some"				1 skin rash in n-3 FA
Grundt 1995	28	EPA+DHA 3.4	29	Corn oil 4.0	12			"some"				
Alaswad 1999	11	EPA+DHA 3.4	42	Placebo	12	1 nose	0					
Bonaa 1992	72	EPA+DHA 5.1	74	Corn oil 6.0	10			10	7			
Wilt 1989	19	EPA+DHA 6.0	19	Placebo	12			8	8			
Silva, 1996	20	EPA+DHA 3.6	15	Soya oil 12 capsules	8			4		4		
Mori 1999a	36	EPA+DHA 4.0	20	Olive oil 4.0	6			1		1		
Mori 2000a	26	EPA+DHA 4.0	14	Olive oil 4.0	6			1		1		
Davidson 1997	18	DHA 1.25 or 2.5	8	Corn and soybean oil 12 capsules	6			"some"				
Contactos 1993	10	EPA+DHA 3.0	11	Placebo	6			1				
Brox 1983	7	Cod liver oil 30 ml	11	ND	6			2	0			
Demke 1988	13	EPA+DHA 1.7	18	Safflower oil 5.0	4			"some"				Some diarrhea and headache
Subtotal	759		753			1	0	34	31			
Diabetes population												
Myrup 2001	14	EPA+DHA 4.6	15	Olive oil 21 ml	52			3	1	3	0	
Rossing 1996	14	EPA+DHA 4.6	15	Olive oil 21 ml	52			2	0	2	0	
Schectman 1988	13	EPA+DHA 4.0	13	Safflower oil 12	24			1	0	1	0	
Vessby 1990	5	EPA+DHA 3.0	9	Olive oil 10	8			"some"		0	1	
Hendra 1990	40	EPA+DHA 3.0	40	Olive oil 5 capsules	6			1	0	1	0	
Mori 1991	9	EPA+DHA 5.2	9	Olive oil ND	3			"some"				

Table 3.52. Randomized Controlled Trials That Reported Adverse Events with Consumption of Omega-3 Fatty Acid Supplements

Author Year	Omega-3 Fatty Acids		Control		Duration (weeks)	Clinical Bleeding		GI Complaints		Withdraw Due to AE		Comments
	n	Type Dose (g/d)	n	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
Fasching 1996	5	EPA+DHA 4.7	5	Gemfibrozil (0.9)	2			2	0			
Subtotal	100		106					9	1	7	1	
Hypertension population												
Margolin 1991	22	n-3 FA 4.7	24	Corn oil 9.0	8		1		4			1.8% dizziness 5.1% diarrhea, 1 skin rash in n-3 FA
Gray 1996	9	EPA+DHA 3.4	10	Corn oil 1 capsule	8			0	3	0	0	4 headaches in n-3 FA
Levinson 1990	8	EPA+DHA 15	8	Vegetable oil 50	6			2	1	1	0	
Landmark 1993	8	EPA+DHA 4.6	10	Olive oil 5 capsules	4			2	1	0	0	No diarrhea
Subtotal	47		52					4	5	1	0	
All Studies												
Total	8805		8680				58	68	575	373	247	140

AE= Adverse Events; C=Control; ND= No data

[1] Serious adverse events defined by Scotia Pharmaceuticals based on a WHO scale, including death, life-threatening illness, significant disability on handicap and in-patient hospitalization for any reason.

[2] Only bleeding episodes detected clinically were recorded. One bleeding episode required transfusion and operation, the other episodes were minor. In addition, a bleeding complication was the reason for withdrawal in 9 out of the 66 patients.

[3] Important bleeding occurred in 4 patients on fish oil and none on placebo. Two patients had severe bleeding at the site of femoral puncture.

[4] one patient with chronic lower GI bleeding + and a known diagnosis of diverticulosis required partial colectomy.

[5] Most bleeding was mild, leading to permanent discontinuation of study medication in 6 patients.

Table 3.53. Adverse Events Reported in Non-randomized Studies of Omega-3 Fatty Acid Supplements

Author Year	n	Omega-3 fatty acids (g/d)	Duration (weeks)	Clinical bleeding	GI complaints	Withdrawal due to AE	Comments
General population							
Schmidt 1992a	24	EPA+DHA 3.2	36		"some"		
Berg 1990	10	n-3 FA 1.3-9	18		"some"		
Brown 1991	12	n-3 FA 5.0	6			5	1 weight gain after 2 wk
Mortensen 1983	20	n-3 FA 4.0	4		1		
Wojenski 1991	9	EPA+DHA 3.0	4		4		
Subtotal	75				4	5	
Cardiovascular disease population							
Bowles 1991	85	EPA 2.8	24		28		"Considerable symptoms" and some diarrhea
Verheugt 1986	5	n-3 FA 3.0	24		1		
Smith 1989	22	EPA+DHA 3.4	4	1 nose	3		
Kahl 1987	16	n-3 FA 8.1	2		10		4 increased appetite
Subtotal	128			1	42		
Hyperlipdemia population							
Dallongeville 1991	18	EPA+DHA 4.8	12		6	0	
Schectman 1989	16	EPA+DHA 6.0	12		18	1	3 diarrhea
Pichter 1992	12	EPA+DHA 3.6	12				Inverse in blood glucose from 97-249 mg/dl, HbA from 5.5 to 7.1%, after removal of n-3 fatty acids, blood glucose normalized.
Otto 1996	23	EPA+DHA 1.5 to 3.0	8		1		
Schmidt 1989a	17	EPA+DHA 5.1	6		"some"		
Subtotal	86				25	1	
Diabetes population							
Tamura 1987	62	EPA 1.8 to 2.7	16		1 or 2		
Mori 1989	10	EPA+DHA 4.3	3		2		
Fasching 1991	8	EPA+DHA 6.3	2		2		

Author Year	n	Omega-3 fatty acids (g/d)	Duration (weeks)	Clinical bleeding	GI complaints	Withdrawal due to AE	Comments
Subtotal	80				5 - 6		

GI = Gastrointestinal (not including liver inflammation). AE= Adverse Events

Table 3.54. Randomized Trials of Omega-3 Fatty Acid Supplements that Reported No Adverse Events

Author, Year	N	Omega-3 Fatty Acids (g/d)	Duration (Weeks)
Nilsen, 2001	150	EPA+DHA 1.7	104
Brox, 2001	36	EPA+DHA 2.6	56
Eritsland, 1994	260	EPA+DHA 3.4	36
Satterfield, 1991	175	n-3 FA 3.0	24
Hamazaki 1996	16	EPA 1.8	24
Radack, 1990	17	n-3 FA 1.1 - 2.2	20
Toft, 1997	38	EPA+DHA 3.4	16
Gans, 1990	16	EPA+DHA 3.0	16
Goodfellow, 2000	15	EPA+DHA 3.4	16
Prisco, 1994	10	EPA+DHA 3.4	16
Prisco, 1995	10	EPA+DHA 3.4	16
Prisco, 1998	8	EPA+DHA 3.4	16
Schmidt, 1988	18	n-3 FA 4.5	12
Radack, 1991	16	n-3 FA 2.0	12
Vandongen, 1993	17	EPA 1.3 - 2.6	12
Nenseter, 2000	34	Fish powder 10	12
Yam, 2002	34	n-3 FA 7.0	12
Adler, 1997	10	n-3 FA 3.6	12
Morris, 1993	12	n-3 FA 3.0 - 6.0	12
Salanchas, 1994	20	EPA+DHA 4.0	12
Warner, 1989	7	Max EPA 50ml	12
Solomon, 1990	5	EPA+DHA 4.6	12
Mehta, 1988	8	EPA+DHA 5.4	12
Calabresi, 2000	14	EPA+DHA 3.4	8
Schmidt, 1992	11	n-3 FA 2.0 - 9.0	8
Steiner, 1989	3	EPA+DHA 1.6	8
Wing, 1990	20	EPA+DHA 4.5	8
Luo, 1998	6	EPA+DHA 1.8	8
Grimsgaard, 1998	147	EPA+DHA 4.0	7
Hansen, 1993	11	EPA+DHA 3.4 to 3.6	7
Grimsgaard 1997	147	EPA 4, DHA 4	7
Honstra, 1990	40	n-3 FA 1.7	6
Van Houwelingen, 1988	40	EPA+DHA 4.7.	6
Howe, 1994	28	n-3 FA 5.0	6
Chan, 2003a	25	EPA+DHA 3.4	6
Pirich, 1999	13	EPA+DHA 0.4	6
Chan, 2002	12	EPA+DHA 3.4	6
Conquer, 1999	10	EPA+DHA 3.0	6
Vericel, 1999	10	EPA+DHA 0.2	6
Axelrod, 1994	9	EPA+DHA 2.6	6
Brox, 1981	6	Cod liver oil 25 ml	6
Chan 2002b	25	EPA+DHA 3.4	6
Balestieri, 1996	8	n-3 FA 5.1	4
Baumann, 1999	7	EPA+DHA 4.6	4
Freese, 1997	24	EPA+DHA 5.2	4

Author, Year	N	Omega-3 Fatty Acids (g/d)	Duration (Weeks)
Mori, 1992	15	EPA+DHA 4.6	4
Nozaki, 1991	12	EPA+DHA 8.0	4
Davi, 1990	10	EPA 1.8	4
Harris, 1991	16	EPA+DHA 2.2	4
Villa, 2002	10	n-3 FA 3.0 – 6.0	4
Swails, 1993	7	EPA+DHA 1.6	1
Total	1,618		

Table: 3.55. Non-Randomized Studies of Omega-3 Fatty Acid Supplements that Reported No Adverse Events

Author, Year	N	Omega-3 Fatty Acid (g/d)	Duration (week)
Saynor, 1992	365	EPA+DHA 1.1 – 1.8	4-364
Shinozaki, 1996	16	EPA 1.8	96
Blok, 1997	44	EPA+DHA 1.0 – 2.9	52
Rhodes, 1994	15	EPA+DHA 3.0	24
Von Schacky, 1985	6	Cod liver oil 10 - 40 ml	20
Nelson, 1997	10	DHA 6.0	17
Russo, 1995	24	EPA+DHA 2.6	16
Meydani, 1991	25	EPA+DHA 2.4	12
Bagdade, 1990	8	EPA+DHA 6.0	12
Nau, 1991	14	EPA+DHA 1.0	8
Toth, 1995	10	n-3 FA 0.2	8
Bonanome, 1996	12	n-3 FA 2.5	8
Bagdade, 1996	9	EPA+DHA 4.6	8
Berg, 1989	10	EPA+DHA 0.7	6
Schmidt, 1991	10	EPA+DHA 0.7	6
Schmidt, 1990	10	EPA+DHA 2.1	6
Schmidt, 1989	10	n-3 FA 4.0	6
Berg, 1989	17	EPA+DHA 5.1	6
Haglund, 1990	13	EPA 2.7 – 5.4	4
Glauber, 1988	6	EPA+DHA 5.5	4
Suehiro, 1994	27	EPA 1.8	4
Harris, 1983	12	n-3 FA 20 - 29	4
Owens, 1990	6	EPA+DHA 4.5	4
Kasim-Karakas, 1995	14	EPA+DHA 3.3	4
Terano, 1983	8	EPA+DHA 0.3	4
Nordoy, 1994	6	EPA+DHA 4.8	3
Total	707		

Chapter 4. Discussion

In this chapter, we discuss the main findings related to the general and cardiovascular disease (CVD) key questions addressed by this evidence report. We also describe limitations of the studies reviewed for the report and future research needs.

Overview

This report summarizes scientific evidence regarding the effects of dietary or supplemental omega-3 fatty acids on CVD outcomes including mortality (e.g., all-cause mortality, sudden death, and deaths due to myocardial infarction and stroke), and summarizes evidence of associations between omega-3 fatty acids and CVD outcomes. To assess the role of omega-3 fatty acids in reducing CVD outcomes, we reviewed the clinical literature on primary and secondary prevention. We analyzed the third National Health and Nutrition Examination Survey (NHANES III) database to assess the dietary intake of omega-3 fatty acids in the US population, and to determine whether there is a difference in the mean intake of omega-3 fatty acids between various sub-populations and between adults with and without CVD. To evaluate adverse events and potential drug interactions associated with omega-3 fatty acids, we reviewed studies that reported any occurrences of these events.

We screened over 7,464 abstracts and retrieved 768 full text articles. We found and analyzed 39 unique studies that reported mortality or CVD clinical outcomes and that had a follow-up duration of 1 year or longer. These studies include 12 randomized controlled trials (RCTs) and 22 prospective cohort studies of at least 1 year in duration, 4 case-control studies, and 1 cross-sectional study. All of these studies quantified the fish or omega-3 fatty acid intake — including fish oil or alpha linolenic acid (ALA, 18:3 n-3) supplements — and assessed the effects of their consumption on CVD outcomes in the general (primary prevention) or CVD (secondary prevention) populations. Our analyses of adverse events and potential drug interactions are based on a review of 148 articles that reported these events.

Main Findings

The main findings of our analyses are presented below. Findings related to the dietary intake of omega-3 fatty acids in the US population are discussed first, followed by findings related to the effects of omega-3 fatty acids on CVD outcomes and adverse events associated with omega-3 fatty acid supplements.

Dietary Intake of Omega-3 Fatty Acids in the US

We analyzed the data from a single 24-hour dietary recall from the NHANES III database to determine the average US population intake of ALA, linoleic acid (LA, 18:2 n-6),

eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3). These analyses showed that the average intake of LA is 14 g/d (5.79 %kcal/d), of ALA is 1.33 g/d (0.55 %kcal/d), of EPA is 0.04 g/d (0.02 %kcal/d), and of DHA is 0.07 g/d (0.03 %kcal/d). Only 25% of the US population reported any amount of daily EPA or DHA intake. These results are similar to the estimates reported in the Multiple Risk Factor Intervention (MRFIT) study in the late 1970s, which estimated that the average intake of LA was 14.6 g/d, of ALA was 1.69 g/d, and of EPA+DHA+docosapentaenoic acid (DPA, 22:5 n-3) was 0.18 g/d. Intake estimates of ALA and EPA+DHA for the US population are much lower than estimates for the Japanese population (which has significantly fewer CVD events). Average Japanese intake in 1985 for ALA was 2.08 g/d, while the intake of EPA+DPA+DHA was 1.56 g/d ⁵².

Additional analyses of the NHANES III database showed that there are significant variations in the dietary intake of omega-3 fatty acids among different US sub-populations. Corrected for energy intake, men consume significantly less ALA than women, adults consume more ALA than youths, and subjects with a history of CVD consume less ALA than those without CVD. People who had a Poverty Index Ratio index (PIR) of ≤ 1.3 consumed less ALA and LA than people who had a PIR >1.3 . Non-Hispanic whites, non-Hispanic blacks, and Mexican Americans all had a significantly higher intake of both ALA and LA compared to other groups.

Effects of Consumption of Omega-3 Fatty Acid from Fish or Overall Diet, or from Supplements of Fish Oil or ALA, on Cardiovascular Disease Outcomes

CVD outcomes of secondary prevention studies. We reviewed 11 RCTs and 1 prospective cohort study that reported outcomes in CVD populations. The trials lasted between 1.5 to 5 years and, together, included over 16,000 patients (mostly outside the US).

Five trials used fish oil (EPA+DHA) supplements with a dose ranging between 0.27 and 4.8 g/d. The largest trial reported that fish oil significantly reduces all-cause mortality (risk ratio [RR] = 0.79, 95% confidence interval [CI] = 0.66-0.93) and CVD outcomes, but has no effect on stroke ³⁵. Other trials that evaluated fish oil supplements reported similar results on CVD and stroke outcomes. One multi-arm trial compared fish oil, mustard oil (ALA), and non-oil placebo ³⁸. In this trial, both fish oil and mustard oil were efficacious in reducing CVD outcomes, although no difference was seen between the 2 oils. The methodological quality of 4 RCTs for EPA+DHA ³⁴⁻³⁷ was generally good (summary quality grade A or B), but the multi-arm trial from India ³⁸ was of poor quality (grade C).

The other 6 trials, involving about 4,000 patients, were diet/dietary advice trials. The duration of these trials ranged from 2 to 5 years. Four of the dietary studies reported estimates of the amount of ALA consumed (1.8 to 6.3 g/d) in the intervention arms ^{42-44 45}. All of the trials were of poor quality. The applicability of these trials ranged from CVD-I (highly applicable) to CVD-III (limited applicability). The subjects were mostly MI survivors or those at significant CVD risk. The 2 largest ALA trials included over 600 patients each and reported reductions in all-cause mortality and CVD events ^{43,44}. The study by Singh 2002 was conducted among patients in India. Two-thirds of the participants were vegetarians, which limits the applicability of the study results to the US population. The smallest ALA trial, which had a duration of 2 years, reported a very low all-cause or CVD mortality event rate (0.6%) and found no beneficial effect from increased ALA intake ⁴⁵. An early trial ⁴², which included 412 post MI patients

randomized to diet and control groups, experienced a significantly lower combined incidence of fatal/non fatal MI and sudden death.

Two all-male trials from the UK reported estimates of EPA intake^{41,47} of 2.4 g and 2.7 g, respectively. Both of these trials were rated as poor quality studies (grade C), and their applicability was rated CVD-II (relevant subgroups). The first trial⁴⁷ found significant reduction of all-cause mortality with a relative risk of 27%. However, the 10-year follow-up to this study found no long-term benefit of fish advice in the same group of patients taking a similar amount of EPA⁴⁸. The second, more recent, trial⁴¹ found that those taking fish oil supplements had an increased sudden death risk.

The single prospective cohort study⁴⁶ also reported an at least 50% relative risk reduction of all cause mortality with any amount of fish intake compared with subjects who consumed no fish.

CVD outcomes of primary prevention studies. Twenty-two prospective cohort studies and 1 RCT reported data on outcomes in general populations. Among the cohort studies, there were considerable differences in the populations studied, the diet of the study populations, and the estimates of fish or omega-3 fatty acids consumed. The duration of the cohort studies ranged from 4 to 30 years. The number of subjects in the studies ranged from 272 to as many as 223,170. The cohort studies have been conducted worldwide, including in the US, China, Japan, the UK, and Scandinavian and Mediterranean countries. Eight cohort studies were conducted in the US. Most of the large cohort studies found that fish consumption reduced all-cause mortality and CVD events, although several studies reported no significant or negative results. Many of the studies that found significant CVD benefit also reported a statistically significant inverse association with fish intake. A significant benefit for ischemic stroke was reported in only 1 study⁶³. The only RCT that evaluated ALA in a large general population lasted 1 year and yielded no significant results. This lack of significance is possibly due to high background omega-3 fatty acids, but there is no evidence available to explain absence of effect. The authors of this study reported that the mortality event rates observed in the study were lower than expected when compared with the general population⁴⁹.

The largest relative reduction of CVD outcomes was seen in trials that reported on sudden death. The relative risk of CVD events in these studies ranged from 0.06 to 0.55. An inverse association between estimated fish or fish oil consumption and a reduction in sudden death events was also reported in several prospective cohort studies^{56,58,60}. One study reported on the effects of fried fish or fish sandwich consumption on CVD outcomes. This study found a trend of increased numbers of arrhythmic death with increased consumption⁶⁰.

Overall, the evidence supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA, or ALA) from fish or from supplements of fish oil reduces all-cause mortality and various CVD events, although the evidence is strongest for fish and fish oil supplements.

Adverse Events Associated with Consumption of Omega-3 Fatty Acid

The FDA has ruled that up to 3g of EPA+DHA is safe to be included in the food supply of Americans without fear of adverse events⁸⁶.

Gastrointestinal symptoms associated with fish oil or ALA supplements are the most commonly reported adverse events in RCTs and non-randomized comparison studies. These symptoms may require dose reduction or discontinuation of the agent in some individuals.

Clinical bleeding is a theoretical concern, but there was no difference in the overall number of bleeding events between the supplement groups and the control groups. Overall, adverse events related to consumption of fish oil or ALA supplements appear to be minor.

Limitations

Our analyses and estimates of omega-3 fatty acids from the NHANES III database are based on a single 24-hour dietary recall. The dietary method is less than optimal for estimating intake of omega-3 fatty acids from foods that are not consumed on a daily basis, such as seafood. Given large variations in intake from day to day, multiple 24-hour recalls are considered to be best suited for most nutrition monitoring⁹. Two additional 24-hour recalls were completed by NHANES III participants age 50 years and older. While it would have been ideal to adjust for the within-person day-to-day variations in dietary intake using all 24-hour recalls²³, we did not have access to the additional data due to resource limitations. We also did not consider additional estimates of omega-3 fatty acid intake developed by other studies, particularly those that focused on the intake of omega-3 polyunsaturated fatty acids (PUFAs) from seafood, in large part because they do not represent national samples.

Overall, the methodological quality of the RCTs was from fair to poor whereas the quality of prospective cohort studies for omega-3 fatty acids was generally graded as good. However, the studies demonstrate a number of limitations, which are highlighted below:

- Almost all of the evidence for the health benefits of omega-3 fatty acids for the general population (i.e., for primary prevention) was derived from cohort studies, whereas almost all the evidence for secondary prevention was derived from RCTs of limited duration. Given the recent observation that flawed assessments of the health benefits of hormone replacement therapy were based on observational studies that were not later verified by RCTs, we propose that recommendations regarding omega-3 fatty acids as a dietary supplement should be developed using RCT evidence.
- The data for secondary prevention appear to be reliable but they are derived from 1 very large study³⁵. Data on women are limited. Data on the exact interventions that are effective (and relative efficacy of different preparations) are very limited. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.
- The single RCT for primary prevention that evaluated ALA supplements in the general population⁴⁹ lasted only 1 year and the study subjects had a lower mortality event rate than the general population. Although this was a large study with over 13,000 subjects, the results were not particularly useful given the short trial duration and the small number of clinical events. The finding of no effect might be explained by high background EPA+DHA in the native populations; however, we have no data to show that is the case. Future RCTs should incorporate sufficient study duration into their design.
- Many of the studies on fish intake do not report the type of fish and the method of preparation. Such information is important, since different types of fish have different amounts of EPA+DHA and the method of preparation may affect the fish oil content.

- The data on the effect of ALA on CVD outcomes is limited. There is only 1 comparative trial of ALA and fish oil and its findings are highly suspect.
- Most of the evidence for primary prevention was derived from prospective cohort studies that examined fish intake, not fish oil supplements.
- The studies included in this evidence review were heterogeneous with regard to the methods of estimating fish or omega-3 fatty acid intake, background diets, settings, and the methods of reporting results. For these reasons, the validity of applying the results of studies conducted in countries outside of the US to the US population is uncertain, and methods used to assess background diet and fish consumption must be improved and standardized.
- Data are limited concerning the effects and associations of omega-3 fatty acids with CVD outcomes in different subpopulations.

Research Recommendations

- In general, future studies of omega-3 fatty acid should include the following:
 - Omega-6/omega-3 ratio should always be estimated and reported
 - Attempts should be made to determine the effect of higher fish intake on the consumption of other foods in the diet, specifically meat and cheese (sources of saturated fat)
 - Future prospective cohort studies and diet trials on fish consumption should place special emphasis on collecting data on fish consumed, type of fish, and method of preparation
- Well-designed, multi-center RCTs are needed to assess the effect of omega-3 fatty acid consumption on CVD outcomes in primary and secondary prevention settings. The trial design should include a period of long-term follow-up for 3 to 5 years so that long-term effects of omega-3 fatty acids can be monitored.
- Additional research should address questions about the effect of omega-3 fatty acid consumption on CVD outcomes in specific populations, including patients with diabetes and other chronic diseases.
- The potential effect of ALA is unknown. Current data sets are of poor quality and are too limited for adequate assessment. More trials are needed to confirm or report the effect of ALA, separate from fish or fish oil, on CVD outcomes. We need to know more about the potential interaction of ALA with EPA+DHA.

- The relative effect of ALA versus fish oil is not well defined. Comparative trials between these 2 supplements should be conducted. Given the abundance of soybean and canola oils relative to fish in the diet, it would be useful to understand the economic and ecological impact of increased fish intake, and the potential to initiate change in US dietary patterns.

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