

## **Effects of Omega-3 Fatty Acids on Cardiovascular Disease**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

**Contract No. 290-02-0022**

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**Suggested Citation:**

Wang C, Chung M, Lichtenstein A, Balk E, Kupelnick B, DeVine D, Lawrence A, Lau J. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Evidence Report/Technology Assessment No. 94 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022). AHRQ Publication No. 04-E009-2. Rockville, MD: Agency for Healthcare Research and Quality. March 2004.

## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 Fatty Acids on Cardiovascular Disease was requested and funded by Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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## Acknowledgments

We would like to acknowledge with appreciation the following members of the Technical Expert Panel for their advice and consultation to the Evidence-based Practice Center during preparation of this evidence synthesis.

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## Structured Abstract

**Context.** Epidemiologic studies and clinical trials have reported beneficial effects of fish consumption on several cardiovascular disease (CVD) outcomes, such as all cause mortality, CVD death, cardiac death, sudden death, myocardial infarction and stroke. However, the mechanisms of this benefit are unclear.

**Objectives.** As the first of a 3-part report on this topic, we analyzed relevant nutrition databases to describe the intake levels of various omega-3 fatty acids in the US population. We also performed a systematic review of the literature to assess the benefits of omega-3 fatty acid supplements or fish consumption on various CVD outcomes and to assess adverse events associated with intake of omega-3 fatty acid supplements.

**Data Sources.** The Continuing Survey of Food Intakes by Individuals (CSFII) was reviewed and the third National Health and Nutrition Examination Survey (NHANES III) was analyzed for dietary intake. Medline, Embase, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau databases were searched for potentially relevant studies to address the questions on the effects of omega-3 fatty acids.

**Study Selection.** We screened over 7,464 abstracts and retrieved 768 full text articles. Thirty-nine studies met our inclusion criteria and provided data to address the key questions in this report. We used randomized controlled trials (RCTs) and observational studies that quantified the amount of fish or omega-3 fatty acid intake and that were at least 1 year in duration to assess the effects of omega-3 fatty acid consumption on CVD outcomes on risk of CVD in the general population (those without known CVD) and in populations at high risk due to pre-existing CVD or multiple CVD risk factors.

**Data Extraction.** From each study that qualified, we extracted information about the study design, population demographics, the prescribed or estimated amount of omega-3 fatty acid supplements or fish consumed, and outcomes. For RCTs, we extracted information about the randomization and blinding techniques to assess methodological quality. For prospective cohort studies, we extracted estimated quantities of fish or fish oil consumed and their associated effect.

**Data Synthesis.** The intake of omega-3 fatty acids in the population varies. Corrected for energy intake, men consume significantly less alpha-linolenic acid (ALA, 18:3 n-3) than women, adults more than youths, and subjects with a history of CVD less than those without CVD. Based on analyses of a single 24-hour dietary recall in NHANES III, only 25% of the US population reported any amount of daily eicosapentaenoic acid (EPA, 20:5 n-3) or docosahexaenoic acid (DHA, 22:6 n-3) intake.

Eleven RCTs and 1 prospective cohort study reported outcomes on CVD populations. The largest trial reported that fish oil (EPA + DHA) reduces all cause mortality and CVD events, although fish oil has no effect on stroke. Most other studies evaluating either fish oil or ALA supplements reported similar findings. There were few trials of ALA. In the only RCT that directly compared ALA and fish oil, both treatments were efficacious in reducing CVD outcome. No significant difference was found between the 2 supplements.

Twenty-two prospective cohort studies and 1 RCT reported data on general populations. Among the cohort studies there were considerable differences among the populations studied, as well as 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 outcomes, 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 RCT which evaluated ALA in a large general population lasted only 1 year yielding no significant results. Gastrointestinal symptoms associated with fish oil or ALA supplements are the most commonly reported adverse event and may require dose reduction or discontinuation in some individuals. Clinical bleeding is a theoretical concern but this was not borne out by the evidence.

**Conclusions.** Overall, consumption of omega-3 fatty acids from fish or from supplements of fish oil reduces all cause mortality and various CVD outcomes. The evidence for ALA supplements is sparse and inconclusive. The adverse events due to consumption of fish oil or ALA supplements appear to be minor. Many questions remain. The studies 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. Due to these reasons, the validity of applying the results of studies conducted in countries outside of the US to the US population is uncertain. The optimal quantity and type of omega-3 fatty acid, and the optimal ratio of omega-3 to omega-6 fatty acid (if such an optimal ratio exists), remain undefined. Not much data exists concerning the needs of different subpopulations. Different types of fish and the method of food preparation may have different effects. Future research needs to address these issues.



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



## Effects of Omega-3 Fatty Acids on Cardiovascular Disease

### Summary

### Introduction

Since the first cross-cultural epidemiological studies in the 1970s<sup>1,2</sup> the body of evidence supporting a role for omega-3 fatty acids in the prevention of cardiovascular disease (CVD) has continued to increase. However, the beneficial effects of omega-3 fatty acids are not consistently observed in all epidemiological studies.

In this report, we review information from experimental and observational studies that investigate the effect of dietary or supplemental omega-3 fatty acids on clinical outcomes. More specifically, we examine how dietary or supplemental omega-3 fatty acids affect particular CVD outcomes such as myocardial infarction and stroke, and investigate whether omega-3 fatty acids can play a role in primary and secondary prevention of these outcomes. In addition, we examine evidence of adverse events and drug interactions associated with omega-3 fatty acids. The report also includes an analysis of dietary intake of omega-3 fatty acids based on the third National Health and Nutrition Examination Survey (NHANES III) database.<sup>3,4</sup> Using NHANES III data, we have determined the mean intake of omega-3 fatty acids in the U.S. population and various subpopulations and whether there is a difference in the mean intake of omega-3 fatty acids between adults with and without cardiovascular disease.

This evidence report is one of three reports prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on cardiovascular diseases. These reports are among several that address

topics related to omega-3 fatty acids, and that were requested by the Office of Dietary Supplements, National Institutes of Health, through the EPC Program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-NEMC EPC, the Southern California/RAND EPC, and the University of Ottawa EPC—each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

### Methods

### Key Questions

Key questions addressed by this report include one general question and three questions specific to CVD:

#### General Question

1. What are the mean and median intakes of docosahexaenoic acid (DHA, 22:6 n-3), eicosapentaenoic acid (EPA, 20:5 n-3), docosapentaenoic acid (DPA, 22:5 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 U.S. population?
  - a. Do consumption levels differ among subpopulations?

#### Cardiovascular Disease Questions

1. 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)?

- a. 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)?
  - b. How does the efficacy or association of omega-3 fatty acids in preventing incident CVD events differ in subpopulations, including men, pre-menopausal women, post-menopausal women, and different age groups?
  - c. What are the effects of potential confounders—such as lipid levels, body mass index, blood pressure, diabetes, aspirin use, hormone replacement therapy, and cardiovascular drugs—on associations found in prospective cohort studies?
  - d. 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?
2. Omega-3 fatty acid variables and modifiers:
- a. 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?
  - b. 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?
  - c. 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)?
  - d. How does the efficacy or association of omega-3 fatty acids on CVD outcomes differ by different ratios of DHA, EPA, and ALA?
  - e. Is there a threshold or dose-response relationship between omega-3 fatty acids and CVD outcomes?
  - f. How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on CVD outcomes?
  - g. Are treatment effects or association of omega-3 fatty acids on CVD events sustained after the intervention or exposure stops?
  - h. 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?
  - i. 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?

3. Adverse events and drug interactions:

- a. What adverse events related to omega-3 fatty acid dietary supplements are reported in studies of CVD outcomes and markers?
- b. 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?
- c. What interactions between omega-3 fatty acid dietary supplements and medications are reported in studies of CVD outcomes and markers?
- d. 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 U.S. Population**

Data from the NHANES III database were analyzed using SAS®-callable SUDAAN®, version 7.5.6 (Research Triangle Institute, Research Triangle Park, NC). All analyses incorporated sampling weights that adjusted for unequal sampling probabilities. Variance estimations were made with the WR (sampling with replacement) method. Each denominator has 49 degrees of freedom. Simple linear regression was used to test the significance of the differences in the daily intake of the polyunsaturated fatty acids between groups. The adjusted means for categorical covariates in the regression model were calculated with the least square 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.

### **Literature Search for Omega-3 Fatty Acids and Cardiovascular Disease**

To address the three key questions related to CVD, we conducted a comprehensive literature search and used the Ovid search engine for all 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 Health from 1973 to December 2002. Additional publications were identified from reference lists and review and primary articles, and from domain experts, the Technical Expert Panel (TEP), and the other two EPCs.

## Selection Criteria and Screening Process

**Abstract and full article screening.** All abstracts identified through the literature search were screened using eligibility criteria developed in conjunction with the TEP. We included all English language original experimental or observational studies that evaluated any potential source of omega-3 fatty acids in at least five 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 one or more of the key questions or as rejects.

Articles that passed the abstract screening process were retrieved and the full articles were screened for eligibility. We accepted randomized controlled trials (RCTs) or prospective cohort studies with a minimum of 1-year followup 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.

**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 Risk Factors and Intermediate Markers of Cardiovascular Disease*) were reviewed for data on adverse events and drug interactions.

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.** From each qualified study, we extracted information about the study design, population demographics, the intervention of exposure, and outcomes. For randomized controlled trials, we extracted information about randomization and blinding status to assess methodological quality. For prospective cohort studies, we extracted data on the estimates of various levels of fish or fish oil consumption and the associated effect.

## Results

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

The intake of omega-3 fatty acids in the population varies. Corrected for energy intake, men consume significantly less ALA than women, adults more than youths, and subjects with

a history of CVD less than those without CVD. Based on analyses of a single 24-hour dietary recall in NHANES III, only 25 percent of the U.S. population reported any amount of daily EPA or DHA intake.

### Effects of Omega-3 Fatty Acid Supplements or Fish Consumption on Cardiovascular Disease Outcomes

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 our screen for studies that might have CVD clinical outcome data, identifying 39 unique studies that fulfilled our inclusion criteria for reporting mortality or CVD clinical outcomes with a followup 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 RCTs, 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 or estimated the intake of fish or omega-3 fatty acids (including fish oil or ALA supplements) and assessed the effects of their consumption on CVD outcomes in the general (primary prevention) or CVD (secondary prevention) populations.

**Secondary prevention studies.** We reviewed 11 RCTs and one prospective cohort study that reported outcomes on CVD populations. Together, the trials included over 16,000 patients and each lasted between 1.5 to 5 years.

Four trials used fish oil (EPA+DHA) supplements in a dosage that ranged from 0.27 to 4.8 g/d.<sup>5-8</sup> The methodological quality was generally good. The largest trial<sup>9</sup> reported that fish oil (EPA + DHA) reduces all-cause mortality and CVD outcomes but does not affect stroke. Other trials that evaluated fish oil supplements reported similar results on CVD and stroke outcomes. A fifth RCT, which was the only multi-arm RCT identified,<sup>9</sup> directly compared mustard seed oil (containing ALA), fish oil, and non-oil placebo. It found that both oil treatments were efficacious in reducing CVD outcomes compared to placebo but found no difference between the two supplements; however, the methodological quality of this study was poor.

Six trials were diet or fish dietary advice trials. Four of the dietary studies generally of poor quality reported estimates of the amount of ALA consumed (1.8 to 6.3 g/d)<sup>10-13</sup> and two reported an estimate of EPA (2.4 to 2.7 g/week) consumed. Two large ALA trials reported reduction of all-cause mortality and CVD events.<sup>11,12</sup> Another study, the smallest ALA trial,<sup>13</sup> had a very low all-cause or CVD mortality event rate (0.6 percent) over the 2-year study duration and found no beneficial effect from increased ALA intake.



Six RCTs<sup>5,9,11,12,14,15</sup> reported data on sudden death. Four of the six studies reported a significant or near-significant large reduction of this outcome (risk ratio [RR] = 0.06 to 0.55).<sup>5,9,11,12</sup> The reduction of sudden death was observed in both the fish oil group as well as in the ALA group. However, the quality of the ALA trials was poor.<sup>9,11,12</sup> A new report by Burr et al. found that those taking fish oil supplements experienced an increase in sudden death risk. The methodological quality of this trial was also poor.<sup>15</sup>

Six trials reported contradictory data on stroke. The control groups reported that strokes occurred in 0 percent to 3 percent of the subjects during the study. The three omega-3 fatty acid supplements trials<sup>5,7,8</sup> reported trends of increased strokes, whereas the three diet/dietary advice trials<sup>11-13</sup> reported trends of fewer strokes. No result from these studies was statistically significant.

One study consistently reported no beneficial effect of omega-3 fatty acid on any of the CVD outcomes.<sup>6</sup> It randomized a total of 300 patients to 1.7 g/d of EPA+DHA or an equivalent amount of corn oil and followed subjects for 1.5 years.

The single prospective cohort study<sup>16</sup> also reported an at least 50 percent relative risk reduction of all cause mortality with any amount of fish intake compared with subjects who consumed no fish.

**Primary prevention studies.** Twenty-two prospective cohort studies, four case-control studies, one cross-sectional study, and one RCT<sup>17</sup> reported data on outcomes in general populations. These studies were conducted in many parts of the world including the United States, China, Japan, and countries in the Mediterranean and Northern Europe. The methodological quality of most of the studies within their study design category was good. Most of the cohorts had several thousand subjects and study duration ranged from 4 to 30 years. Most of the large cohort studies found that fish consumption reduces all-cause mortality and CVD events, although several studies reported no significant or negative results. A significant benefit for stroke was reported in only one study.<sup>18</sup> The only RCT,<sup>17</sup> which evaluated ALA in a large general population, lasted 1 year and yielded no significant results. Presumably, subjects in this study had high background omega-3 fatty acid levels because of characteristically large consumption of fish in their native lands.

For each study, outcomes in terms of CVD deaths, cardiac deaths, and myocardial infarction (MI) were similar. Most of the large cohort studies reported significant reduction of clinical events. Among the large studies, only the Physicians' Health Study<sup>19</sup> consistently reported no beneficial effect from fish consumption.

Two prospective cohort studies<sup>19,20</sup> reported data on sudden death. 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 percent overall relative risk reduction even with a small amount of fish intake (>0.3g of fish oil per month or eating fish once a month).<sup>19</sup> A smaller study also found significant reduction of arrhythmic deaths at higher levels of fish intake. However, in the same study, opposite results were observed with consumption of fried fish or fish sandwiches.<sup>20</sup> A case-control study of 827 subjects in the United States also reported a significant inverse association of sudden death with increasing fish intake.<sup>21</sup>

Nine prospective cohort studies and one case-control study provided data on stroke. Five of the cohort studies estimated the amount of fish oil consumed and eight estimated fish intake. These studies included the large U.S. cohorts of the Nurses' Health Study,<sup>22</sup> Health Professionals Study,<sup>18</sup> and the Physicians' Health Study<sup>23</sup> which followed subjects for 14, 12, and 4 years, respectively. Together, these three studies comprised a total of about 145,000 men and women. Only the Health Professionals Study reported a significant reduction of ischemic strokes with any level of fish consumption above the lowest quintile. In the Nurses' Health Study, 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 gave similar results.

Overall, the evidence from the primary and secondary prevention studies supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA, ALA), fish, and fish oil reduces all-cause mortality and various CVD outcomes such as sudden death, cardiac death (coronary or MI death), and MI, although the evidence is strongest for fish or fish oil.

**CVD question 1a.** We identified one RCT and 22 prospective cohort studies that provided data on primary prevention. Eleven RCTs and one prospective cohort study provided data on secondary prevention. These studies were summarized in previous sections.

**CVD question 1b.** CVD question 1b. concerns the efficacy or association of omega-3 fatty acids and prevention of incident CVD events in selected subpopulations. There were no subgroup data from RCTs to address differences between men and women. However, the proportion of women in RCTs was small, four cohort studies and one case-control study reported data on men and women separately. Overall, these studies found no consistent difference in the effect of omega-3 fatty acids on CVD outcomes between men and women.

A report based on 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 not for men.<sup>24</sup>

The Adventist Health Study, which grouped subjects into those who ate fish less than once a week and those who ate more, did not find a beneficial effect of fish intake on all-cause

or coronary-disease mortality. There were also no differences between men and women.<sup>25</sup> Osler et al. reported a similar finding.<sup>26</sup> However, Nagata et al. followed a cohort of 13,355 men and 15,742 women in Japan for 7 years and reported that 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, and the association between fish oil intake and all-cause mortality was significant for women (trend  $P = 0.01$ ) and non-significant for men (trend  $P = 0.38$ ).<sup>27</sup> Results from 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 ALA.<sup>28</sup> 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.<sup>29,30</sup> The Adventist Health Study found no difference in all-cause mortality between fish intake of less than or greater than once a week in a subgroup of 603 oldest old ( $\geq 84$  years old) subjects.<sup>31</sup>

**CVD question 1c.** Key question 1c. asks about the effects of potential confounders on associations found in prospective cohort studies. Because only summary data about potential confounders was available (and this data was insufficiently detailed), we were unable to analyze the effect of confounders across studies. To fully answer question 1c. would require a meta-analysis of the original data from the cohort studies.

Only one study addressed the potential confounding effect of a specific variable (i.e., aspirin treatment).<sup>32</sup> Iso et al. analyzed subgroups of women in the Nurses' Health Study who took aspirin regularly versus those who did not.<sup>30</sup> 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.

**CVD question 1d.** There is limited evidence from RCTs and cohort studies to answer question 1d. regarding the relative efficacy or association of omega-3 fatty acids on different CVD events. Because of large heterogeneity across studies and inconsistent reporting of outcomes, it is difficult to compare the magnitude of outcomes across studies. Evidence from RCTs is strongest for all-cause mortality and sudden death, while evidence from the cohort studies is strongest for all-cause mortality, cardiac mortality, MI, and stroke. All the prospective cohort studies showed a similar order; however, the effect on total mortality (assuming benefits are restricted to CVD) were 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 relative effect of omega-3 fatty acids on stroke is uncertain.

**CVD question 2a.** Question 2a. asks about the efficacy of different omega-3 fatty acids and ratios of omega-3 fatty acid components on CVD outcomes. This question is difficult to

answer since data on specific omega-3 fatty acids are very limited. The only RCT that directly compared ALA (at 2.9 g/d) with fish oil (EPA+DHA at 1.8 g/d) found that total cardiac deaths, nonfatal MI, and CVD events in the fish oil group were significantly lower compared to placebo. There were no differences in CVD outcomes between the two supplements.<sup>9</sup>

**CVD question 2b.** To determine whether the ratio of omega-6 to omega-3 fatty acid intake affects the efficacy of omega-3 fatty acid intake on CVD events, we identified two cohort studies<sup>33,34</sup> and one cross-sectional study<sup>28</sup> that reported associations between omega-3/omega-6 ratios and CVD outcomes.

Using data from the Multiple Risk Factor Intervention study, Dolecek divided omega-3/omega-6 ratios into five quintiles and reported near significant trends ( $P < 0.1$ ) 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 0.199.<sup>34</sup> 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 disease.<sup>28</sup> 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 linoleic acid (LA, 18:2 n-6) and highest tertile of ALA.

In another study, Hu et al. stratified the omega-6/omega-3 ratio into two 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 significant.<sup>29</sup>

**CVD question 2c.** Question 2c. asks how the efficacy or association of omega-3 fatty acids on CVD events differs by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, and flax seed supplement). To address this question, we needed to compare the efficacy of different sources of omega-3 fatty acids; however, 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, fish oil is more efficacious than ALA. In the Nurses' Health Study, Hu 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 only.<sup>35</sup> Results for fatal ischemic heart disease outcomes were similar for the two ALA estimates.

**CVD question 2d.** 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.

**CVD question 2e.** Question 2e. asks whether there is a threshold or dose-response relationship between omega-3 fatty acids and CVD events. To answer this question we identified several RCTs that reported beneficial effects from fish oil at a relatively low daily dose. The GISSI-Prevention trial used a fish oil (EPA+DHA) dose of 0.85 g/d and reported significant beneficial effects on CVD outcomes. Leng et al. showed that no beneficial effect was observed with a daily EPA dosage of 0.27 g/d in a 2-year trial involving 120 CVD patients.<sup>7</sup> Nilsen et al. used 1.7 g/d EPA+DHA which showed no effects on CVD outcomes.<sup>6</sup> Two ALA diet trials<sup>11,12</sup> which estimated a daily ALA intake of 1.8 or 1.9 g/d, reported significant or near-significant beneficial effects on CVD outcomes compared with control diets with estimated ALA intakes of 0.67 or 0.8 g/d, respectively.

**CVD question 2f.** To address this question about how the duration of intervention or exposure affects the treatment effect of omega-3 fatty acids on CVD events, we examined the duration of the RCTs in the CVD population and found that it ranged from 1.5 to 5 years. The largest RCT (13,000 subjects), which had a 1-year duration in the non-CVD population, found no effect on any of the CVD outcomes.<sup>17</sup> 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 for clinical effects. The Physicians' Health Study reported no significant effect on CVD outcomes after 4 years of followup.<sup>23</sup>

**CVD question 2g.** Only one study,<sup>36</sup> which is the 10-year followup to the Diet and Reinfarction (DART) study, addressed the question of whether treatment effects of omega-3 fatty acids on CVD events were sustained after the intervention stopped. This study showed no long-term benefit from being in the fish advice group in the DART study.

**CVD question 2h.** Question 2h. asks about the effect or association of baseline dietary intake of omega-3 fatty acid supplements on CVD events. We found only a few dietary RCTs that provide some information about the benefits of adding omega-3 fatty acids to baseline intake. Two ALA diet trials,<sup>11,12</sup> each of 2-years duration, estimated daily ALA intake at 1.8 or 1.9 g/d and reported significant or near-significant beneficial effects on multiple CVD outcomes compared to control diets with an estimated ALA intake of 0.67 or 0.8 g/d. 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 interventional group (2.4 g/week).<sup>37,38</sup>

**CVD question 2i.** None of the RCTs were specifically designed to determine whether the addition of CVD risk factor

medications (lipid lowering agents or diabetes medications) affects the efficacy of omega-3 fatty acids. Similarly, none of the cohort studies specifically adjusted for CVD risk factor medications.

## Adverse Events Associated With Omega-3 Fatty Acid Consumption

We reviewed 395 human clinical articles for reports of adverse events associated with omega-3 fatty acid consumption. We rejected 247 articles because they did not provide adverse event information and two additional articles that were duplicate publications. Of the remaining 148 articles in the general and CVD populations, a variety of adverse events were reported in 71 studies, but 77 RCTs and non-randomized comparison studies reported no adverse events.

One hundred and forty-two articles provided data on about 20,000 subjects, about one-half of whom were exposed to different forms and dosages of omega-3 fatty acid 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-Prevention trial, that had over 11,000 subjects and a followup duration of 182 weeks, reported the largest number of adverse events.<sup>5</sup> This trial contributed about one-third of the total number of gastrointestinal complaints (in both the omega-3 fatty acid arm and the control arm) from all the studies combined, and also contributed almost all the withdrawals due to adverse events (although the reasons for withdrawals were not given). This discordance suggests that most other studies did not adequately report adverse event data, especially concerning withdrawals.

None of the serious adverse events that were reported associated omega-3 fatty acid consumption with events such as death, life-threatening illness, or significant disability or handicap, although two studies reported that some important bleeding occurred with fish oil combined with aspirin or warfarin.<sup>39,40</sup>

## Discussion

Overall, a number of studies offer evidence to support the hypothesis that fish, fish oil, or ALA supplement consumption reduces all-cause mortality and various CVD outcomes, although the evidence is strongest for fish or fish oil.

The overall methodological quality of the studies included in this evidence review was graded as good for fish oil (EPA+DHA), but RCT data for ALA was poor. The adverse events due to fish oil or ALA supplement consumption appear to be minor.

However, there is an imbalance in the design of studies available. Almost all of the evidence for health benefits of



omega-3 fatty acid in the general population (primary prevention studies) derives from cohort studies, whereas almost all the evidence, however limited, for secondary prevention derives from RCTs. The data for secondary prevention mostly derives from one very large study, and data on women are limited. The specific effects on different CVD outcomes (especially MI and stroke) are uncertain.

In addition, the studies were heterogeneous with regard to the methods of estimating fish or omega-3 fatty acid intake, background diets, background risk for heart disease, settings, and the methods of reporting results. For these reasons, the validity of applying the results of studies conducted in countries outside of the United States to the U.S. population is uncertain. Moreover, dietary intervention trials, such as DART,<sup>38</sup> the Lyon Heart,<sup>11</sup> and the Indian Experiment of Infarct Survival,<sup>12</sup> are limited by multiple and complex dietary changes in the trials that do not permit easy differentiation among components and make it difficult to determine which specific components or combinations of these diets are most beneficial. Furthermore, the optimal quantity and type of omega-3 fatty acid, and the optimal ratio of omega-3 to omega-6 fatty acid, if any, still remain undefined. Finally, different types of fish and the method of food preparation may cause different effects.

Therefore, future research needs to address all these lingering issues. Well-designed multinational trials that assess the effect of EPA+DHA on CVD outcomes during a long followup period are especially needed. RCTs should be performed in the general population since there is still a gap in information about the general versus CVD population. They should not only confirm the pharmacological approach of the GISSI-Prevention trial in countries with different background habits and risk, but should also explore in parallel the various mechanistic hypotheses. In addition, studies must adequately assess background diet and fish consumption, particularly the type of fish and method of preparation. Attempts should always 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). In addition, the omega-3/omega-6 ratio should always be estimated and reported.

The potential effect of ALA is unknown. Current data sets are too limited for adequate assessment. To address this issue, a cardioprotective diet rich in ALA should be included in a comprehensive strategy to decrease cardiovascular morbidity and mortality, and more trials are needed to confirm the effect of ALA, independent of fish oil and fish intake, on the secondary prevention of CVD outcomes. The relative effect of ALA versus fish oil is also unknown and should be explored in the future studies.

The relative effect of ALA versus fish oil is not well defined. Comparative trials between these two 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 changes in the U.S. dietary patterns.

Our evidence review also indicates that there is little data concerning the needs of different high-risk subpopulations. Additional research should address questions about the effect of omega-3 fatty acid on CVD outcomes in specific populations, including people at high risk of sudden death or with diabetes, congestive heart failure, or other chronic diseases.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Tufts-New England Medical Center Evidence-based Practice Center, Boston, MA, under Contract No. 290-02-0022. The full report is expected to be available in March 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 94, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at [www.ahrq.gov](http://www.ahrq.gov).

## Suggested Citation

Wang C, Chung M, Lichtenstein A, Balk E, Kupelnick B, DeVine D, Lawrence A, Lau J. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Summary, Evidence Report/Technology Assessment No. 94. (Prepared by the Tufts-New England Medical Center Evidence-based Practice Center, Boston, MA.) AHRQ Publication No. 04-E009-1. Rockville, MD: Agency for Healthcare Research and Quality. March 2004.

## References

1. Dyerberg J, Bang HO, Stoffersen E, et al. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 1978; 2(8081):117-119.
2. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. *Am J Clin Nutr* 1980; 33(12):2657-2661.
3. NHANES III Series 11, No.2A, April 1998. Electrocardiogram, Dietary Recall, Laboratory, Dietary Supplement and Prescription Drug. Available online at <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>. Accessed August 2003. National Center for Health Statistics. 1998.
4. NHANES III Series 11, No 3A, July 1999. Second Exam files for Dietary Recall, Examination, Laboratory, Additional Laboratory Analyses. Available online at <http://www.cdc.gov.nchs/about/major/nhanes/nh3data.htm>. Accessed August 2003. National Center for Health Statistics. 1999.
5. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio

- della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione [see comments]. *Circulation* 2002; 105(16):1897-1903.
6. Nilsen DW, Albrektsen G, Landmark K, et al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001; 74(1):50-56.
  7. Leng GC, Lee AJ, Fowkes FG, et al. Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease. *Clin Nutr* 1998; 17(6):265-271.
  8. Sacks FM, Stone PH, Gibson CM, et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *J Am Coll Cardiol* 1995; 25(7):1492-1498.
  9. Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival—4. *Cardiovasc Drugs Ther* 1997; 11(3):485-491.
  10. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Medica Scandinavica—Supplementum* 1966; 466:1-92.
  11. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study [see comments]. *Circulation* 1999; 99(6):779-785.
  12. Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 2002; 360(9344):1455-1461.
  13. Bemelmans WJ, Broer J, Feskens EJ, et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean Alpha-linolenic Enriched Groningen Dietary Intervention (MARGARIN) study. *Am J Clin Nutr* 2002; 75(2):221-227.
  14. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Medica Scandinavica—Supplementum* 1966; 466:1-92.
  15. Burr ML, Ashfield-Watt PAL, Dunstan FDJ, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003; 57(2):193-200.
  16. Erkkila AT, Lehto S, Pyorala K, et al. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease [comment]. *Am J Clin Nutr* 2003; 78(1):65-71.
  17. Natvig H, Borchgrevink CF, Dedichen J, et al. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. *Scandinavian Journal of Clinical & Laboratory Investigation—Supplement* 1968; 105:1-20.
  18. He K, Rimm EB, Merchant A, et al. Fish consumption and risk of stroke in men. *JAMA* 2002; 288(24):3130-3136.
  19. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998; 279(1):23-28.
  20. Mozaffarian DLR. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: The Cardiovascular Health Study. *Circulation* 2003; 107(10):1372-1377.
  21. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995; 274(17):1363-1367.
  22. Iso H, Rexrode KM, Stampfer MJ, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001; 285(3):304-312.
  23. Morris MC, Manson JE, Rosner B, et al. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *Am J Epidemiol* 1995; 142(2):166-175.
  24. Gillum RF, Mussolino ME, Madans JH. The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey). *Arch Intern Med* 1996; 156(5):537-542.
  25. Fraser GE, Strahan TM, Sabate J, et al. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. *Circulation* 1992; 86(2):406-413.
  26. Osler M, Andreasen AH, Hoidrup S. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *J Clin Epidemiol* 2003; 56(3):274-279.
  27. Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. *Am J Epidemiol* 2002; 156(9):824-831.
  28. Djousse L, Pankow JS, Eckfeldt JH, et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr* 2001; 74(5):612-619.
  29. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002; 287(14):1815-1821.
  30. Iso H, Stampfer MJ, Manson JE et al. Prospective study of fat and protein intake and risk of intraparenchymal hemorrhage in women. *Circulation* 2001; 103(6):856-863.
  31. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Arch Intern Med* 1997; 157(19):2249-2258.
  32. Iso H, Sato S, Umemura U, et al. Linoleic acid, other fatty acids, and the risk of stroke. *Stroke* 2002; 33(8):2086-2093.
  33. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002; 288(20):2569-2578.
  34. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. *Proceedings of the Society for Experimental Biology & Medicine* 1992; 200(2):177-182.
  35. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 1999; 69(5):890-897.
  36. Ness AR, Hughes J, Elwood PC, et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the diet and reinfarction trial (DART). *Eur J Clin Nutr* 2002; 56(6):512-518.
  37. Burr ML, Fehily AM, Rogers S, et al. Diet and reinfarction trial (DART): design, recruitment, and compliance. *Eur Heart J* 1989; 10(6):558-567.
  38. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fiber intakes on death and myocardial reinfarction: diet and reinfarction trial (DART) [see comments]. *Lancet* 1989; 2(8666):757-761.
  39. Eritsland J. Safety considerations of polyunsaturated fatty acids. *Am J Clin Nutr* 2000; 71(1 suppl.):197S-201S.
  40. Reis GJ, Boucher TM, Sipperly ME, et al. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. *Lancet* 1989; 2(8656):177-181.



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AHRQ Pub. No. 04-E009-1  
March 2004

ISSN 1530-440X

# Chapter 1. Introduction

This evidence report is 1 of 3 reports prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the health benefits of omega-3 fatty acids on cardiovascular diseases. These reports are among several that address topics related to omega-3 fatty acids, and that were requested by the Office of Dietary Supplements, National Institutes of Health, through the EPC Program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs — the Tufts-NEMC EPC, the Southern California-RAND EPC, and the University of Ottawa EPC — each produced evidence reports. To ensure consistency of approach, the 3 EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of the reports is to summarize the current evidence on the health effects of omega-3 fatty acids on the following: CVD, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, autoimmune diseases, immune-mediated diseases, transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

The focus of this report is on CVD outcomes in humans. The other 2 reports by the Tufts-NEMC EPC focus on risk factors of cardiovascular disease and on arrhythmic electrophysiology in animal and in-vitro studies. In this chapter, the metabolism, physiological functions, and the sources of omega-3 fatty acids are briefly discussed. Subsequent chapters describe the methods used to identify and review studies related to omega-3 fatty acids and CVD — including the analytic framework for this report, findings related to the effects of omega-3 fatty acids on cardiovascular conditions, and recommendations for future research in this area.

## Background

### Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. Dietary fat encompasses saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. Unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Polyunsaturated fatty acids (PUFAs) can be classified on the basis of their chemical structure into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The *omega-3* or *n-3* notation means that the first double bond from the methyl end of the molecule is in the third. The same principle applies to the *omega-6* or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (9 kcal/g or 37 kJ/g).

Of all fats found in food, 2 — alpha-linolenic acid (chemical abbreviation: ALA, 18:3 n-3) and linoleic acid (LA, 18:2 n-6) — cannot be synthesized in the human body, yet are necessary for proper physiological functioning. These 2 fats are called essential fatty acids. The essential fatty acids can be converted in the liver to long-chain polyunsaturated fatty acids (LC PUFAs),

which have a higher number of carbon atoms and double bonds. These LC PUFAs retain the omega type (n-3 or n-6) of the parent essential fatty acids.

ALA and LA comprise the bulk of the total PUFAs consumed in a typical North American diet. Typically, LA comprises 89% of the total PUFAs consumed, while ALA comprises 9%. Smaller amounts of other PUFAs make up the remainder <sup>1</sup>. Both ALA and LA are present in a variety of foods. For example, LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA, which is consumed in smaller quantities, is present in leafy green vegetables and in some commonly used oils, including canola and soybean oil. Some novelty oils, such as flaxseed oil, contain relatively high concentrations of ALA, but these oils are not commonly found in the food supply.

The Institute of Medicine suggests that, for adults 19 and older, an adequate intake (AI) of ALA is 1.1-1.6 g/day, while an adequate daily intake of LA is 11-17 g/day <sup>2</sup>. Recommendations regarding AI differ by age and gender groups, and for special conditions such as pregnancy and lactation.

As shown in Figure 1.1, EPA and DHA can act as competitors for the same metabolic pathways as AA. In human studies, the analyses of fatty-acid compositions in both blood phospholipids and adipose tissue showed similar competitive relationship between omega-3 LC PUFAs and AA. General scientific agreement supports an increased consumption of omega-3 fatty acids and reduced intake of omega-6 fatty acids to promote good health. However, for omega-3 fatty acid intakes, the specific quantitative recommendations vary widely among countries not only in terms of different units - ratio, gram, total energy intake - but also in quantity <sup>3</sup>. Furthermore, there remain numerous questions relating to the inherent complexities about omega-3 and omega-6 fatty acid metabolism, in particular regarding the inter-relationships between the 2 fatty acids. For example, it remains unclear to what extent ALA is converted to EPA and DHA in humans, and to what extent high intake of omega-6 fatty acids compromises any benefits of omega-3 fatty acid consumption. Without resolution of these 2 foundational questions, it remains difficult to study the importance of omega-6 to omega-3 fatty acid ratio.

## Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids share the same pools of enzymes and go through the same oxidation pathways while being metabolized (Figure 1.1). Once ingested, ALA and LA can be elongated and desaturated into LC PUFAs. LA is converted into gamma-linolenic acid (GLA, 18:3 n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the long-chain omega-6 fatty acid, arachidonic acid (AA, 20:4 n-6). ALA can be converted, to a lesser extent, to the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3). However, the conversion from parent fatty acids into LC PUFAs occurs slowly in humans, and conversion rates are not well understood. Because of the slow rate of conversion and the importance of LC PUFAs to many physiological processes, humans must augment their level of LC PUFAs by consuming foods that are rich in these important compounds. Meat is the primary food source of AA, while fish is the primary food source of EPA.

The specific biological functions of fatty acids depend on the number and position of double bonds and the length of the acyl chain. Both EPA and AA are 20-carbon fatty acids and are precursors for the formation of prostaglandins, thromboxane, and leukotrienes — hormone-like

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 <sup>4</sup>.

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 <sup>4</sup>. 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 mechanisms<sup>5</sup>. Arrhythmias are thought to be the cause of “sudden death” in heart disease.

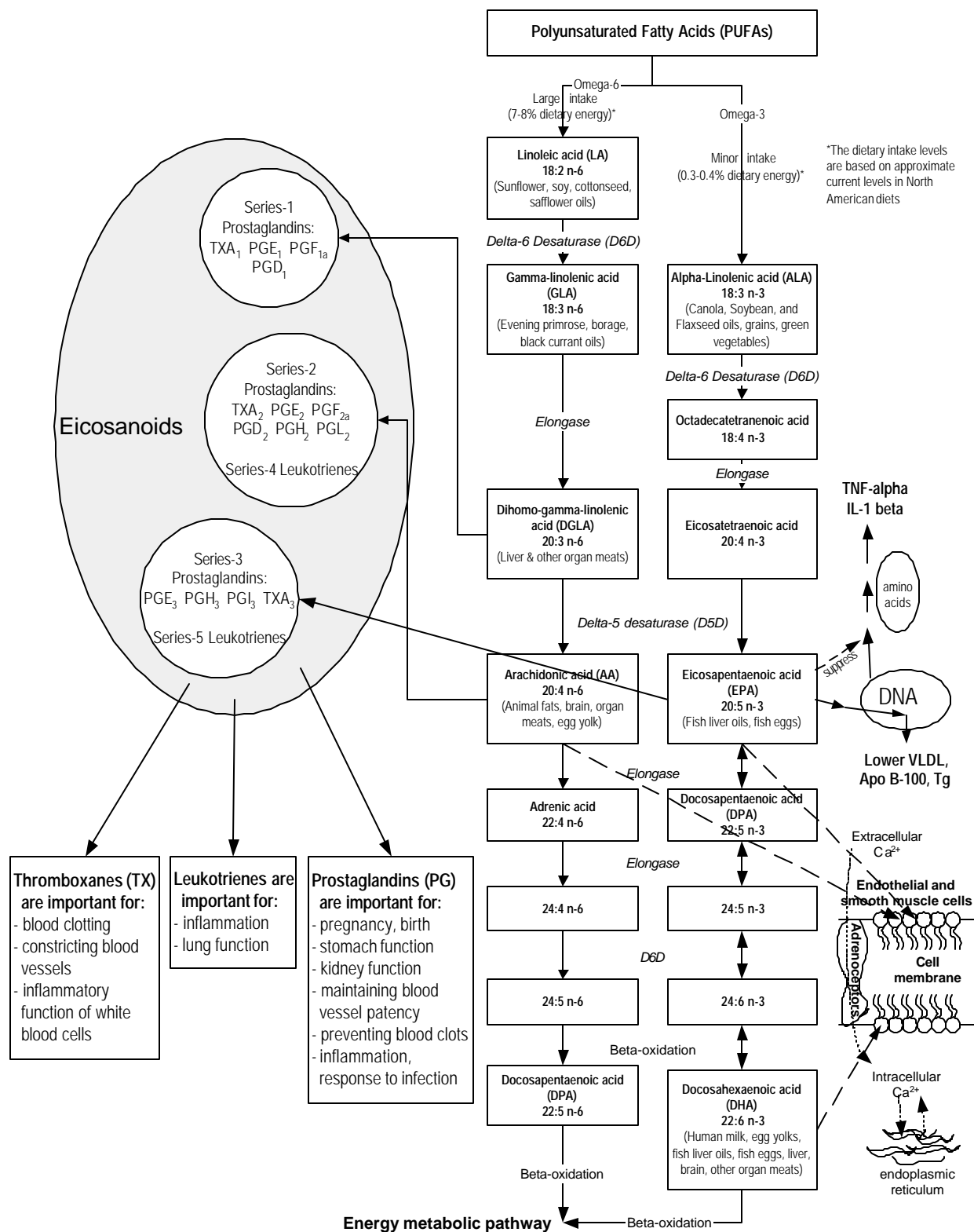
In addition to affecting eicosanoid production as described above, EPA also affects lipoprotein metabolism and decreases the production of other compounds — including cytokines, interleukin 1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) —that have pro-inflammatory effects. 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 <sup>6</sup>. 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 <sup>7</sup>. 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 <sup>8</sup>.

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  $\geq 2$  months. Mexican Americans and non-Hispanic African-Americans, children  $\geq 5$  years old, and adults  $\geq 60$  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-hours 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<sup>9</sup>. 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<sup>2</sup>.

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

<sup>a</sup> The distributions are not adjusted for the over-sampling of Mexican Americans, non-Hispanic African-Americans, children  $\geq 5$  years old, and adults  $\geq 60$  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>	
	<b>Mean±SEM</b>	<b>Median±SEM</b>
<b>LA (18:2 n-6)</b>	13.0±0.1	12.0±0.1
<b>Total n-3 FA</b>	1.40±0.01	1.30±0.01
<b>ALA (18:3 n-3)</b>	1.30±0.01	1.21±0.01
<b>EPA (20:5 n-3)</b>	0.028	0.004
<b>DPA (22:5 n-3)</b>	0.013	0.005
<b>DHA (22:6 n-3)</b>	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)

10.

**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
<b>Fish (Raw <sup>a</sup>)</b>				<b>Fish, continued</b>			
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 <sup>e</sup>	trace	0.1	trace
Bass, Striped	0.2	0.6	trace	Tuna, Light, Canned in Water <sup>e</sup>	trace	0.2	trace
Bluefish	0.2	0.5	-	Tuna, White, Canned in Oil <sup>e</sup>	trace	0.2	0.2
Carp	0.2	0.1	0.3	Tuna, White, Canned in Water <sup>e</sup>	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	<b>Shellfish (Raw)</b>			
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	-	<b>Fish Oils</b>			
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 <sup>b</sup>	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	<b>Nuts and Seeds</b>			
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 <sup>c</sup>	0.9	0.8	trace	Walnuts, English	-	-	9.1
Salmon, Sockeye	0.6	0.7	trace				
Sardine, Atlantic, Canned in Oil <sup>d</sup>	0.5	0.5	0.5	<b>Plant Oils</b>			
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<sup>11,12</sup>, 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 levels<sup>12</sup>. Similar results were found among inhabitants of Greenland and Denmark who were followed for over 25 years<sup>13</sup>.

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 atherosclerosis<sup>14</sup>. 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 CVD<sup>13</sup>. 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 diseases<sup>15</sup>. 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 day<sup>16</sup>. Two other cohort studies carried out in Hawaii and Norway also found no relationship between fish consumption and CVD<sup>17,18</sup>.

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 <sup>19,20</sup>.

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) <sup>21</sup>. The framework graphically presents the key components of well-formulated study questions:

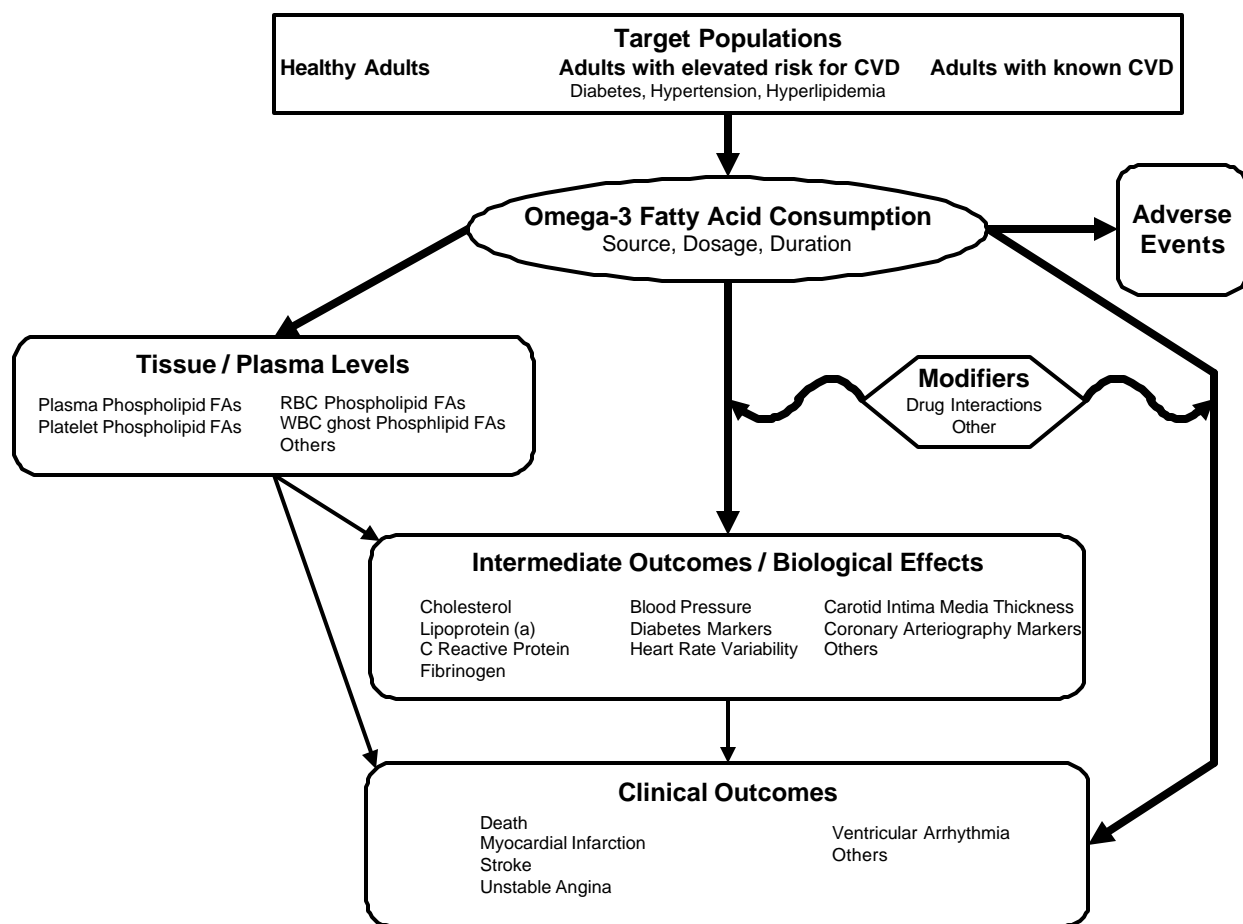
- 1) Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
- 2) What are the interventions?
- 3) What are the outcomes of interest (intermediate and health outcomes)?



#### 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 population<sup>22</sup>. 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 monitoring<sup>9</sup> 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 large<sup>23</sup>. 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 3<sup>rd</sup> 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 Statistics <sup>2</sup>. 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 IOM <sup>2</sup>. 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 = 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 supplements<sup>24</sup> 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 size<sup>25</sup>. 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<sup>26,27</sup>. 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 arbitrary<sup>28</sup>.

The Jadad Score assesses the quality of RCTs using 3 criteria: adequacy of randomization, double blinding, and dropouts<sup>26</sup>. 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 al<sup>27</sup>.

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 practice<sup>29</sup>. 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 = 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  $1.33 \pm 0.02$ ,  $0.04 \pm 0.003$ ,  $0.07 \pm 0.004$ , and  $14.13 \pm 0.20$  grams per day, respectively. These estimates were equivalent to  $0.55 \pm 0.004$ ,  $0.02 \pm 0.001$ ,  $0.03 \pm 0.002$ , and  $5.79 \pm 0.05$  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 ( $-0.02 \pm 0.01$  %kcal/day) and LA ( $-0.28 \pm 0.07$  %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  $0.04 \pm 0.01$  to  $0.09 \pm 0.01$  (%kcal/day) for ALA, and from  $0.43 \pm 0.14$  to  $0.61 \pm 0.15$  (%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 ( $-0.04 \pm 0.01$  %kcal/day) and LA ( $-0.28 \pm 0.06$  %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 ( $-0.02 \pm 0.01$  %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 ( $0.54 \pm 0.01$  vs  $0.57 \pm 0.01$  %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 population<sup>30</sup>. 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)<sup>31</sup>. 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/day<sup>32</sup>. An increased trend in per capita fish and shellfish consumption (62-88 g/capita/day) was found in Spain between 1964 and 1991<sup>33</sup>.

**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<sup>§</sup>**

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 <sup>¶</sup>	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
<b>All individuals</b>	<b>29,099</b>	<b>238,221,947</b>	<b>14.13</b>	<b>5.79</b>	<b>21,159</b>	<b>13.00</b>
<b>SEM</b>			<b>0.20</b>	<b>0.05</b>		<b>0.10</b>

<sup>§</sup> All NHANES III variance estimates were based on Taylor Series (WR) method.

<sup>¶</sup> 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
<b>Both Sexes, Total</b>	<b>10,634</b>	<b>14.27</b>	<b>0.24</b>	<b>8,510</b>	<b>14.23</b>	<b>0.20</b>	<b>8,626</b>	<b>14.07</b>	<b>0.20</b>	<b>1,329</b>	<b>12.77</b>	<b>0.48</b>
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
<b>M, Total</b>	<b>5,028</b>	<b>16.70</b>	<b>0.34</b>	<b>4,001</b>	<b>15.87</b>	<b>0.25</b>	<b>4,264</b>	<b>15.84</b>	<b>0.25</b>	<b>628</b>	<b>14.40</b>	<b>0.66</b>
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
<b>F, Total</b>	<b>5,606</b>	<b>11.96</b>	<b>0.19</b>	<b>4,509</b>	<b>12.82</b>	<b>0.21</b>	<b>4,362</b>	<b>12.20</b>	<b>0.21</b>	<b>701</b>	<b>11.23</b>	<b>0.61</b>
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
<b>All individuals</b>	<b>29,099</b>	<b>238,221,947</b>	<b>1.33</b>	<b>0.55</b>	<b>21,159</b>	<b>1.30</b>
<b>SEM</b>			<b>0.02</b>	<b>0.004</b>		<b>0.01</b>

§ 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 3.5. 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
<b>Both Sexes, Total</b>	<b>10,634</b>	<b>1.37</b>	<b>0.02</b>	<b>8,510</b>	<b>1.27</b>	<b>0.02</b>	<b>8,626</b>	<b>1.20</b>	<b>0.02</b>	<b>1,329</b>	<b>1.12</b>	<b>0.04</b>
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
<b>M, Total</b>	<b>5,028</b>	<b>1.60</b>	<b>0.03</b>	<b>4,001</b>	<b>1.43</b>	<b>0.02</b>	<b>4,264</b>	<b>1.36</b>	<b>0.02</b>	<b>628</b>	<b>1.29</b>	<b>0.06</b>
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
<b>F, Total</b>	<b>5,606</b>	<b>1.15</b>	<b>0.02</b>	<b>4,509</b>	<b>1.14</b>	<b>0.02</b>	<b>4,326</b>	<b>1.05</b>	<b>0.02</b>	<b>701</b>	<b>0.97</b>	<b>0.04</b>
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 0.002	0.010 0.002	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 0.005	†	854	0.030
M, 31-50 y SEM	2,579	35,368,777	0.060 0.007	0.02 0.003	1,684	0.038
M, 51-70 y SEM	1,934	18,623,500	0.050 0.005	0.02 0.002	1,606	0.046
M, 71+ y SEM	1,296	6,723,233	0.050 0.006	0.02 0.003	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 0.003	†	436	0.016
F, 19-30 y SEM	2,181	22,809,351	0.030 0.005	0.01 0.002	760	0.024
F, 31-50 y SEM	3,097	37,172,408	0.040 0.005	0.01 0.002	1,614	0.027
F, 51-70 y SEM	2,075	20,961,630	0.040 0.005	0.03 0.003	1,539	0.035
F, 71+ y SEM	1,421	9,687,597	0.030 0.006	†	623	0.029
<b>All individuals SEM</b>	<b>29,099</b>	<b>238,221,947</b>	<b>0.040 0.003</b>	<b>0.02 0.001</b>	<b>20,108</b>	<b>0.03</b>

§ 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
<b>Both Sexes, Total</b>	<b>10,634</b>	<b>0.03</b>	<b>0.003</b>	<b>8,510</b>	<b>0.05</b>	<b>0.002</b>	<b>8,626</b>	<b>0.02</b>	<b>0.003</b>	<b>1,329</b>	<b>0.06</b>	<b>0.012</b>
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	†	
<b>M, Total</b>	<b>5,028</b>	<b>0.04</b>	<b>0.004</b>	<b>4,001</b>	<b>0.05</b>	<b>0.005</b>	<b>4,264</b>	<b>0.03</b>	<b>0.004</b>	<b>628</b>	<b>0.06</b>	<b>0.010</b>
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	†	
<b>F, Total</b>	<b>5,606</b>	<b>0.03</b>	<b>0.003</b>	<b>4,509</b>	<b>0.04</b>	<b>0.002</b>	<b>4,362</b>	<b>0.02</b>	<b>0.003</b>	<b>701</b>	<b>†</b>	
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
<b>All individuals SEM</b>	<b>29,099</b>	<b>238,221,947</b>	<b>0.070 0.004</b>	<b>0.03 0.002</b>	<b>21,159</b>	<b>0.057 0.018</b>

§ 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 UNIVARIATE, 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
<b>Both Sexes, Total</b>	<b>10,634</b>	<b>0.07</b>	<b>0.005</b>	<b>8,510</b>	<b>0.09</b>	<b>0.004</b>	<b>8,626</b>	<b>0.05</b>	<b>0.003</b>	<b>1,329</b>	<b>0.10</b>	<b>0.015</b>
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	†	
<b>M, Total</b>	<b>5,028</b>	<b>0.08</b>	<b>0.006</b>	<b>4,001</b>	<b>0.11</b>	<b>0.008</b>	<b>4,264</b>	<b>0.06</b>	<b>0.004</b>	<b>628</b>	<b>0.10</b>	<b>0.012</b>
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+ y	892	0.08	0.009	201	†		173	0.06	0.016	30	†	
<b>F, Total</b>	<b>5,606</b>	<b>0.05</b>	<b>0.005</b>	<b>4,509</b>	<b>0.07</b>	<b>0.003</b>	<b>4,326</b>	<b>0.04</b>	<b>0.004</b>	<b>701</b>	<b>†</b>	
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+ y	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
Male	13,923	115,778,180		16.36	0.2841
Female	15,182	122,467,717		12.02	0.1618
ALA (18:3 n-3) (g/d) †					
Total	29,105	238,245,897		1.33	0.0154
Male	13,923	115,778,180		1.54	0.0233
Female	15,182	122,467,717		1.13	0.0134
¶ EPA (20:5 n-3) (g/d)					
Total	29,105	238,245,897		0.04	0.0026
Male	13,923	115,778,180		0.04	0.0032
Female	15,182	122,467,717		0.03	0.0031
¶ DHA (22:6 n-3) (g/d)					
Total	29,105	238,245,897		0.07	0.0044
Male	13,923	115,778,180		0.08	0.0050
Female	15,182	122,467,717		0.06	0.0051
LA (18:2 n-6) (%kcal/d) †					
Total	29,103	238,242,673		5.79	0.0458
Male	13,922	115,776,672		5.65	0.0526
Female	15,181	122,466,001		5.93	0.0606
ALA (18:3 n-3) (%kcal/d) †					
Total	29,103	238,242,673		0.55	0.0041
Male	13,922	115,776,672		0.54	0.0047
Female	15,181	122,466,001		0.56	0.0054
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673		0.02	0.0011
Male	13,922	115,776,672		0.02	0.0011
Female	15,181	122,466,001		0.02	0.0014
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673		0.03	0.0019
Male	13,922	115,776,672		0.03	0.0020
Female	15,181	122,466,001		0.03	0.0023

†  $P < .001$  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
* Non-Hispanic white	10,634	174,119,805		5.79	0.0579
† Non-Hispanic black	8,512	29,353,940		5.98	0.0592
† Mexican-American	8,626	14,877,359		5.93	0.0476
Other	1,331	19,891,569		5.37	0.1279
ALA (18:3 n-3) (%kcal/d)					
Total	29,103	238,242,673		0.55	0.0041
† Non-Hispanic white	10,634	174,119,805		0.56	0.0054
† Non-Hispanic black	8,512	29,353,940		0.54	0.0051
† Mexican-American	8,626	14,877,359		0.52	0.0063
Other	1,331	19,891,569		0.48	0.0106
¶ EPA (20:5 n-3) (%kcal/d)					
Total	29,103	238,242,673		0.02	0.0011
Non-Hispanic white	10,634	174,119,805		0.01	0.0010
Non-Hispanic black	8,512	29,353,940		0.02	0.0009
Mexican-American	8,626	14,877,359		0.01	0.0009
Other	1,331	19,891,569		0.03	0.0057
¶ DHA (22:6 n-3) (%kcal/d)					
Total	29,103	238,242,673		0.03	0.0019
Non-Hispanic white	10,634	174,119,805		0.03	0.0019
Non-Hispanic black	8,512	29,353,940		0.04	0.0016
Mexican-American	8,626	14,877,359		0.02	0.0013
Other	1,331	19,891,569		0.05	0.0079

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	Population	Mean	Design	Effect
	Size	Size		SEM	
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)<sup>\*</sup>, 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

<sup>\*</sup> 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
<b>Total</b>	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
<b>Non-Hispanic White</b>				
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
<b>Non-Hispanic Black</b>				
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
<b>Mexican-American</b>				
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
<b>Other</b>				
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) <sup>§</sup>**

	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

<sup>§</sup> 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)<sup>34-37</sup>. 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)<sup>38</sup>.

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<sup>35,39</sup>. 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 placebo<sup>38</sup>. 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	Quality			
														Alloc. conceal.	Jadad score		Summary
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 <sup>1</sup> 0.66-0.93	6.5	0.70 <sup>1</sup> 0.56-0.86	5.4	0.65 <sup>1</sup> 0.51-0.82	2.7	0.55 <sup>1</sup> 0.39-0.77	B 3	A	CVD I
	Nilssen 2001 Norway	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
1998	Leng 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

<sup>1</sup> 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	Jadad 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 <sup>1</sup> 0.53-0.88	4.1	0.91 <sup>1</sup> 0.70-1.2	1.4	1.2 <sup>1</sup> 0.81- 1.9	11	0.80 <sup>1</sup> 0.68-0.94	B 3	A		CVD I
		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
		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 <sup>2</sup> 0.43- 1.7	A 5	A		CVD II
		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

<sup>1</sup> RR adjusted for main confounders as reported in article. <sup>2</sup> 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			RR	95% CI	Control group event rate (%)	RR	95% CI	Control group event rate (%)	RR	95% CI	Summary	Jadad score	Alloc. conceal.	
<b>EPA estimate</b>																		
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
<b>ALA estimate</b>																		
Singh 2002 India	499	Indo Mediterranean diet <sup>1</sup> 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 <sup>1</sup> ALA 1-1.9 g/d (soybean oil)	406	Usual diet	5	27	0.75 0.52-1.06	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 <sup>1</sup> ALA 1.9 g/d	303	Prudent diet <sup>2</sup> ALA 0.67 g/d	2.3	7.9	0.44 <sup>3</sup> 0.21-0.94	nd	6.3	0.35 <sup>3</sup> 0.15-0.83	2.6	0.06 0.003-1.02	C 4	A				CVD II
Beemelmans 2002 Netherlands	109	ALA 6.3 g/d	157	ALA 1.0 g/d	2	0.6	4.3 0.46-41	1.44 0.09-23	-	nd	-	nd	B 3	A				CVD I

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

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

<sup>3</sup> 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
						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.	
	N	Estimated omega-3 fatty acid intake	N	Estimated omega-3 fatty acid intake													
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	1	U	CVD III
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	1	U	CVD III
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	3	U	CVD II
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	2	I	CVD II
DeLorgeril 1999 France	302	Cretan Mediterranean diet <sup>1</sup> ALA 1.9 g/d	303	Prudent diet <sup>2</sup> 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 <sup>3</sup> 0.38-0.74	C 4	4	A	CVD III
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	3	A	CVD I

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

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

<sup>3</sup> Total 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 <sup>40,41</sup>. 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<sup>42 43-45</sup>). 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 <sup>45</sup>. The amount of margarine prescribed was not fixed, but instead was based on the participants' usual consumption patterns. The study by <sup>44</sup> 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 study<sup>46</sup> (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, 4<sup>34-37</sup> 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 study<sup>35</sup> 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<sup>41,47</sup> were both of poor quality (Grade C). In the first trial<sup>47</sup>, 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%<sup>47</sup>. 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 EPA<sup>48</sup>.

Of the 4 diet/dietary advice trials that provided estimates of ALA consumption<sup>42,43,44,45</sup>, 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 intake<sup>46</sup>.

**Sudden death.** (Tables 3.20, 3.22, 3.25). Six RCTs reported data on sudden deaths Four studies<sup>35 38,43,44</sup> 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 study<sup>43</sup> and 2 Indian studies<sup>38,44</sup>) were poorly designed (grade C).

An early trial by Leren<sup>42</sup> 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 al<sup>41</sup> 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<sup>34,35,37</sup> 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<sup>43 44,45</sup> (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)<sup>36</sup>. 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<sup>34,37</sup>, or had too few CVD events<sup>45</sup> 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	Control group event rate (%)	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 <sup>1</sup>	Trend P-value <sup>2</sup>	Overall effect	Quality	Applicability
				Estimated omega-3 fatty acid consumption Relative risk (unless stated otherwise)				
Nagata 2002 Japan	29079	7	FFQ	EPA+DHA 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*	NS 0.01	++	A	GEN II
Yuan 2001 China	18244	12	FFQ	EPA+DHA 0.15 0.38 0.65 0.91 1.7 g/wk 1.0 0.79* 0.76* 0.86* 0.79*	0.01	++	A	GEN II
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA 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	0.014 0.01	++	A	GEN II

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

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

<sup>2</sup> 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 46 68 87 112 158 g/d Hazard ratio 1.0 0.92 0.91 0.90 0.94 Women 37 54 69 88 122 g/d Hazard ratio 1.0 0.93 0.96 0.93 0.86	NS	0	A	GEN II
Albert 1998 US PHS	20551	12	FFQ	<1/mo 1-3/mo 1-2/wk 2-5/wk =5/wk 1.0 0.79 0.71* 0.70* 0.73*	0.045	++	A	GEN II
Yuan 2001 China	18244	12	FFQ	<50 50-100 100-150 150-200 =200 g/wk 1.0 0.79* 0.76* 0.86* 0.79*	0.01	++	A	GEN II
Mann 1997 UK	10802	13.3	FFQ	Death rate ratio 0 <1 =1/wk 100 97 96	NS	0	B	GEN II
Gillum 2000 US NHANES	8825	18.8	FFQ + 24-hr recall	Never <1 1 >1/wk White Men 1.0 0.88 0.76* 0.85 Black Men 1.0 1.0 1.0 1.1 White Women 1.0 1.0 1.0 0.90 Black Women 1.0 0.77 0.79 0.82	0.01 NS nd nd	+	B	GEN I
Osler 2003 Denmark	8497	18	FFQ	=1/mo 2/mo 1/wk >2/wk Hazard ratio 0.88 0.84* 1.0 (ref) 1.1	0.02-	-	B	GEN I
Daviglus 1997 US WES	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 1.02 0.98 0.85	NS	0	A	GEN II
Fraser 1997 US Adventist	603	12	FFQ	>84 years old subset of Adventist Health Study <1/wk >1/wk Hazard ratio 1.0 0.98	NS	0	B	GEN III
Kromhout 1995 Holland	272	17	CCD	Non-fish eaters Fish Eaters (24 g/d) 1.0 0.96	NS	0	C	GEN II

**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	<u>Quintiles (amount not reported)</u> Men 1.0 0.74 0.71 0.82 0.76 Hazard Women 1.0 0.82 0.79 0.86 0.77* ratio	NS NS	+	A	GEN II
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA 0.87 1.3 1.6 1.9 2.8 g/d 1.0 0.89 0.64 0.83 0.6 EPA+DHA 0.0 0.009 0.046 0.15 0.66 g/d 1.0 1.06 0.92 0.92 0.59	0.067 0.004	++	A	GEN II

**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 1.0 0.96 0.79 0.84 0.81	NS	+	A	GEN II
Gillum 2000 US NHANES	8825	18.8	FFQ + 24-hr recall	Never <1 1 >1 /wk White men 1.0 0.98 0.87 0.95 Black men 1.0 0.96 0.99 1.1 White women 1.0 1.1 1.1 1.1 Black women 1.0 0.85 0.94 0.99	NS NS nd nd	0	B	GEN II
Daviglus 1997 US WES	1822	30	FFQ	0 1-17 18-34 =35 g/d 1.0 0.94 0.89 0.74	0.01	++	A	GEN II

**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 g/d 1.0 0.94 0.98 1.03 0.99 EPA+DHA 0.2 0.3 0.4 0.5 0.8 g/d 1.0 0.94 1.0 1.1 1.3	NS	0	A	GEN II
Dolecek 1992 US MRFIT	6250	10.5	Multiple 24-hr recall	ALA 0.87 1.3 1.6 1.9 2.8 g/d 1.0 0.98 0.57 0.98 0.68 EPA+DHA 0 0.009 0.046 0.15 0.66 g/d 1.0 1.1 0.91 0.88 0.60	NS 0.01	++	A	GEN II

**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	<u>&lt;1/mo</u> <u>1-3/mo</u> <u>1/wk</u> <u>2-4/wk</u> <u>&gt;5/wk</u> 1.0 0.80 0.65* 0.72 0.55*	0.01	++	A	GEN II
Ascherio 1995, US HPS	44895	6	FFQ	<u>1-3/mo</u> <u>1/wk</u> <u>2-3/wk</u> <u>4-5/wk</u> <u>&gt;6/wk</u> 0.74 0.86 0.71 0.54* 0.77	NS	+	A	GEN II
Egeland 2001 Norway	42612	7	Dietary quest- ionnaire	None Cod liver oil Never smoker Hazard ratio 1.0 0.7 Current smoker 1.0 0.8	NS	+	C	GEN II
Fraser 1997, US Adventist	26743	6	FFQ	<u>0</u> <u>&lt;1/wk</u> <u>&gt;1/wk</u> Hazard ratio 1.0 1.1 0.74	nd	0	B	GEN II
Albert 1998, US PHS	20551	11	FFQ	<u>&lt;1/mo</u> <u>1-3/mo</u> <u>1-&lt;2/wk</u> <u>2-&lt;5/wk</u> <u>=5/wk</u> 1.0 1.18 0.82 0.91 0.81	NS	+	A	GEN II
Mann 1997 UK	10802	13.3	FFQ	<u>0</u> <u>&lt;1</u> <u>=1</u> /wk Death Rate Ratio 100 121 123	NS	—	B	GEN II
Rodriguez 1996 US Honolulu	8006	23	Dietary quest- ionnaire	<u>Cigarettes/d</u> <u>&lt;2/wk</u> <u>=2/wk</u> Fish consumption <20 0.30 0.42 20-30 0.38 0.45 >30 1.0 0.50*	NS NS nd	+	C	GEN II
Osler 2003 Denmark	8497	18	FFQ	<u>=1/mo</u> <u>2/mo</u> <u>1/wk</u> <u>&gt;2/wk</u> Hazard ratio 1.1 0.98 1.0 (ref) 0.98	NS	0	B	GEN I
Mozaffarian 2003 US CHS	3910	9.3	FFQ	Tuna/other fish <u>&lt;1/mo</u> <u>1-3/mo</u> <u>1/wk</u> <u>2/wk</u> <u>&gt;3/wk</u> Total IHD death 1.0 0.78 0.77 0.53* 0.47* Fried fish/sand. <u>&lt;1/mo</u> <u>1-3/mo</u> <u>1/wk</u> <u>2/wk</u> <u>&gt;3/wk</u> Total IHD death 1.0 1.2 1.6 1.1 1.4 Hazard ratios	0.002 NS	++ —	A	GEN II
Oomen 2000 Finland Italy Holland	2738	20	CCD	<u>1-19</u> <u>20-39</u> <u>&gt;40</u> g/d Total fish 0.93 0.95 1.1 Fatty fish 0.57* 0.87(=20 g/d)	NS	+	A	GEN II
Daviglus 1997, US WES	1822	30	FFQ	<u>0</u> <u>1-17</u> <u>18-34</u> <u>=35</u> g/d 1.0 0.88 0.84 0.62*	0.04	++	A	GEN II
Kromhout 1985 Holland	852	20	CCD	<u>0</u> <u>1-14</u> <u>5-29</u> <u>30-44</u> <u>45</u> g/d 1.0 0.64 0.56 0.36* 0.39	nd	+	B	GEN II
Kromhout 1995 Holland	272	17	CCD	<u>No fish</u> <u>Fish eater</u> 1.0 0.51*	nd	+	C	GEN I

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

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 $\frac{<0.3}{1.0} \frac{0.3-2.7}{0.58} \frac{2.7-4.9}{0.34^*} \frac{4.9-7.4}{0.60} \frac{>7.4}{0.43^*}$ g/mo	NS	++	A	GEN II
Case control								
Siscovick 1995 US	827	na	FFQ	EPA+DHA $\frac{0}{1.0} \frac{0.96}{0.9^*} \frac{2.9}{0.7^*} \frac{5.5}{0.5^*} \frac{13.7}{0.4^*}$ g/mo Odds ratio	ND	++	A	GEN I

**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	$\frac{<1/\text{mo}}{1.0} \frac{1-3/\text{mo}}{0.64} \frac{1-2/\text{wk}}{0.47^*} \frac{2-5/\text{wk}}{0.51} \frac{=5/\text{wk}}{0.39^*}$	NS	++	A	GEN II
Daviglus 1997 US WES	1822	30	FFQ	$\frac{0}{1.0} \frac{1-17}{0.78} \frac{18-34}{0.80} \frac{=35}{0.68}$ g/d	NS	+	A	GEN II

**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
		Median intake (% energy) <u>0.03 0.05 0.08 0.14 0.24</u>										
Hu 1999 US NHS		Nonfatal MI 1.0 0.92 0.83 0.75* 0.69*										
	10		FFQ	ALA					0.001 0.05	++		
				Median intake g/d <u>0.71 0.86 0.98 1.12 1.36</u>								
				Fatal IHD 1.0 0.99 0.90 0.67 0.55*								
				Non-fatal MI 1.0 0.92 0.94 1.02 0.85								
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					NS NS	+	A	GEN II
	Total MI 1.0 1.0 0.92 0.86 1.1											
	Nonfatal MI 1.0 0.93 0.89 0.78 1.1											
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					NS	-	A	GEN II
	Total MI 1.0 1.6 1.4 1.2 1.2											
	Nonfatal MI 1.0 1.5 1.3 1.2 1.1											
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					0.02	++	A	GEN II
	Fatal MI 1.0 0.39* 0.67 0.53* 0.43*											
Oomen 2001 Holland	67	0	CD	ALA (% energy) <0.45 0.45-0.58 >0.58					NS NS	-	B	GEN III
	Fatal and nonfatal CAD 1.0 1.5 1.7											
	Fatal CAD 1.0 0.99 1.6											
Case control												
Tavani 2001 Italy	975	na	FFQ	EPA+DHA <0.81 0.81-1.28 >1.28 g/wk					0.03	++	B	GEN II
	Nonfatal MI odds ratio 1.0 0.71* 0.67*											

**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><tr><td></td><td>1-3/mo</td><td>1/wk</td><td>2-4/wk</td><td>&gt;5/wk</td></tr><tr><td>Nonfatal MI</td><td>0.78*</td><td>0.74*</td><td>0.68*</td><td>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><tr><td></td><td>&lt;1/mo</td><td>1-3/mo</td><td>1/wk</td><td>2-3/wk</td><td>4-5/wk</td><td>&gt;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><tr><td></td><td>0</td><td>&lt;1</td><td>&gt;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><tr><td></td><td>&lt;1/mo</td><td>1-3/mo</td><td>1-2/wk</td><td>2-5/wk</td><td>&gt;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><tr><td></td><td>&lt;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><tr><td>Tuna/other fish</td><td>1-3/m</td><td>1/wk</td><td>2/wk</td><td>&gt;3/wk</td></tr><tr><td>Nonfatal MI</td><td>0.81</td><td>0.71</td><td>0.75</td><td>0.67</td></tr><tr><td>Fried fish/sandwich</td><td>1-3/m</td><td>1/wk</td><td>2/wk</td><td>&gt;3/wk</td></tr><tr><td>Nonfatal MI</td><td>1.3</td><td>1.6</td><td>1.2</td><td>1.9</td></tr><tr><td colspan="5">Hazard ratio</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	Hazard ratio					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																																
Hazard ratio																																				
Daviglus 1997 US WES	1822	30	FFQ	<table><tr><td></td><td>0</td><td>1-17</td><td>18-34</td><td>=35 g/d</td></tr><tr><td>All MI</td><td>1.0</td><td>0.88</td><td>0.76</td><td>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><tr><td></td><td>&lt;1</td><td>1-&lt;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><tr><td></td><td>&lt;2</td><td>2-3</td><td>&gt;4 /wk</td></tr><tr><td>Nonfatal MI odds ratio</td><td>Men</td><td>1.0</td><td>0.6*</td><td>0.7*</td></tr><tr><td></td><td>Women</td><td>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 <u>0.077 0.12 0.17 0.22 0.48</u> g/d Ischemic 1.0 0.83 0.67* 0.82 0.71 Hemorrhagic 1.0 0.94 0.66 0.93 0.76	NS NS	+	A	GEN II
He 2002 US HPS	43671	12	FQ	EPA+DHA <u>&lt;0.05 0.05-&lt;0.2 0.2-0.4 0.4-&lt;0.6 &gt;0.6</u> g/d Ischemic 1.0 0.56* 0.63* 0.54* 0.73 Hemorrhagic 1.0 1.3 1.0 0.89 1.1	NS NS	++	A	GEN II
Morris 1995 US PHS	21185	4	FQ	EPA+DHA <u>&lt;0.5 0.5-&lt;1.0 1.0-&lt;1.7 1.7-&lt;2.3 &gt;2.3</u> g/wk All strokes 1.0 0.9 1.1 0.7 1.0	NS	0	A	GEN II
Yuan 2001 China	18244	9	FFQ	EPA+DHA <u>&lt;0.26 0.27-0.43 0.44-0.72 0.73-1.1 ≥1.1</u> g/wk Fatal strokes 1.0 0.76 0.76* 0.93 1.0	NS	+	A	GEN II
Seino 1997 Japan	2283	15.5	FFQ	n-3 fatty acid <u>1.8 2.3 2.7 3.2</u> g/d Ischemic stroke 1.0 0.99 1.6 1.4	NS	—	B	GEN II
Case control								
Caicoya 2002 Spain	913	na	FQ	EPA+DHA <u>&lt;0.12 0.12-0.32 0.32-0.66 &gt;0.66</u> g/d All strokes odds ratio 1.0 1.1 1.4 1.8	0.01-	—	A	GEN II



**Table 3.38 Association of estimates of fish consumption with stroke 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													
Kinjo 1999 Japan	223170	15	1-page quest- ionnaire	Ischemic deaths	$\geq 1$ 1.0	1-3 1.05	$\geq 4$ 0.99	/wk	nd	0	C	GEN II	
				Hemorrhagic deaths	1.0	1.02	0.87*		nd				
Iso 2001 US NHS	79839	14	FQ	Ischemic	$<1/m$ 1.0	1-3/m 0.83	1/wk 0.69	2-4/wk 0.63	$>5/wk$ 0.38	0.09 NS	+	A	GEN II
				Hemorrhagic	1.0	1.4	1.1	0.93	1.0				
He 2002 US HPS	43671	12	FQ	Ischemic	$<1/mo$ 1.0	1-3/mo 0.57*	1/wk 0.56*	2-4/wk 0.55*	$>5/wk$ 0.54*	NS	++	A	GEN II
				Hemorrhagic	1.0	1.8	1.4	0.96	1.6	NS			
Morris 1995 US PHS	21185	4	FFQ	Non-fatal strokes	$<1$ 1.0	1 1.3*	2-4 1.1	$>5$ 0.9	/wk	NS	–	A	GEN II
Yuan 2001 China	18244	9	FQ	Fatal strokes	$<50$ 1.0	50-100 0.93	100-150 0.79	150-200 1.01	$\geq 200$ g/wk 1.11	NS	0	A	GEN II
Gillum 1996 US  NHANES	5192	12	FFQ	Ischemic stroke	0 1.0	$<1$ 0.78	1 0.77	$>1$ 0.55*	/wk	nd	+	B	GEN I
				Women aged 45-74									
				Men aged 45-74	1.0	1.3	1.2	0.85					
				Black men+women	Never fish		some fish			na			
				Stroke incidence	1.0		0.51*						
				Stroke death	1.0		0.26*						
Orencia 1996 USA WES	1847	30	FFQ / 24-hr recall	All strokes	0 1.0	1-17 0.94	18-34 0.89	$>35$ g/d 1.3	Hazard ratio	NS	0	A	GEN II
Keli 1994 Holland	872	15	CCD	All strokes	$6.3 (<20)$ 1.0	$35.4 (\geq 20)$ g/d 0.49	Hazard ratio			0.06	+	B	GEN II
Case control													
Caicoya 2002 Spain	913	na	FFQ	Total	0 1.0	1-22.5 0.30*	23-45 0.44	46-90 0.59	$>91$ g/d 0.76	nd	+	A	GEN II
				Ischemic	0-11.2 1.0	11.3-28.7 1.1	28.8-46.5 0.90	$>46.5$ g/d 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 men 1.0 0.77 0.61* 0.58* 0.60*	0.012	+ +	B	GEN I
				ALA 0.46 0.58 0.65 0.76 0.96 g/d women 1.0 0.57 0.52 0.30* 0.42*	0.014			

## 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 ago<sup>49</sup> 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 mortality<sup>50-52</sup>. The results of studies reporting estimates of fish intake were heterogeneous — 1 study<sup>53</sup> reported a small but significant increase of all-cause mortality with increasing fish intake, and 5 studies found no benefit<sup>50,54-57</sup>. 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 benefit<sup>58</sup>, and 1 study showed a trend for benefit<sup>59</sup>.

**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 consumption<sup>58</sup>.

**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)<sup>58</sup>. A smaller study also found a significant reduction of arrhythmic deaths at higher levels of fish intake<sup>60</sup>. However, in the same study opposite results were seen with consumption of fried fish or fish sandwiches<sup>60</sup>. Another smaller follow-up study of 30 years duration found a significant trend of reduction in sudden death<sup>56</sup>. A case-control study of 827 subjects in the US also reported a significant inverse association of sudden death with increasing fish intake<sup>61</sup>.

**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)<sup>62</sup>, Health Professionals Study (HPS)<sup>63</sup>, and the Physicians' Health Study<sup>64</sup>, 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 Study<sup>63</sup> reported a significant reduction of ischemic strokes with any level of fish consumption above the lowest quintile. In the Nurses' Health Study<sup>62</sup>, 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)**

Applicability	Methodological Quality			
		A	B	C
	I			
	II	<u>Study Year N Effect</u> 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)**

Applicability	Methodological Quality			
		A	B	C
	I		<u>Study Year N Effect</u> NHANES 2000 8825 + Osler 2003 8487 -	
	II	<u>Study Year N Effect</u> Nagata 2002 29079 0 PHS 1998 20551 ++ Yuan 2001 18244 ++ WES 1997 1822 0	<u>Study Year N Effect</u> Mann 1997 10802 0	<u>Study Year N Effect</u> Kromhout 1995 272 0
	III		<u>Study Year N Effect</u> Adventist 1997 603 0	

**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	Study Nagata MRFIT	Year 2002 1992	N 29079 6250	Effect + ++	
	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	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>		
		PHS	1998	20551	+	NHANES	2000	8825	0		
	WES	1997	1822	++							
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	<div>Study</div> <div>ABCC</div> <div>MRFIT</div>	<div>Year</div> <div>1997</div> <div>1992</div>	<div>N</div> <div>21930</div> <div>6250</div>	<div>Effect</div> <div>0</div> <div>++</div>	
	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					<u>Study</u> Osler	<u>Year</u> 2003	<u>N</u> 8497	<u>Effect</u> 0	<u>Study</u> Kromhout				<u>Year</u> 1985	<u>N</u> 272	<u>Effect</u> +
	II	<u>Study</u> NHS	<u>Year</u> 2002	<u>N</u> 84688	<u>Effect</u> ++	<u>Study</u> Adventist	<u>Year</u> 1997	<u>N</u> 26743	<u>Effect</u> 0	<u>Study</u> Egeland	<u>Year</u> 2001	<u>N</u> 42612	<u>Effect</u> +			
		HPS	1995	44895	+	Mann	1997	10802	-	Honolulu	1996	8006	+			
		PHS	1998	20551	+	Kromhout	1985	852	+							
		CHS	2003	3910	++											
		Oomen	2000	2738	+											
		WES	1997	1822	++											
	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	<div>Study</div> PHS	<div>Year</div> 1998	<div>N</div> 20551	<div>Effect</div> ++	
	III	CHS	2003	3910	+	

**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	<div>Study</div> PHS	<div>Year</div> 1998	<div>N</div> 20551	<div>Effect</div> ++	
	III	CHS	2003	3910	+	

**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	Study	Year	N	Effect				
		NHS <sup>1</sup>	2002	84688	++				
		HPS	1995	44895	+				
	PHS	1995	21185	-					
	Yuan	2001	18244	++					
III						Study	Year	N	Effect
						Oomen	2001	667	-

<sup>1</sup> 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>	<u>Study</u>	<u>Year</u>	<u>N</u>	<u>Effect</u>		
		NHS	2002	84688	++	Adventist	1992	26743	0		
		HPS	1995	44895	++						
PHS		1998	20551	0							
Yuan		2001	18244	++							
III	CHS	2003	3910	+							
	WES	1997	1822	++							



**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										
Applicability		A				B				C	
	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							
III	Yuan	2001	18244	+							

**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												
Applicability		A				B				C			
	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.”<sup>65</sup>. 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 men <sup>66</sup>. 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 women <sup>67</sup>. 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 different<sup>53</sup>. 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 evaluated<sup>50</sup>. 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 ALA<sup>68</sup>. 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<sup>69 62</sup>. The Adventist Health Study examined a subgroup of 603 oldest old ( $\geq 84$  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 week<sup>57</sup>.

- *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 not<sup>62</sup>. 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 question<sup>38</sup> 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<sup>52,69</sup> and 1 cross-sectional study<sup>68</sup> 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 0.199<sup>52</sup>.

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 disease<sup>68</sup>. 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 significant<sup>69</sup>.

- *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 only<sup>70</sup>. 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 patients<sup>34</sup>. Nilsen et al used 1.7 g/d of EPA+DHA and showed no effects on CVD outcomes<sup>36</sup>. Two diet trials<sup>43,44</sup> 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 outcomes<sup>49</sup>. 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-up<sup>64</sup>.

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

Only 1 study<sup>48</sup> 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<sup>43,44</sup> 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)<sup>47</sup> 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 events<sup>34</sup> 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<sup>71, 72, 73, 74</sup>.

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 events<sup>39</sup>. 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<sup>75-78 79-81</sup> 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<sup>74,82 83 84 85</sup> 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 patients<sup>82</sup> 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, Reis<sup>74</sup> 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. Cairns<sup>84</sup> 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. Leaf<sup>83</sup> reported that 3% of patients in each treatment group experienced bleeding episodes<sup>85</sup> 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
	<i>n</i>	Type Dose (g/d)	<i>n</i>	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 to1.7	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
Borchgre- vink 1966	100	Linseed oil 10 ml	100	Corn oil 10 ml	40			7	7	3	0	All taking anticoagulants
Eritsland 1995	119	EPA+DHA <sup>2</sup> 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
	<i>n</i>	Type Dose (g/d)	<i>n</i>	Type Dose (g/d)		N-3	C	N-3	C	N-3	C	
General population												
	132	EPA+DHA <sup>2</sup> 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 <sup>3</sup>	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	1 <sup>4</sup>	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 EPA+DHA 2.4	15	Olive oil 20 capsules	4							1 diarrhea in olive oil
Total	7712		7623			57	68	512	300	236	139	
Hyperlipdemia 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"				
Contacos 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	
Schect- man 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
	<i>n</i>	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
<b>General population</b>							
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		
<b>Subtotal</b>	<b>75</b>				<b>4</b>	<b>5</b>	
<b>Cardiovascular disease population</b>							
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
<b>Subtotal</b>	<b>128</b>			<b>1</b>	<b>42</b>		
<b>Hyperlipdemia population</b>							
Dallongeville 1991	18	EPA+DHA 4.8	12		6	0	
Schectman 1989	16	EPA+DHA 6.0	12		18	1	<b>3 diarrhea</b>
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"		
<b>Subtotal</b>	<b>86</b>				<b>25</b>	<b>1</b>	
<b>Diabetes population</b>							
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
Nenseler, 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
<b>Total</b>	<b>1,618</b>		

**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
<b>Total</b>	<b>707</b>		

## 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 <sup>52</sup>.

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  $\leq 1.3$  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 <sup>35</sup>. 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 <sup>38</sup>. 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 <sup>34-37</sup> was generally good (summary quality grade A or B), but the multi-arm trial from India <sup>38</sup> 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 <sup>42-44 45</sup>. 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 <sup>43,44</sup>. 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 <sup>45</sup>. An early trial <sup>42</sup>, 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<sup>41,47</sup> 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 trial<sup>47</sup> 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 EPA<sup>48</sup>. The second, more recent, trial<sup>41</sup> found that those taking fish oil supplements had an increased sudden death risk.

The single prospective cohort study<sup>46</sup> 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 study<sup>63</sup>. 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 population<sup>49</sup>.

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<sup>56,58,60</sup>. 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 consumption<sup>60</sup>.

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 events<sup>86</sup>.

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 monitoring<sup>9</sup>. 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 recalls<sup>23</sup>, 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 derive from 1 very large study<sup>35</sup>. 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 population<sup>49</sup> 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.

# References and Bibliography

## References

1. USDA. Individual Fatty Acid Intakes: Results from the 1995 Continuing Survey of Food Intakes by Individuals (data table set 4). Available online at <<http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm>>.
2. Institute of Medicine. Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrition). 2002. The National Academy Press.
3. Simopoulos AP, Leaf A. Essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. *Ann Nutr Metab* 1999; 43(2):127-130.
4. Fallon S, Enig MG. Tripping Lightly Down the Prostaglandin Pathways. The Price-Pottenger Nutrition Foundation. Available online at <<http://www.price-pottenger.org/Articles/Prostaglandin.htm>>. 2001.
5. Nair SS, Leitch JW, Falconer J, Garg ML. Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. [Review] [93 refs]. *Journal of Nutrition* 1997; 127(3):383-393.
6. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000; 71(1 SUPPL.):343S-348S.
7. Krummel D. Nutrition in Cardiovascular Disease. In: Mahan LK, Escot-Stump S, editors. *Krause's Food, Nutrition, and Diet Therapy*. W.B. Saunder Company, 1996.
8. Hornstra G. Omega-3 long-chain polyunsaturated fatty acids and health benefits. Amended and updated version of the English translation of <<Oméga-3 et bénéfice santé>>, initially published by Catherine Anselmino, Centre d'Etude et d'Information sur les Vitamines, Roche Vitamines France, Neuilly-sur-Seine (NutriScience). Available online: <<http://www.vita-web.com/whatsnew/Omega3.pdf>>. Catherine Anselmino, Centre d'Etude et d'Information sur les Vitamines, Roche Vitamines France, Neuilly-sur-Seine (NutriScience).
9. Wright JD, Ervin B, Briefel RR. Consensus workshop on dietary assessment: nutrition monitoring and tracking the year 2000 objectives. Available on line at <http://www.cdc.gov/nchs/data/misc/nutri94acc.pdf>. 1994. Hyattsville, MD, National Center for Health Statistics.
10. U.S. Department of Agriculture Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 16. Nutrient Data Laboratory Home Page. . 2003.
11. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. *Am J Clin Nutr* 1980; 33(12):2657-2661.
12. Dyerberg J, Bang HO, Stoffensen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 1978; 2(8081):117-119.
13. Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland. Incidence of some chronic diseases 1950-1974. *Acta Medica Scandinavica* 1980; 208(5):401-406.
14. Kinjo Y, Beral V, Akiba S et al. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. *Journal of Epidemiology* 1999; 9(4):268-274.
15. Crombie IK, McLoone P, Smith WC, Thomson M, Pedoe HT. International differences in coronary heart disease mortality and consumption of fish and other foodstuffs. *European Heart Journal* 1987; 8(6):560-563.

16. Kromhout D, Bloemberg BP, Feskens EJ et al. Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality. *International Journal of Epidemiology* 1996; 25(4):753-759.
17. Curb JD, Reed DM. Fish consumption and mortality from coronary heart disease (Letter). *New Engl J Med* 1985; 313:821.
18. Vollset SE, Heuch I, Bjelke E. Fish consumption and mortality from coronary heart disease. *New Engl J Med* 1985; 313:820-827.
19. Guallar E, Sanz-Gallardo MI, Van'T VP et al. Mercury, fish oils, and the risk of myocardial infarction. *New England Journal of Medicine* 2002; 347(22):1747-1754.
20. Yoshizawa K, Rimm EB, Morris JS et al. Mercury and the risk of coronary heart disease in men. *New England Journal of Medicine* 2002; 347(22):1755-1760.
21. Harris RP, Helfand M, Woolf SH et al. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine* 2001; 20(3:Suppl):Suppl-35.
22. Tippet K, Enns C, Moshfegh A. Food Consumption Survey in the U.S. Department of Agriculture. *National Today* 34[1], 33-46. 1999.
23. Institute of Medicine Food and Nutrition Board. Dietary Reference Intakes: Applications in Dietary Assessment. Washington DC: National Academy Press, 2000.
24. Damico K, Stoll A, Marangell L, Cohen B. How blind is double-blind? A study of fish oil versus placebo. *Prostaglandins Leukotrienes & Essential Fatty Acids* 66[393], 395. 2003.
25. Balk EM, Bonis PA, Moskowitz H et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002; 287(22):2973-2982.
26. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; 17(1):1-12.
27. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials.[comment]. *JAMA* 1995; 273(5):408-412.
28. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis.[comment]. *JAMA* 1999; 282(11):1054-1060.
29. Levey AS, Coresh J, Balk E et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Annals of Internal Medicine* 2003; 139(2):137-147.
30. Slimani N, Ferrari P, Ocke M et al. Standardization of the 24-hour diet recall calibration method used in the european prospective investigation into cancer and nutrition (EPIC): general concepts and preliminary results. *European Journal of Clinical Nutrition* 2000; 54(12):900-917.
31. Welch AA, Lund E, Amiano P et al. Variability of fish consumption within the 10 European countries participating in the European Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutrition* 2002; 5(6B):1273-1285.
32. Kromhout D, Keys A, Aravanis C et al. Food consumption patterns in the 1960s in seven countries. *Am J Clin Nutr* 1989; 49(5):889-894.
33. Moreno LA, Sarria A, Popkin BM. The nutrition transition in Spain: A European Mediterranean country. *Eur J Clin Nutr* 2002; 56(10):992-1003.
34. Leng GC, Lee AJ, Fowkes FG et al. Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease. *Clinical Nutrition* 1998; 17(6):265-271.
35. Marchioli R, Barzi F, Bomba E et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. [see comments.]. *Circulation* 2002; 105(16):1897-1903.
36. Nilsen DW, Albrektsen G, Landmark K et al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001; 74(1):50-56.

37. Sacks FM, Stone PH, Gibson CM et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *Journal of the American College of Cardiology* 1995; 25(7):1492-1498.
38. Singh RB, Niaz MA, Sharma JP et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival-4. *Cardiovascular Drugs & Therapy* 1997; 11(3):485-491.
39. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 1999; 354(9177):447-455.
40. Burr ML, Fehily AM, Rogers S et al. Diet and reinfarction trial (DART): design, recruitment, and compliance. *European Heart Journal* 1989; 10(6):558-567.
41. Burr ML, Ashfield-Watt PAL, Dunstan FDJ et al. Lack of benefit of dietary advice to men with angina: Results of a controlled trial. *Eur J Clin Nutr* 2003; 57(2):193-200.
42. Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. *Acta Medica Scandinavica - Supplementum* 1966; 466:1-92.
43. de Lorgeril M, Salen P, Martin JL et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. [see comments.]. *Circulation* 1999; 99(6):779-785.
44. Singh RB, Dubnov G, Niaz MA et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): A randomised single-blind trial. *Lancet* 2002; 360(9344):1455-1461.
45. Bemelmans WJ, Broer J, Feskens EJ et al. Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean Alpha-linolenic Enriched Groningen Dietary Intervention (MARGARIN) study. *Am J Clin Nutr* 2002; 75(2):221-227.
46. Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease.[comment]. *American Journal of Clinical Nutrition* 2003; 78(1):65-71.
47. Burr ML, Fehily AM, Gilbert JF et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). [see comments.]. *Lancet* 1989; 2(8666):757-761.
48. Ness AR, Hughes J, Elwood PC et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). *European Journal of Clinical Nutrition* 2002; 56(6):512-518.
49. Natvig H, Borchgrevink CF, Dedichen J et al. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. *Scandinavian Journal of Clinical & Laboratory Investigation - Supplement* 1968; 105:1-20.
50. Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. *Am J Epidemiol* 2002; 156(9):824-831.
51. Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *American Journal of Epidemiology* 2001; 154(9):809-816.
52. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. *Proceedings of the Society for Experimental Biology & Medicine* 1992; 200(2):177-182.
53. Osler M, Andreassen AH, Hoidrup S. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *Journal of Clinical Epidemiology* 2003; 56(3):274-279.
54. Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *International Journal of Epidemiology* 1995; 24(2):340-345.
55. Mann N, Sinclair A, Pille M et al. The effect of short-term diets rich in fish, red meat, or white meat on thromboxane and prostacyclin



- synthesis in humans. *Lipids* 1997; 32(6):635-644.
56. Daviglius ML, Stamler J, Orenchia AJ et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *New England Journal of Medicine* 1997; 336(15):1046-1053.
  57. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Archives of Internal Medicine* 1997; 157(19):2249-2258.
  58. Albert CM, Hennekens CH, O'Donnell CJ et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998; 279(1):23-28.
  59. Gillum RF, Mussolino M, Madans JH. The relation between fish consumption, death from all causes, and incidence of coronary heart disease. the NHANES I Epidemiologic Follow-up Study. *Journal of Clinical Epidemiology* 2000; 53(3):237-244.
  60. Mozaffarian DLR. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: The Cardiovascular Health Study. *Circulation* 2003; 107(10):1372-1377.
  61. Siscovick DS, Raghunathan TE, King I et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995; 274(17):1363-1367.
  62. Iso H, Rexrode KM, Stampfer MJ et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001; 285(3):304-312.
  63. He K, Rimm EB, Merchant A et al. Fish consumption and risk of stroke in men. *JAMA* 2002; 288(24):3130-3136.
  64. Morris MC, Manson JE, Rosner B et al. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *American Journal of Epidemiology* 1995; 142(2):166-175.
  65. Institute of Medicine. *Methods of Technology Assessment*. Washington DC: National Academy Press, 1985.
  66. Gillum RF, Mussolino ME, Madans JH. The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey). *Archives of Internal Medicine* 1996; 156(5):537-542.
  67. Fraser GE, Strahan TM, Sabate J, Beeson WL, Kissinger D. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. *Circulation* 1992; 86(2):406-413.
  68. Djousse L, Pankow JS, Eckfeldt JH et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *American Journal of Clinical Nutrition* 2001; 74(5):612-619.
  69. Hu FB, Bronner L, Willett WC et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002; 287(14):1815-1821.
  70. Hu FB, Stampfer MJ, Manson JE et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 1999; 69(5):890-897.
  71. Eritsland J, Arnesen H, Seljeflot I, Hostmark AT. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *Am J Clin Nutr* 1995; 61(4):831-836.
  72. Eritsland J, Arnesen H, Berg K, Seljeflot I, Abdelnoor M. Serum Lp(a) lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. *Scandinavian Journal of Clinical & Laboratory Investigation* 1995; 55(4):295-300.
  73. Eritsland J, Seljeflot I, Arnesen H, Westvik A-B, Kierulf P. Effect of long-term, moderate-dose supplementation with omega-3 fatty acids on monocyte procoagulant activity and release of interleukin-6 in patients with coronary artery disease. *Thromb Res* 1995; 77(4):337-346.
  74. Reis GJ, Boucher TM, Sipperly ME et al. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. *Lancet* 1989; 2(8656):177-181.
  75. Schectman G, Kaul S, Kissebah AH. Effect of fish oil concentrate on lipoprotein composition in NIDDM. *Diabetes* 1988; 37(11):1567-1573.
  76. Vessby B, Boberg M. Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-

- dependent diabetes mellitus. *J Intern Med* 1990; 228(2):165-171.
77. Hendra TJ, Britton ME, Roper DR et al. Effects of fish oil supplements in NIDDM subjects. Controlled study. *Diabetes Care* 1990; 13(8):821-829.
  78. Mori TA, Vandongen R, Mahanian F, Douglas A. The effect of fish oil on plasma lipids, platelet and neutrophil function in patients with vascular disease. *Advances in Prostaglandin, Thromboxane, & Leukotriene Research* 1991; 21A:229-232.
  79. Rossing P, Hansen BV, Nielsen FS et al. Fish oil in diabetic nephropathy. *Diabetes Care* 1996; 19(11):1214-1219.
  80. Fasching P, Rohac M, Liener K et al. Fish oil supplementation versus gemfibrozil treatment in hyperlipidemic NIDDM. A randomized crossover study. *Hormone & Metabolic Research* 1996; 28(5):230-236.
  81. Myrup B, Rossing P, Jensen T et al. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. *Scandinavian Journal of Clinical & Laboratory Investigation* 2001; 61(5):349-356.
  82. Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagulation & Fibrinolysis* 1995; 6(1):17-22.
  83. Leaf A, Jorgensen MB, Jacobs AK et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994; 90(5):2248-2257.
  84. Cairns JA, Gill J, Morton B et al. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. *Circulation* 1996; 94(7):1553-1560.
  85. Milner MR, Gallino RA, Leffingwell A et al. Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal coronary angioplasty. *American Journal of Cardiology* 1989; 64(5):294-299.
  86. Food and Drug Administration. Safety Reporting Requirements for Human Drug and Biological Products. 21 CFR Part 310, 312, 314, 320, 600, and 606. Proposed Rules. Available on line at:  
<http://www.fda.gov/ohrms/dockets>. Food and Drug Administration, HHS , 12405-12497. 2003. 8-1-0003.

# Bibliography

Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. *Am J Kid Dis* [39(Suppl 1)], S223-S231. 2002.

Comparative Dietary Risks: Balancing the risk and benefits of fish consumption. The U.S. Environmental Protection Agency and Toxicology Excellence for Risk Assessment (TERA), 1999. Accessed August 3, 2003. Available online at <http://www.tera.org/pubs/cdrpage.htm>. U.S.Environmental Protection Agency 2003.

Estimated Per Capita Fish Consumption in the United States. Available online at [http://www.epa.gov/waterscience/fish/consumption\\_report.pdf](http://www.epa.gov/waterscience/fish/consumption_report.pdf). Accessed August 9, 2003. Environmental Protection Agency . 2002. United States Environmental Protection Agency.

NHANES III Series 11, No.2A, April 1998. Electrocardiogram, Dietary Recall, Laboratory, Dietary Supplement and Prescription Drug. Available online at <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>. Accessed August 2003. National Center for Health Statistics. 1998.

NHANES III Series 11, No 3A, July 1999. Second Exam files for Dietary Recall, Examination, Laboratory, Additional Laboratory Analyses. Available online at <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>. Accessed August 2003. National Center for Health Statistics . 1999.

Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men.[comment]. *American Journal of Clinical Nutrition* 1997 Feb;65(2):445-50.

Alaswad K, Pogson GW, Harris WS, et al. Effects of phenytoin, niacin, gemfibrozil, and omega-3 fatty acids on high density lipoproteins in patients with hypoalphalipoproteinemia. *Preventive Cardiology* 1999;2(4):144-50.

Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998 Jan 7;279(1):23-8.

Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *New England Journal of Medicine* 2002 Apr 11;346(15):1113-8.

Allard JP, Kurian R, Aghdassi E, et al. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. *Lipids* 1997 May;32(5):535-41.

Ascherio A, Rimm EB, Stampfer MJ, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *New England Journal of Medicine* 1995 Apr 13;332(15):977-82.

Axelrod L, Camuso J, Williams E, et al. Effects of a small quantity of omega-3 fatty acids on cardiovascular risk factors in NIDDM. A randomized, prospective, double-blind, controlled study. *Diabetes Care* 1994 Jan;17(1):37-44.

Bagdade JD, Buchanan WE, Levy RA, et al. Effects of omega-3 fish oils on plasma lipids, lipoprotein composition, and postheparin lipoprotein lipase in women with IDDM. *Diabetes* 1990 Apr;39(4):426-31.

Bagdade JD, Ritter M, Subbaiah PV. Marine lipids normalize cholesteryl ester transfer in IDDM. *Diabetologia* 1996 Apr;39(4):487-91.

Bairati I, Roy L, Meyer F. Double-blind, randomized, controlled trial of fish oil supplements in prevention of recurrence of stenosis after coronary angioplasty. *Circulation* 1992 Mar;85(3):950-6.

Bairati I, Roy L, Meyer F. Effects of a fish oil supplement on blood pressure and serum lipids in patients treated for coronary artery disease. *Canadian Journal of Cardiology* 1992 Jan;8(1):41-6.

Balestrieri GP, Maffi V, Sleiman I, et al. Fish oil supplementation in patients with heterozygous familial hypercholesterolemia. *Recenti Progressi in Medicina* 1996 Mar;87(3):102-5.

Balk EM, Bonis PA, Moskowitz H, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA* 2002 Jun 12;287(22):2973-82.

Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. *Am J Clin Nutr* 1980 Dec;33(12):2657-61.

- Baumann KH, Hessel F, Larass I, et al. Dietary omega-3, omega-6, and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A ran-domized volunteer study. *Arteriosclerosis Thromb Vasc Biol* 1999 Jan;19(1):59-66.
- Bellamy CM, Schofield PM, Faragher EB, et al. Can supplementation of diet with omega-3 polyunsaturated fatty acids reduce coronary angioplasty restenosis rate? *European Heart Journal* 1992 Dec;13(12):1626-31.
- Bemelmanns WJ, Muskiet FA, Feskens EJ, et al. Associations of alpha-linolenic acid and linoleic acid with risk factors for coronary heart disease. *European Journal of Clinical Nutrition* 2000 Dec;54(12):865-71.
- Berg KJ, Skaga E, Skjaeggstad O, et al. Effect of linseed oil on platelet adhesiveness and bleeding-time in patients with coronary heart-disease. *Lancet* 1965 Nov 13;2(7420):980-2.
- Berg SE, Kristensen SD, Dyerberg J. The effect of fish oil on lipids, coagulation and fibrinolysis in patients with angina pectoris. *Artery* 1988;15(6):316-29.
- Berg SE, Ernst E, Varming K, et al. The effect of n-3 fatty acids on lipids and haemostasis in patients with type IIa and type IV hyperlipidaemia. *Thrombosis & Haemostasis* 1989;62(2):797-801.
- Berrettini M, Parise P, Ricotta S, et al. Increased plasma levels of tissue factor pathway inhibitor (TFPI) after n-3 polyunsaturated fatty acids supplementation in patients with chronic atherosclerotic disease. *Thrombosis & Haemostasis* 1996 Mar;75(3):395-400.
- Bialostosky, K. Dietary intake of macronutrients, micronutrients and other dietary constituents: United States, 1988-1994. National Center for Health Statistics. *Vital Health Stat* 11(245). 2002.
- Blok WL, Deslypere JP, Demacker PN, et al. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *European Journal of Clinical Investigation* 1997 Dec;27(12):1003-8.
- Boberg M, Vessby B, Selinus I. Effects of dietary supplementation with n-6 and n-3 long-chain polyunsaturated fatty acids on serum lipoproteins and platelet function in hypertriglyceridaemic patients. *Acta Medica Scandinavica* 1986;220(2):153-60.
- Boberg M, Pollare T, Siegbahn A, et al. Supplementation with n-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin-dependent diabetes mellitus. *European Journal of Clinical Investigation* 1992 Oct;22(10):645-50.
- Bonaa KH, Bjerve KS, Nordoy A. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arteriosclerosis & Thrombosis* 1992 Jun;12(6):675-81.
- Bonanome A, Biasia F, De Luca M, et al. n-3 fatty acids do not enhance LDL susceptibility to oxidation in hypertriacylglycerolemic hemodialyzed subjects. *Am J Clin Nutr* 1996 Feb;63(2):261-6.
- Borchgrevink CF, Skaga E, Berg KJ, et al. Absence of prophylactic effect of linolenic acid in patients with coronary heart-disease. *Lancet* 1966 Jul 23;2(7456):187-9.
- Bowles MH, Klonis D, Plavac TG, et al. EPA in the prevention of restenosis post PTCA. *Angiology* 1991 Mar;42(3):187-94.
- Brown AJ, Roberts DC. Fish and fish oil intake: effect on haematological variables related to cardiovascular disease. *Thrombosis Research* 1991 Oct 15;64(2):169-78.
- Brox J, Olaussen K, Osterud B, et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. *Lipids* 2001 Jan;36(1):7-13.
- Brox JH, Killie JE, Gunnes S, et al. The effect of cod liver oil and corn oil on platelets and vessel wall in man. *Thrombosis & Haemostasis* 1981 Oct;46(3):604-11.
- Brox JH, Killie JE, Osterud B, et al. Effects of cod liver oil on platelets and coagulation in familial hypercholesterolemia (type IIa). *Acta Medica Scandinavica* 1983;213(2):137-44.
- Burr ML, Ashfield-Watt PA, Dunstan FD et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57:193-200.
- Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). [see comments.]. *Lancet* 1989 Sep 30;2(8666):757-61.
- Burr ML, Fehily AM. Fatty fish and heart disease: a randomized controlled trial. *World Review of Nutrition & Dietetics* 1991;66:306-12.
- Caicoya M. Fish consumption and stroke: a community case-control study in Asturias, Spain. [see comments.]. *Neuroepidemiology* 2002 May;21(3):107-14.
- Cairns JA, Gill J, Morton B, et al. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. *Circulation* 1996 Oct 1;94(7):1553-60.
- Calabresi L, Donati D, Pazzucconi F, et al. Omacor in familial combined hyperlipidemia: effects on lipids and low density lipoprotein subclasses. *Atherosclerosis* 2000 Feb;148(2):387-96.

- Chan DC, Watts GF, Barrett PH, et al. Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. *Clinical Chemistry* 2002 Jun;48(6:Pt 1):t-83.
- Chan DC, Watts GF, Mori TA, et al. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. *Eur J Clin Invest* 2002 Jun;32(6):429-36.
- Chan DC, Watts GF, Barrett PH, et al. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes* 2002 Aug;51(8):2377-86.
- Chan DC, Watts GF, Mori TA, et al. Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of apolipoprotein B-100 and chylomicron remnants in men with visceral obesity. *Am J Clin Nutr* 2003 Feb;77(2):300-7.
- Conquer JA, Cheryk LA, Chan E, et al. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. *Thromb Res* 1999;96(3):239-50.
- Contacos C, Barter PJ, Sullivan DR. Effect of pravastatin and omega-3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia. *Arteriosclerosis & Thrombosis* 1993 Dec;13(12):1755-62.
- Crombie IK, McLoone P, Smith WC, et al. International differences in coronary heart disease mortality and consumption of fish and other foodstuffs. *European Heart Journal* 1987 Jun;8(6):560-3.
- Curb JD, Reed DM. Fish consumption and mortality from coronary heart disease (Letter). *New Engl J Med* 1985;313:821.
- Dallongeville J, Boulet L, Davignon J, et al. Fish oil supplementation reduces beta-very low density lipoprotein in type III dysbetalipoproteinemia. *Arteriosclerosis & Thrombosis* 1991 Jul;11(4):864-71.
- Damico, K, Stoll, A, Marangell, LB, and Cohen, BM. How blind is double-blind? A study of fish oil versus placebo. *Prostaglandins Leukotrienes & Essential Fatty Acids* 66[393], 395. 2003.
- Davi G, Belvedere M, Catalano I, et al. Platelet function during ticlopidine and eicosapentaenoic acid administration in patients with coronary heart disease. *Platelets* 1990;1(2):81-4.
- Davidson MH, Bagdade JD, Liebson PR, et al. Comparative effects of marine and olive oil dietary supplementation on coronary risk factors. *Journal of Applied Cardiology* 1989;4(3):145-51.
- Davidson MH, Maki KC, Kalkowski J, et al. Effects of docosahexaenoic acid on serum lipoproteins in patients with combined hyperlipidemia: a randomized, double-blind, placebo-controlled trial. *Journal of the American College of Nutrition* 1997 Jun;16(3):236-43.
- Daviglus ML, Stamler J, Orenca AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *New England Journal of Medicine* 1997 Apr 10;336(15):1046-53.
- de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994 Jun 11;343(8911):1454-9.
- de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. [see comments.]. *Circulation* 1999 Feb 16;99(6):779-85.
- Dehmer GJ, Popma JJ, van den Berg EK, et al. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. *New England Journal of Medicine* 1988 Sep 22;319(12):733-40.
- Demke DM, Peters GR, Linet OI, et al. Effects of a fish oil concentrate in patients with hypercholesterolemia. *Atherosclerosis* 1988 Mar;70(1-2):73-80.
- Djousse L, Pankow JS, Eckfeldt JH, et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart Study. *American Journal of Clinical Nutrition* 2001 Nov;74(5):612-9.
- Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. *Proceedings of the Society for Experimental Biology & Medicine* 1992 Jun;200(2):177-82.
- Dyerberg J, Bang HO, Stoffersen E, et al. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 1978 Jul 15;2(8081):117-9.
- Egeland GM, Meyer HE, Selmer R, et al. Cod liver oil consumption, smoking, and coronary heart disease mortality: three counties, Norway. *International Journal of Circumpolar Health* 2001 Apr;60(2):143-9.
- Emken EA, Adlof RO, Gulley RM. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. *Biochimica et Biophysica Acta* 1994 Aug 4;1213(3):277-88.
- Eritsland J, Arnesen H, Seljeflot I, et al. Influence of serum lipoprotein(a) and homocyst(e)ine levels on graft patency

after coronary artery bypass grafting. *Am J Cardiol* 1994 Dec 1;74(11):1099-102.

Eritsland J, Arnesen H, Seljeflot I, et al. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *Am J Clin Nutr* 1995 Apr;61(4):831-6.

Eritsland J, Arnesen H, Seljeflot I, et al. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coag Fibrinol* 1995 Feb;6(1):17-22.

Eritsland J, Arnesen H, Berg K et al. Serum lipoprotein levels in patients with coronary artery disease and the influence of long-term n-3 fatty acid supplementation. *Scand J Clin Lab Invest* 1995;55(4):295-300.

Eritsland J, Seljeflot I, Arnesen H et al. Effect of long-term moderate-dose supplementation with omega-3 fatty acids on monocyte proagulant activity and release of interleukin-6 in patients with coronary artery disease. *Thromb Res* 1995;77(4):337-46.

Erkkila AT, Sarkkinen ES, Lehto S, et al. Dietary associates of serum total, LDL, and HDL cholesterol and triglycerides in patients with coronary heart disease. *Preventive Medicine* 1999 Jun;28(6):558-65.

Fallon, S and Enig MG. Tripping Lightly Down the Prostaglandin Pathways. The Price-Pottenger Nutrition Foundation. Available online at <<http://www.price-pottenger.org/Articles/Prostaglandin.htm>>. 2001.

Fasching P, Ratheiser K, Waldhausl W, et al. Metabolic effects of fish-oil supplementation in patients with impaired glucose tolerance. *Diabetes* 1991;40(5):583-9.

Fasching P, Rohac M, Liener K, et al. Fish oil supplementation versus gemfibrozil treatment in hyperlipidemic NIDDM. A randomized crossover study. *Hormone & Metabolic Research* 1996 May;28(5):230-6.

FDA. Safety Reporting Requirements for Human Drug and Biological Products. 21 CFR Part 310, 312, 314, 320, 600, and 606. Food and Drug Administration, Health and Human Services. 2003. 8-1-0003.

Franzen D, Schannwell M, Oette K, et al. A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following PTCA. *Catheterization & Cardiovascular Diagnosis* 1993 Apr;28(4):301-10.

Fraser GE, Strahan TM, Sabate J et al. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. *Circulation* 1992;86(2):406-13.

Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Arch Intern Med* 1997;157(19):2249-58.

Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* 1992;152(7):1416-24.

Freese R, Mutanen M. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. *Am J Clin Nutr* 1997 Sep;66(3):591-8.

Gans RO, Bilo HJ, Weersink EG, et al. Fish oil supplementation in patients with stable claudication. *American Journal of Surgery* 1990 Nov;160(5):490-5.

Gartside PS, Wang P, Glueck CJ. Prospective assessment of coronary heart disease risk factors: the NHANES I epidemiologic follow-up study (NHEFS) 16-year follow-up. *Journal of the American College of Nutrition* 1998 Jun;17(3):263-9.

Gillum RF, Mussolino ME, Madans JH. The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey). *Archives of Internal Medicine* 1996 Mar 11;156(5):537-42.

Gillum RF, Mussolino M, Madans JH. The relation between fish consumption, death from all causes, and incidence of coronary heart disease. the NHANES I Epidemiologic Follow-up Study. *Journal of Clinical Epidemiology* 2000 Mar 1;53(3):237-44.

Glauber H, Wallace P, Griver K, et al. Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1988 May;108(5):663-8.

Goodfellow J, Bellamy MF, Ramsey MW, et al. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *Journal of the American College of Cardiology* 2000 Feb;35(2):265-70.

Grimsgaard S, Bonaa KH, Hansen JB, et al. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. *Am J Clin Nutr* 1998 Jul;68(1):52-9.

Grundt H, Nilsen DW, Hetland O, et al. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. *Journal of Internal Medicine* 1995 Mar;237(3):249-59.

Grynberg A, Fournier A, Sergiel JP, et al. Membrane docosahexaenoic acid vs. eicosapentaenoic acid and the

- beating function of the cardiomyocyte and its regulation through the adrenergic receptors. *Lipids* 1996 Mar;31 Suppl:S205-S210.
- Guallar E, Sanz-Gallardo MI, Van'T VP, et al. Mercury, fish oils, and the risk of myocardial infarction. *New England Journal of Medicine* 2002;347(22):1747-54.
- Haglund O, Wallin R, Luostarinen R, et al. Effects of a new fluid fish oil concentrate, ESKIMO-3, on triglycerides, cholesterol, fibrinogen and blood pressure. *Journal of Internal Medicine* 1990 May;227(5):347-53.
- Hamazaki T, Sawazaki S, Asaoka E, et al. Docosahexaenoic acid-rich fish oil does not affect serum lipid concentrations of normolipidemic young adults. *Journal of Nutrition* 1996 Nov;126(11):2784-9.
- Hansen JB, Olsen JO, Wilsgard L, et al. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipidaemic men. *European Journal of Clinical Nutrition* 1993 Jul;47(7):497-507.
- Harris WS, Connor WE, McMurry MP. The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oils. *Metabolism: Clinical & Experimental* 1983 Feb;32(2):179-84.
- Harris WS, Silveira S, Dujovne CA. The combined effects of N-3 fatty acids and aspirin on hemostatic parameters in man. *Thrombosis Research* 1990 Feb 15;57(4):517-26.
- Harris WS, Windsor SL. N-3 fatty acid supplements reduce chylomicron levels in healthy volunteers. *Journal of Applied Nutrition* 1991;43(1):5-15.
- Harris WS, Muzio F. Fish oil reduces postprandial triglyceride concentrations without accelerating lipid-emulsion removal rates. *Am J Clin Nutr* 1993 Jul;58(1):68-74.
- Harris WS, Ginsberg HN, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. *Journal of Cardiovascular Risk* 1997 Oct;4(5-6):385-91.
- Harris WS, Isley WL. Clinical trial evidence for the cardioprotective effects of omega-3 fatty acids. *Curr Atherosclerosis Rep* 2001;3(2):174-9.
- Hawkes JS, Bryan DL, Makrides M, et al. A randomized trial of supplementation with docosahexaenoic acid-rich tuna oil and its effects on the human milk cytokines interleukin 1 beta, interleukin 6, and tumor necrosis factor alpha. *Am J Clin Nutr* 2002 Apr;75(4):754-60.
- He K, Rimm EB, Merchant A, et al. Fish consumption and risk of stroke in men. *JAMA* 2002 Dec 25;288(24):3130-6.
- Hendra TJ, Britton ME, Roper DR, et al. Effects of fish oil supplements in NIDDM subjects. Controlled study. *Diabetes Care* 1990 Aug;13(8):821-9.
- Hjermann I. Dietary trials for the prevention of coronary heart disease. *Eur Heart J* 1987;8 Suppl E:39-44.
- Honstra G, van Houwelingen AC, Kivits GA, et al. Influence of dietary fish on eicosanoid metabolism in man. *Prostaglandins* 1990 Sep;40(3):311-29.
- Honstra, G. Omega-3 long-chain polyunsaturated fatty acids and health benefits. Amended and updated version of the English translation of <<Oméga-3 et bénéfice santé>>, initially published by Catherine Anselmino, Centre d'Etude et d'Information sur les Vitamines, Roche Vitamines France, Neuilly-sur-Seine (NutriScience). Available online: <<http://www.vita-web.com/whatsnew/Omega3.pdf>>. Catherine Anselmino, Centre d'Etude et d'Information sur les Vitamines, Roche Vitamines France, Neuilly-sur-Seine (NutriScience).
- Howe PR, Lungershausen YK, Cobiac L, et al. Effect of sodium restriction and fish oil supplementation on BP and thrombotic risk factors in patients treated with ACE inhibitors. *Journal of Human Hypertension* 1994 Jan;8(1):43-9.
- Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 1999 May;69(5):890-7.
- Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. [see comments.]. *American Journal of Epidemiology* 1999 Mar 15;149(6):531-40.
- Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002 Apr 10;287(14):1815-21.
- Institute of Medicine. Chapter 3. Methods of Technology Assessment in Assessing Medical Technologies. Washington DC, National Academy Press, 1985.
- Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Applications in Dietary Assessment. 2000. Washington DC, National Academy Press.
- Institute of Medicine. Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fat ty Acids, Cholesterol, Protein, and Amino Acids (Macronutrition). National Academy Press, 2002
- Iso H, Stampfer MJ, Manson JE, et al. Prospective study of fat and protein intake and risk of intraparenchymal

- hemorrhage in women. *Circulation* 2001 Feb 13;103(6):856-63.
- Iso H, Rexrode KM, Stampfer MJ, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA* 2001 Jan 17;285(3):304-12.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996 Feb;17(1):1-12.
- James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71(1 SUPPL.):343S-8S.
- Johansen O, Brekke M, Seljeflot I, et al. N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. *Coronary Angioplasty Restenosis Trial. Journal of the American College of Cardiology* 1999 May;33(6):1619-26.
- Kahl PE, Schimke E, Hildebrandt R, et al. The influence of cod-liver oil diet on various lipid metabolism parameters, the thromboxane formation capacity, platelet function and the serum MDA level in patients suffering from myocardial infarction. *Cor et Vasa* 1987;29(3):199-208.
- Kaminski WE, Jendraschak E, Kiefl R, et al. Dietary omega-3 fatty acids lower levels of platelet-derived growth factor mRNA in human mononuclear cells. *Blood* 1993;81(7):1871-9.
- Kaul U, Sanghvi S, Bahl VK, et al. Fish oil supplements for prevention of restenosis after coronary angioplasty. *International Journal of Cardiology* 1992 Apr;35(1):87-93.
- Keli SO, Feskens EJ, Kromhout D. Fish consumption and risk of stroke. The Zutphen Study. *Stroke* 1994 Feb;25(2):328-32.
- Kinjo Y, Beral V, Akiba S, et al. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. *Journal of Epidemiology* 1999 Aug;9(4):268-74.
- Kristensen SD, Iversen AM, Schmidt EB. N-3 polyunsaturated fatty acids and coronary thrombosis. [Review] [39 refs]. *Lipids* 2001;36:S79-S82.
- Kromhout D, Bosschieter EB, de Lezenne CC. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *New England Journal of Medicine* 1985 May 9;312(19):1205-9.
- Kromhout D. N-3 fatty acids and coronary heart disease: epidemiology from Eskimos to Western populations. *Journal of Internal Medicine Supplement* 1989;225(731):47-51.
- Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *International Journal of Epidemiology* 1995 Apr;24(2):340-5.
- Krummel, D. "Chapter 23: Nutrition in Cardiovascular Disease". In Krause's food, nutrition, and diet therapy. L. Kathleen Mahan, Sylvia Escot-Stump.-9th ed. 1996. W.B. Saunders Company.
- Landmark K, Thaulow E, Hysing J, et al. Effects of fish oil, nifedipine and their combination on blood pressure and lipids in primary hypertension. *Journal of Human Hypertension* 1993 Feb;7(1):25-32.
- Leaf A, Weber PC. Cardiovascular effects of n-3 fatty acids. [Review] [86 refs]. *New England Journal of Medicine* 1988 Mar 3;318(9):549-57.
- Leaf A, Jorgensen MB, Jacobs AK, et al. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 1994 Nov;90(5):2248-57.
- Leng GC, Lee AJ, Fowkes FG, et al. Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease. *Clinical Nutrition* 1998 Dec;17(6):265-71.
- Leren P. The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. *Acta Med Scand* 1966; Suppl 466:1-92.
- Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Annals of Internal Medicine* 2003 Jul 15;139(2):137-47.
- Levinson PD, Iosiphidis AH, Saritelli AL, et al. Effects of n-3 fatty acids in essential hypertension. *American Journal of Hypertension* 1990 Oct;3(10):754-60.
- Luo J, Rizkalla SW, Vidal H, et al. Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men. Results of a controlled study. *Diabetes Care* 1998 May;21(5):717-24.
- Marchioli R, Schweiger C, Tavazzi L, et al. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lipids* 2001;36:Suppl-26.
- Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. [see comments.]. *Circulation* 2002 Apr 23;105(16):1897-903.



- Maresta A, Balducci M, Varani E, et al. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis Italian Study (ESPRIT). *American Heart Journal* 2002 Jun;143(6):E5.
- Margolin G, Huster G, Glueck CJ, et al. Blood pressure lowering in elderly subjects: a double-blind crossover study of omega-3 and omega-6 fatty acids. *Am J Clin Nutr* 1991 Feb;53(2):562-72.
- Mehta J, Lawson D, Saldeen TJ. Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acid (PUFA) intake. *American Heart Journal* 1988 Nov;116(5:Pt 1):t-6.
- Mehta JL, Lopez LM, Lawson D, et al. Dietary supplementation with omega-3 polyunsaturated fatty acids in patients with stable coronary heart disease. Effects on indices of platelet and neutrophil function and exercise performance. *Am J Med* 1988 Jan;84(1):45-52.
- Meydani M, Natiello F, Goldin B, et al. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *Journal of Nutrition* 1991 Apr;121(4):484-91.
- Meydani SN, Endres S, Woods MM, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *Journal of Nutrition* 1991 Apr;121(4):547-55.
- Milner MR, Gallino RA, Leffingwell A, et al. Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal coronary angioplasty. *American Journal of Cardiology* 1989 Aug 1;64(5):294-9.
- Moreno LA, Sarria A, Popkin BM. The nutrition transition in Spain: A European Mediterranean country. *Eur J Clin Nutr* 2002;56(10):992-1003.
- Mori TA, Vandongen R, Masarei JR, et al. Dietary fish oils increase serum lipids in insulin-dependent diabetics compared with healthy controls. *Metabolism: Clinical & Experimental* 1989 May;38(5):404-9.
- Mori TA, Vandongen R, Masarei JRL, et al. Comparison of diets supplemented with fish oil or olive oil on plasma lipoproteins in insulin-dependent diabetics. *Metabolism: Clinical & Experimental* 1991;40(3):241-6.
- Mori TA, Vandongen R, Mahanian F, et al. The effect of fish oil on plasma lipids, platelet and neutrophil function in patients with vascular disease. *Advances in Prostaglandin, Thromboxane, & Leukotriene Research* 1991;21A:229-32.
- Mori TA, Vandongen R, Mahanian F, et al. Plasma lipid levels and platelet and neutrophil function in patients with vascular disease following fish oil and olive oil supplementation. *Metabolism: Clinical & Experimental* 1992 Oct;41(10):1059-67.
- Mori TA, Bao DQ, Burke V, et al. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* 1999 Aug;34(2):253-60.
- Mori TA, Bao DQ, Burke V, et al. Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *Am J Clin Nutr* 1999 Nov;70(5):817-25.
- Mori TA, Dunstan DW, Burke V, et al. Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients. *Metabolism: Clinical & Experimental* 1999 Nov;48(11):1402-8.
- Mori TA, Burke V, Puddey IB, et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *Am J Clin Nutr* 2000 May;71(5):1085-94.
- Mori TA, Puddey IB, Burke V, et al. Effect of omega 3 fatty acids on oxidative stress in humans: GC-MS measurement of urinary F2-isoprostane excretion. *Redox Report* 2000;5(1):45-6.
- Mori TA, Watts GF, Burke V, et al. Differential effects of eicosapentaenoic acid and docosahexaenoic acid on vascular reactivity of the forearm microcirculation in hyperlipidemic, overweight men. *Circulation* 2000 Sep 12;102(11):1264-9.
- Morris MC, Taylor JO, Stampfer MJ, et al. The effect of fish oil on blood pressure in mild hypertensive subjects: a randomized crossover trial. *Am J Clin Nutr* 1993 Jan;57(1):59-64.
- Morris MC, Manson JE, Rosner B, et al. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *American Journal of Epidemiology* 1995 Jul 15;142(2):166-75.
- Mozaffarian DLR. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation* 2003 Mar 18;107(10):1372-7.
- Mueller BA, Talbert RL, Tegeler CH, et al. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. *Journal of Clinical Pharmacology* 1991 Feb;31(2):185-90.
- Myrup B, Rossing P, Jensen T, et al. Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic

- patients with diabetic nephropathy. *Scandinavian Journal of Clinical & Laboratory Investigation* 2001;61(5):349-56.
- Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. *Am J Epidemiol* 2002;156(9):824-31.
- Nair SS, Leitch JW, Falconer J, et al. Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. [Review] [93 refs]. *Journal of Nutrition* 1997 Mar;127(3):383-93.
- Natvig H, Borchgrevink CF, Dedichen J, et al. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. *Scandinavian Journal of Clinical & Laboratory Investigation - Supplement* 1968;105:1-20.
- Nau KL, Katch VL, Tsai AC. Omega-3 polyunsaturated fatty acid supplementation alters selective plasma lipid values in adults with heart disease. *Journal of Cardiopulmonary Rehabilitation* 1991;11(6):386-91.
- Nelson GJ, Kelley DS, Emken EA, et al. A human dietary arachidonic acid supplementation study conducted in a metabolic research unit: rationale and design. *Lipids* 1997 Apr;32(4):415-20.
- Nelson GJ, Schmidt PS, Bartolini GL, et al. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids* 1997 Nov;32(11):1129-36.
- Nenseter MS, Osterud B, Larsen T, et al. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutrition Metabolism & Cardiovascular Diseases* 2000 Dec;10(6):323-30.
- Ness AR, Hughes J, Elwood PC et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet Reinfarction Trial (DART). *Eur J Clin Nutr* 2002;56:512-8.
- Nielsen NS, Pedersen A, Sandstrom B, et al. Different effects of diets rich in olive oil, rapeseed oil and sunflower-seed oil on postprandial lipid and lipoprotein concentrations and on lipoprotein oxidation susceptibility. *Br J Nutr* 2002 May;87(5):489-99.
- Nilsen DW, Dalaker K, Nordoy A, et al. Influence of a concentrated ethylester compound of n-3 fatty acids on lipids, platelets and coagulation in patients undergoing coronary bypass surgery. *Thrombosis & Haemostasis* 1991 Aug 1;66(2):195-201.
- Nilsen DW, Albrektsen G, Landmark K, et al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001 Jul;74(1):50-6.
- Nordoy A, Hatcher L, Goodnight S, et al. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid production and hemostatic parameters in normal men. *Journal of Laboratory & Clinical Medicine* 1994 Jun;123(6):914-20.
- Nozaki S, Garg A, Vega GL, et al. Postheparin lipolytic activity and plasma lipoprotein response to omega-3 polyunsaturated fatty acids in patients with primary hypertriglyceridemia. *American Journal of Clinical Nutrition* 1991 Mar;53(3):638-42.
- Oomen CM, Feskens EJ, Rasanen L, et al. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *American Journal of Epidemiology* 2000 May 15;151(10):999-1006.
- Oomen CM, Ocke MC, Feskens EJ, et al. alpha-Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. [see comments.]. *Am J Clin Nutr* 2001 Oct;74(4):457-63.
- Orencia AJ, Daviglus ML, Dyer AR, et al. Fish consumption and stroke in men. 30-year findings of the Chicago Western Electric Study. *Stroke* 1996 Feb;27(2):204-9.
- Osler M, Andreasen AH, Hoidrup S. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged Danish adults. *J Clin Epidemiol* 2003;56:274-9.
- Otto C, Ritter MM, Soennichsen AC, et al. Effects of n-3 fatty acids and fenofibrate on lipid and hemorheological parameters in familial dysbetalipoproteinemia and familial hypertriglyceridemia. *Metabolism, Clinical and Experimental* 1996 Apr;45(10):1305-11.
- Owens MR, Cave WT, Jr. Dietary fish lipids do not diminish platelet adhesion to subendothelium. *British Journal of Haematology* 1990 May;75(1):82-5.
- Phillipson BE, Rothrock DR, Connor WE et al. Reduction of plasma lipids, lipoproteins and apoproteins by dietary fish oils in patients with hypertriglyceridemia. *N Engl J Med* 1985;312:1210-6.
- Pietinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *American Journal of Epidemiology* 1997 May 15;145(10):876-87.
- Pirich C, Gaszo A, Granegger S, et al. Effects of fish oil supplementation on platelet survival and ex vivo platelet function in hypercholesterolemic patients. *Thrombosis Research* 1999 Nov 1;96(3):219-27.

- Prisco D, Paniccia R, Filippini M, et al. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. *Thrombosis Research* 1994 Nov 1;76(3):237-44.
- Prisco D, Filippini M, Francalanci I, et al. Effect of n-3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet phospholipids and on platelet functions. *Metabolism: Clinical & Experimental* 1995 May;44(5):562-9.
- Prisco D, Paniccia R, Bandinelli B, et al. Effect of medium-term supplementation with a moderate dose of n-3 polyunsaturated fatty acids on blood pressure in mild hypertensive patients. *Thrombosis Research* 1998 Aug 1;91(3):105-12.
- Radack K, Deck C, Huster G. The effects of low doses of n-3 fatty acid supplementation on blood pressure in hypertensive subjects. A randomized controlled trial. *Archives of Internal Medicine* 1991 Jun;151(6):1173-80.
- Radack KL, Deck CC, Huster GA. N-3 fatty acid effects on lipids, lipoproteins, and apolipoproteins at very low doses: results of a randomized controlled trial in hypertriglyceridemic subjects. *Am J Clin Nutr* 1990 Apr;51(4):599-605.
- Reis GJ, Kuntz RE, Silverman DI, et al. Effects of serum lipid levels on restenosis after coronary angioplasty. *American Journal of Cardiology* 1991 Dec 1;68(15):1431-5.
- Reis GJ, Silverman DI, Boucher DM et al. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. *Am J Cardiol* 1990;66(17):1171-5.
- Renaud S, de Lorgeril M, Delaye J, et al. Cretan Mediterranean diet for prevention of coronary heart disease. *Am J Clin Nutr* 1995 Jun;61(6:Suppl):Suppl-1367S.
- Rhodes LE, O'Farrell S, Jackson MJ, et al. Dietary fish-oil supplementation in humans reduces UVB-erythral sensitivity but increases epidermal lipid peroxidation. *Journal of Investigative Dermatology* 1994 Aug;103(2):151-4.
- Rodriguez AF, Guallar-Castillon P, Banegas B, Jr., et al. Consumption of fruit and wine and the decline in cerebrovascular disease mortality in Spain (1975-1993). [see comments.]. *Stroke* 1998 Aug;29(8):1556-61.
- Rodriguez BL, Sharp DS, Abbott RD, et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. *Circulation* 1996 Sep 1;94(5):952-6.
- Rossing P, Hansen BV, Nielsen FS, et al. Fish oil in diabetic nephropathy. *Diabetes Care* 1996 Nov;19(11):1214-9.
- Russo C, Olivieri O, Girelli D, et al. Omega-3 polyunsaturated fatty acid supplements and ambulatory blood pressure monitoring parameters in patients with mild essential hypertension. *Journal of Hypertension* 1995 Dec;13(12:Pt 2):t-6.
- Sacks FM, Stone PH, Gibson CM, et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. *Journal of the American College of Cardiology* 1995 Jun;25(7):1492-8.
- Salachas A, Papadopoulos C, Sakadamis G, et al. Effects of a low-dose fish oil concentrate on angina, exercise tolerance time, serum triglycerides, and platelet function. *Angiology* 1994 Dec;45(12):1023-31.
- Sasazuki S, Fukuoka Heart Study Group. Case-control study of nonfatal myocardial infarction in relation to selected foods in Japanese men and women. *Japanese Circulation Journal* 2001 Mar;65(3):200-6.
- Satterfield S, Cutler JA, Langford HG, et al. Trials of hypertension prevention. Phase I design. *Annals of Epidemiology* 1991 Aug;1(5):455-71.
- Saynor R, Gillott T. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids* 1992;27(7):533-8.
- Schechtman G, Kaul S, Kissebah AH. Effect of fish oil concentrate on lipoprotein composition in NIDDM. *Diabetes* 1988 Nov;37(11):1567-73.
- Schechtman G, Kaul S, Cherayil GD, et al. Can the hypotriglyceridemic effect of fish oil concentrate be sustained? *Annals of Internal Medicine* 1989 Mar 1;110(5):346-52.
- Schmidt EB, Kristensen SD, Sorensen PJ, et al. Antithrombin III and protein C in stable angina pectoris--influence of dietary supplementation with polyunsaturated fatty acids. *Scandinavian Journal of Clinical & Laboratory Investigation* 1988 Sep;48(5):469-73.
- Schmidt EB, Ernst E, Varming K, et al. The effect of n-3 fatty acids on lipids and haemostasis in patients with type IIa and type IV hyperlipidaemia. *Thrombosis & Haemostasis* 1989 Sep 29;62(2):797-801.
- Schmidt EB, Sorensen PJ, Pedersen JO, et al. The effect of n-3 polyunsaturated fatty acids on lipids, haemostasis, neutrophil and monocyte chemotaxis in insulin-dependent diabetes mellitus. *Journal of Internal Medicine Supplement* 1989;225(731):201-6.

- Schmidt EB, Nielsen LK, Pedersen JO, et al. The effect of n-3 polyunsaturated fatty acids on lipids, platelet function, coagulation, fibrinolysis and monocyte chemotaxis in patients with hypertension. *Clinica Chimica Acta* 1990 Jul;189(1):25-32.
- Schmidt EB, Pedersen JO, Varming K, et al. n-3 fatty acids and leukocyte chemotaxis. Effects in hyperlipidemia and dose-response studies in healthy men. *Arteriosclerosis & Thrombosis* 1991 Mar;11(2):429-35.
- Schmidt EB, Lervang H-H, Varming K, et al. Long-term supplementation with n-3 fatty acids, I: Effect on blood lipids, haemostasis and blood pressure. *Scandinavian Journal of Clinical & Laboratory Investigation* 1992;52(3):221-8.
- Schmidt EB, Varming K, Svaneborg N, et al. n-3 polyunsaturated fatty acid supplementation (Pikasol) in men with moderate and severe hypertriglyceridaemia: a dose-response study. *Annals of Nutrition & Metabolism* 1992;36(5-6):283-7.
- Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials.[comment]. *JAMA* 1995 Feb 1;273(5):408-12.
- Seino F, Date C, Nakayama T, et al. Dietary lipids and incidence of cerebral infarction in a Japanese rural community. *Journal of Nutritional Science & Vitaminology* 1997 Feb;43(1):83-99.
- Shah, BV, Barnwell, BG, and Bieler, GS. SUDAAN User's Manual, Release 7.5. Research Triangle Institute. 1997. Research Triangle Park, NC.
- Shinozaki K, Kambayashi J, Kawasaki T, et al. The long-term effect of eicosapentaenoic acid on serum levels of lipoprotein (a) and lipids in patients with vascular disease. *Journal of Atherosclerosis & Thrombosis* 1996;2(2):107-9.
- Silva JM, Souza I, Silva R, et al. The triglyceride lowering effect of fish oils is affected by fish consumption. *International Journal of Cardiology* 1996 May;57(1):75-80.
- Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival--4. *Cardiovascular Drugs & Therapy* 1997 Jul;11(3):485-91.
- Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): A randomised single-blind trial. *Lancet* 2002;360(9344):1455-61.
- Sirtori CR, Paoletti R, Mancini M, et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. *Italian Fish Oil Multicenter Study. American Journal of Clinical Nutrition* 1997 Jun;65(6):1874-81.
- Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995 Nov 1;274(17):1363-7.
- Slimani N, Ferrari P, Ocke M, et al. Standardization of the 24-hour diet recall calibration method used in the European prospective investigation into cancer and nutrition (EPIC): general concepts and preliminary results. *European Journal of Clinical Nutrition* 2000 Dec;54(12):900-17.
- Smith P, Arnesen H, Opstad T, et al. Influence of highly concentrated n-3 fatty acids on serum lipids and hemostatic variables in survivors of myocardial infarction receiving either oral anticoagulants or matching placebo. *Thrombosis Research* 1989 Mar 1;53(5):467-74.
- Solomon SA, Cartwright I, Pockley G, et al. A placebo-controlled, double-blind study of eicosapentaenoic acid-rich fish oil in patients with stable angina pectoris. *Current Medical Research & Opinion* 1990;12(1):1-11.
- Stark KD, Park EJ, Maines VA, et al. Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial. *Am J Clin Nutr* 2000 Aug;72(2):389-94.
- Steiner A, Oertel R, Battig B, et al. Effect of fish oil on blood pressure and serum lipids in hypertension and hyperlipidaemia. *J Hypertens* 1989;7(SUPPL. 3):S73-S76.
- Suehiro A, Higasa S, Ueda M, et al. Combination effect of eicosapentaenoic acid and platelet suppressive agents on platelets. *Current Therapeutic Research, Clinical & Experimental* 1994;55(6):653-9.
- Swails WS, Bell SJ, Bistrian BR, et al. Fish-oil-containing diet and platelet aggregation. *Nutrition* 1993 May;9(3):211-7.
- Tamura Y, Hirai A, Terano T, et al. Anti-thrombotic and anti-atherogenic action of eicosapentaenoic acid. *Japanese Circulation Journal* 1987 Apr;51(4):471-7.
- Tavani A, Pelucchi C, Negri E, et al. n-3 Polyunsaturated fatty acids, fish, and nonfatal acute myocardial infarction. *Circulation* 2001 Nov 6;104(19):2269-72.
- Terano T, Hirai A, Hamazaki T, et al. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis* 1983 Mar;46(3):321-31.
- Tippett, KS, Enns, CW, and Moshfegh, AJ. Food Consumption Survey in the U.S. Department of

Agriculture. National Today 34[1], 33-46. 1999.

Toft I, Bonna KH, Ingebrechtsen OC, et al. Fibrinolytic function after dietary supplementation with omega-3 polyunsaturated fatty acids. *Arteriosclerosis Thrombosis & Vascular Biology* 1997 May;17(5):814-9.

Toth K, Ernst E, Habon T, et al. Hemorheological and hemodynamical effects of fish oil (Ameu) in patients with ischemic heart disease and hyperlipoproteinemia. *Clinical Hemorheology* 1995;15(6):867-75.

USDA. Individual Fatty Acid Intakes: Results from the 1995 Continuing Survey of Food Intakes by Individuals (data table set 4). Available online at <http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm>.

van Houwelingen AC, Hennissen AA, Verbeek-Schippers F, et al. Effect of a moderate fish intake on platelet aggregation in human platelet-rich plasma. *Thrombosis & Haemostasis* 1988 Jun 16;59(3):507-13.

Vane JR, Flower RJ, Botting RM. History of aspirin and its mechanism of action. *Stroke* 1990 Dec;21(12(Suppl)):Suppl-23.

Verheugt FWA, Schouten JA, Eeltink JC, et al. Omega-3 polyunsaturated fatty acids in the treatment of angina pectoris: Effect on objective signs of exercise-induced myocardial ischemia. *Current Therapeutic Research, Clinical & Experimental* 1986;39(2):208-13.

Vericel E, Calzada C, Chapuy P, et al. The influence of low intake of n-3 fatty acids on platelets in elderly people. *Atherosclerosis* 1999 Nov 1;147(1):187-92.

Vessby B, Boberg M. Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-dependent diabetes mellitus. *J Intern Med* 1990 Aug;228(2):165-71.

Villa B, Calabresi L, Chiesa G, et al. Omega-3 fatty acid ethyl esters increase heart rate variability in patients with coronary disease. *Pharmacol Res* 2002 Jun;45(6):475.

Vollset SE, Heuch I, Bjelke E. Fish consumption and mortality from coronary heart disease. *New Engl J Med* 1985;313:820-7.

von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *Journal of Clinical Investigation* 1985 Oct;76(4):1626-31.

von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. *Journal of Clinical Investigation* 1985 Dec;76(6):2446-50.

von Schacky C, Angerer P, Kothny W, et al. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999 Apr 6;130(7):554-62.

Wander RC, Du S-H, Ketchum SO, et al. Effects of interaction of RRR-alpha-tocopheryl acetate and fish oil on low-density-lipoprotein oxidation in postmenopausal women with and without hormone-replacement therapy. *Am J Clin Nutr* 1996;63(2):184-93.

Warner JG, Ullrich IH, Albrink MJ, et al. Combined effects of aerobic exercise and omega-3 fatty acids in hyperlipidemic persons. *Medicine & Science in Sports & Exercise* 1989;21(5):498-505.

Welch AA, Lund E, Amiano P, et al. Variability in fish consumption in 10 European countries. *IARC Scientific Publications* 2002;156:221-2.

Welch AA, Lund E, Amiano P, et al. Variability of fish consumption within the 10 European countries participating in the European Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutrition* 2002 Dec;5(6B):1273-85.

Wing LM, Nestel PJ, Chalmers JP, et al. Lack of effect of fish oil supplementation on blood pressure in treated hypertensives. *Journal of Hypertension* 1990 Apr;8(4):339-43.

Wojenski CM, Silver MJ, Walker J. Eicosapentaenoic acid ethyl ester as an antithrombotic agent: comparison to an extract of fish oil. *Biochimica et Biophysica Acta* 1991 Jan 4;1081(1):33-8.

Wright, JD, Ervin, B, and Briefel, RR. Consensus workshop on dietary assessment: nutrition monitoring and tracking the year 2000 objectives. Available on line at <http://www.cdc.gov/nchs/data/misc/nutri94acc.pdf>. 1994. Hyattsville, MD, National Center for Health Statistics.

Yam D, Friedman J, Bott-Kanner G, et al. Omega-3 fatty acids reduce hyperlipidaemia, hyperinsulinaemia and hypertension in cardiovascular patients. *Journal of Clinical & Basic Cardiology* 2002;5(3):229-31.

Yoshizawa K, Rimm EB, Morris JS, et al. Mercury and the risk of coronary heart disease in men. *New England Journal of Medicine* 2002;347(22):1755-60.

Yuan JM, Ross RK, Gao YT, et al. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *American Journal of Epidemiology* 2001 Nov 1;154(9):809-16.

## Excluded Studies

Author, Year	Title	Reason
Bainton, 1992 British Heart Journal, 68:60-66	Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Bairati, 1993 Canadian Journal of Cardiology, 9:225-230	Measurement errors in standard visual analysis of coronary angiograms: consequences on clinical trials.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Bang, 1980 American Journal of Clinical Nutrition, 33:2657-2661	Personal reflections on the incidence of ischaemic heart disease in Oslo during the Second World War.	No outcome of interest
Bang, 1981 Acta Medica Scandinavia, 210:245-248	The consumption of the Eskimo food in north Western Greenland.	Review (not primary study)
Bates, 1985 Prostaglandins Leukotrienes & Medicine, 17:77-84	Plasma essential fatty acids in pure and mixed race American Indians on and off a diet exceptionally rich in salmon.	Measurements of serum fatty acid
Baylin, 2003 Circulation, 17:1586-1591	Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica.	Adipose tissue
Berg, 1991 Clinica Chimica Acta, 198:271-277	The effect of n-3 polyunsaturated fatty acids on Lp(a).	No outcome of interest
Boniface, 2002 European Journal of Clinical Nutrition, 56:786-792	Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Brox, 2002 European Journal of Clinical Nutrition, 56:694-700	Blood lipids, fatty acids, diet and lifestyle parameters in adolescents from a region in northern Norway with a high mortality from coronary heart disease.	No outcomes of interest; age less than "adult"
Burr, 2001 European Heart Journal Supplements, 3:D75-D78	Evidence and perspectives on n-3 polyunsaturated fatty acids in cardiovascular disease 2001; biological background, and research priorities on n-3 fatty acids.	Review (not primary study)
Crombie, 1987 European Heart Journal, 6:560-563	International differences in coronary heart disease mortality and consumption of fish and other foodstuffs.	Inappropriate Intervention/Exposure (No fish intake data)
Das, 1995 Prostaglandins Leukotrienes & Essential Fatty Acids, 52:387-391	Essential fatty acid metabolism in patients with essential hypertension, diabetes mellitus and coronary heart disease.	Inappropriate Intervention/Exposure (No fish or omega-3 fatty acid intake data)
Dayton, 1968 Lancet, 2:1060-1062	Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications.	Serum composition
Djoussé, 2003 American Journal of Clinical Nutrition, 77:819-825	Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung and Blood Institute Family Heart Study.	Inappropriate Intervention/Exposure
Guallar, 1995 Journal of the American	A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians.	Plasma fish oil level

Author, Year	Title	Reason
College of Cardiology, 25:387-394		
Guallar, 1999 Arteriosclerosis Thrombosis & Vascular Biology, 19:1111- 1118	Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study.	Adipose tissue level
Haligren, 2001 British Journal of Nutrition, 86:397-404	Markers of high fish intake are associated with decreased risk of a first myocardial infarction.	No outcome of interest
Hardarson, 1989 Journal of Internal Medicine, 226:33-37	Cod liver oil does not reduce ventricular extrasystoles after myocardial infarction.	No outcome of interest
Hu, 1999 American Journal of Clinical Nutrition, 70:1001-1008	Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women.	Inappropriate Intervention/Exposure (No fish or omega-3 fatty acid data)
Hunter, 1988 American Journal of Preventive Medicine, 4:5-10	Fish consumption and cardiovascular mortality in Canada: an inter-regional comparison.	Inappropriate Intervention/Exposure (No fish intake data quantified)
Iso, 2002 Stroke, 22:2086-2093	Linoleic acid, other fatty acids, and the risk of stroke.	Serum composition
Joossens, 1989 Acta Cardiologica, 44:157- 182	Nutrition and cardiovascular mortality in Belgium. For the B.I.R.N.H. study group.	Inappropriate Intervention/Exposure (No omega-3 fatty acid data)
Lancet, 1968 2:693-699	Controlled trial of soya-bean oil in myocardial infarction.	Inappropriate Intervention/Exposure (No omega-3 fatty acid data)
Laurenzi, 1989 Preventive Medicine, 18:35- 44	Is Italy losing the "Mediterranean advantage?" Report on the Gubbio population study: cardiovascular risk factors at baseline.	Inappropriate Intervention/Exposure (No omega-3 fatty acid data)
Lemaitre, 2002 Circulation, 105:697-701	Cell membrane trans-fatty acids and the risk of primary cardiac arrest.	Inappropriate Intervention/Exposure (No omega-3 fatty acid data)
Lemaitre, 2003 Am J Clin Nutr, 77:319-325	n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study.	Serum composition
Leng, 1999 Vascular Medicine, 4:219-226	Essential fatty acids and cardiovascular disease: the Edinburgh Artery Study.	Serum composition
Martinez- Gonzalez, 2002 European Journal of Nutrition, 41:153-160	Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score.	Inappropriate Intervention/Exposure (No fish intake data)
Mehta, 1988 American Journal of Medicine, 84:45-52	Dietary supplementation with omega-3 polyunsaturated fatty acids in patients with stable coronary heart disease. Effects on indices of platelet and neutrophil function and exercise performance.	No outcome of interest
Miettinen, 1982 British Medical Journal, 285:993-996	Fatty-acid composition of serum lipids predicts myocardial infarction.	Inappropriate Intervention/Exposure (No omega-3 fatty acid data)
Nakamura, 2003	Serum fatty acid levels, dietary style and coronary heart	Serum composition

Author, Year	Title	Reason
Br J Nutr, 89:267-272	disease in three neighboring areas in Japan: the Kumihama study.	
Nobmann, 1998 International Journal of Circumpolar Health, 57:4-17	Dietary intakes among Siberian Yupiks of Alaska and implications for cardiovascular disease.	No outcome of interest
Norell, 1986 BMJ, 293:436	Fish consumption and mortality from coronary heart disease.	No outcome of interest (letter only)
Omoto, 1984 Nippon Eiseigaku Zasshi – Japanese Journal of Hygiene, 38:887-898	Dietary habits and cardiovascular diseases (I). The mortality rate from cerebrovascular and cardiovascular diseases and the eicosapentaenoic acid and arachidonic acid ratio in the blood of the inland- and coast-dwellers in Japan.	No outcome of interest
Paganelli, 2001 International Journal of Cardiology, 78:27-32	Altered erythrocyte n-3 fatty acids in Mediterranean patients with coronary artery disease.	Serum composition
Pedersen, 1999 Lancet, 353:812-813	N-3 fatty acids as a risk factor for haemorrhagic stroke.	N<=5 in omega-3 treatment arm (4 cases)
Pitsavos, 2002 Coronary Artery Disease, 13:295-300	The effect of Mediterranean diet on the risk of the development of acute coronary syndromes in hypercholesterolemic people: a case-control study.	Inappropriate Intervention/Exposure (Mediterranean diet, fish intake not quantified)
Rodriguez, 1998 Stroke, 29:1556-1561	Consumption of fruit and wine and the decline in cerebrovascular disease mortality in Spain.	Review (not primary studies)
Schmidt, 1988 Scandinavian Journal of Clinical & Laboratory Investigation, 48:469-473	Antithrombin III and protein C in stable angina pectoris— influence of dietary supplementation with polyunsaturated fatty acids.	No outcomes of interest
Simon, 1995 American Journal of Epidemiology, 142:469-476	Serum fatty acids and the risk of coronary heart disease.	Serum composition
Singh, 1991 Nutrition, 7:125-129	The effect of diet and aspirin on patient outcome after myocardial infarction.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Singh, 1995 Journal of the American Dietetic Association, 95:775-780	Effect of antioxidant-rich goods on plasma ascorbic acid, cardiac enzymes, and lipid peroxide levels in patients hospitalized with acute myocardial infarction.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Stampfer, 2000 New England Journal of Medicine, 343:16-22	Primary prevention of coronary heart disease in women through diet and lifestyle.	Inappropriate Intervention/Exposure (No omega-3 fatty acid)
Tornwall, 1996 Nutritional Metabolism and Cardiovascular Diseases, 6:73-80	Effect of serum and dietary fatty acids on the short-term risk of acute myocardial infarction in male smokers.	Serum composition
Vacek, 1989 Biomedicine & Pharmacotherapy, 43:375-79	Short-term effects of mega-3 fatty acids on exercise stress test parameters, angina and lipoproteins.	No outcome of interest; Dose>5 g/d
Watts, 1995 Canadian Journal of	Relationships between nutrient intake and progression/regression of coronary atherosclerosis as	Inappropriate Intervention/Exposure (No



Author, Year	Title	Reason
Cardiology, 11:110G-114G	assessed by serial quantitative angiography.	omega-3 fatty acid data)
Woo, 2002 Gerontology, 48:234-240	Lifestyle factors and health outcomes in elderly Hong Kong chinese aged 70 years and over.	Inappropriate Intervention/Exposure (No fish intake data)
Yamori, 1994 Health Reports, 6:22-27	Nutritional factors for stroke and major cardiovascular diseases: international epidemiological comparison of dietary prevention.	Inappropriate Intervention/Exposure (No intake data)
Yli-Jama, 2002 Journal of Internal Medicine, 251:19-28	Serum free fatty acid pattern and risk of myocardial infarction: a case-control study.	Serum level
Zhang, 1999 Preventive Medicine, 28:520-529	Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study.	Review (not primary study)

# Acronyms and Abbreviations

Acronyms	Abbreviation
AA (20:4 n-6)	Arachidonic acid
ABCC	Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial
ADVENTIST	Adventist Health Study
AE	Adverse events
AHRQ	Agency for Healthcare Research and Quality
ALA (18:3 n-3)	Alpha linolenic acid
AMI	Acute myocardial infarction
BMI	Body mass index
CAD	Coronary artery disease
CCD	Cross check dietary history
CCTR	Cochrane Central Register of Controlled Trials
CHD	Coronary heart disease
CHS	Cardiovascular Health Study
CI	Confidence interval
CSF II	Continuing Food Survey of Intakes by Individuals 1994-1998
CVD	Cardiovascular disease
DART	Diet and Reinfarction Trial
DHA (22:6 n-3)	Decosahexaenoic acid
DM	Diabetes mellitus
DPA (22:5 n-3 or n-6)	Docosapentaenoic acid
DRI	Dietary References Intakes
EAR	Estimated Average Requirement
ECG	Electrocardiogram
EFA	Essential fatty acid
EPA (20:5 n-3)	Eicosapentaenoic acid
EPC	Evidence-based Practice Center
EPIC	European Investigation into Cancer and Nutrition Study
FA	Fatty acid
FDA	Food and Drug Administration
FFQ	Food frequency questionnaire
GEN	General population—applicability category
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio
GLA (18:3 n-6)	Gamma linolenic acid
HPS, HPFS	Health Professionals Follow-up Study
HR	Hazard ratio
HRT	Hormone replacement therapy
HTN	Hypertension
IHD	Ischemic heart disease
IOM	Institute of Medicine
LA (18:2 n-6)	Linoleic acid
LC PUFA	Long-chain polyunsaturated fatty acid
MARGARIN	Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention Study
MI	Myocardial infarction
MRFIT	Multiple Risk Factor Intervention Trial
MUFA	Mono unsaturated fatty acid
n-3 FA	Omega-3 fatty acids
NA	Not applicable
NCHS	National Center for Health Statistics
ND	No data

<b>Acronyms</b>	<b>Abbreviation</b>
NEMC	New England Medical Center
NHANES III	National Health and Nutrition Examination 1988-1994
NHEFS	NHANES I Epidemiological Follow-up Study
NHLBI	National Heart Lung and Blood Institute (Family Heart Study)
NHS	Nurses' Health Study
NIH	National Institutes of Health
ns	not significant
ODS	Office of Dietary Supplements
PHS	Physicians' Health Study
PUFA	Polyunsaturated fatty acid
RDA	Recommended Dietary Allowances
RBC	Red blood cells
RCT	Randomized controlled trial
RR	Relative risk
RSE	Relative standard error
SC-RAND	Southern California-RAND
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SREBP	Sterol regulatory element binding protein
TC	Total cholesterol
TEP	Technical Expert Panel
TNF	Tumor necrosis factor
UO	University of Ottawa
USDA	United States Department of Agriculture
WES	(Chicago) Western Electric Study