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Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease

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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 Risk Factors and Intermediate Markers of Cardiovascular Disease was requested and funded by the 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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Structured Abstract

Context. Epidemiologic studies and clinical trials have reported beneficial effects of fish/omega-3 fatty acid consumption on several cardiovascular disease (CVD) outcomes, such as sudden death, cardiac death, and stroke. However, the mechanisms of this benefit are unclear.

Objectives. As the second of a 3-part report on this topic, we performed a systematic review of the literature to assess the effect of consumption of omega-3 fatty acids (eicosapentaenoic acid [EPA; 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], and alpha-linolenic acid [ALA, 18:3 n-3])on various CVD risk factors and intermediate markers of CVD in healthy people, people with dyslipidemia, diabetes, or known CVD.

Data Sources. We searched Medline, Embase, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau databases for potentially relevant studies.

Study Selection. We screened over 7,464 abstracts and retrieved 807 full text articles. We analyzed 123 studies that met inclusion criteria to address the key questions in this report. We included studies in which the amount of fish or omega-3 fatty acid intake was quantified, less than 6 g of omega-3 fatty acid per day was consumed, and of at least 4 weeks' duration.

Data Extraction. From each eligible study, we extracted information about the study design, population demographics, the amount of omega-3 fatty acids (in supplements or diet) or fish consumed, and outcomes. For RCTs, we extracted information about the randomization, allocation, and blinding techniques to assess methodological quality.

Data Synthesis. We examined the effect of omega-3 fatty acids on potential CVD risk factors – including lipoproteins, apolipoproteins, blood pressure, hemoglobin (Hgb) A_{1c}, C-reactive protein (CRP), hemostatic factors, platelet aggregation, and markers of diabetes – and intermediate markers of CVD – including coronary artery restenosis, carotid intima-media thickness (IMT), exercise tolerance testing, and heart rate variability. We also assessed correlations between long-chain omega-3 fatty acids intake and tissue phospholipid levels.

Among the outcomes we analyzed, omega-3 fatty acids demonstrated a consistently large, significant effect on triglycerides. The trials of triglycerides reported a net decrease in triglycerides of about 10% to 33%. The effect was dose dependent, generally consistent in different populations, and was generally larger in studies with higher mean baseline triglyceride levels. In contrast to studies of fish oils, the single study of a plant oil (ALA) found a net increase in triglycerides. The effect of omega-3 fatty acids on other serum lipids was weaker (up to a 6% increase in HDL).

Outcomes for which a small beneficial effect was found with fish oil supplementation include blood pressure (about 2 mm Hg reduction), restenosis rates after coronary angioplasty (14% reduction), exercise tolerance testing, and heart rate variability. For other evaluated outcomes, including measures of glucose tolerance, the effects of omega-3 fatty acids were either small or inconsistent across studies.

Across studies, we found a direct relationships between dose of consumed omega-3 fatty acids and changes in measured levels of EPA+DHA, either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membrane phospholipids. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA corresponds to approximately a 1% increase in EPA+DHA level.

Conclusions. A large, consistent beneficial effect of omega-3 fatty acids was found only for triglyceride levels. Little or no effect of omega-3 fatty acids was found for a variety of other cardiovascular risk factors and markers of cardiovascular disease. The benefits of omega-3 fatty acids on reducing cardiovascular disease are not well explained by the fatty acids' effects on the cardiovascular risk factors we examined. A strong, linear association was found across studies between omega-3 fatty acid intake and tissue levels.

Heterogeneity of treatment effect was common among studies across the outcomes evaluated. Given the large amount of heterogeneity across studies, many questions remain about the effect of omega-3 fatty acids in improving potential CVD risk factors and intermediate markers of CVD. Few studies addressed questions related to effect modifiers and only limited conclusions could be made regarding these factors. The optimal quantity and type of omega-3 fatty acid, ratio of dietary omega-6 to omega-3, and duration of treatment remain undefined. Future research is needed to address these issues.

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Summary

Introduction

Numerous studies have examined the relationship between dietary fat and cardiovascular disease (CVD). Most early epidemiology studies noted very low cardiovascular mortality in populations with high fish consumption.[1-4] The apparent benefit of dietary fish is explained by the intake of very long chain, highly polyunsaturated omega-3 fatty acids.[5] Since these early studies, hundreds of observational and clinical trials have been conducted to analyze the effect of both marine and plant sources of omega-3 fatty acids on CVD and a wide range of risk factors and intermediate markers of CVD, and to define and explain the potential benefits of increased intake of the omega-3 fatty acids. The primary omega-3 fatty acids of interest include eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), which are derived primarily from marine sources, and alpha-linolenic acid (ALA, 18:3 n-3), which is derived primarily from plant sources.

This report examines evidence addressing both the association in humans between omega-3 fatty acids and cardiovascular intermediate outcomes and risk factors and the association between omega-3 fatty acids and tissue or plasma levels of omega-3 fatty acids. The three specific populations of interest are healthy adults with no known CVD or risk factors; adults at increased risk of CVD due specifically to diabetes, hypertension, or hyperlipidemia; and adults with known CVD. The exposure of interest is omega-3 fatty acids. 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 exposure. In addition, because of a lack of clarity regarding the most accurate measure of levels of omega-3 fatty acids in the body, we also address how omega-3 fatty acid intake relates to different measures of tissue and plasma fatty acid levels.

A large number of putative risk factors for and intermediate markers of CVD exist, including markers for different aspects of CVD, markers for risk factors of CVD, and markers for other factors related to cardiovascular health. However, the relationship between most of these laboratory measurements or diagnostic tests and aspects of atherosclerosis such as inflammation, are generally unproven. The relationships between these factors and actual clinical disease and events are generally even more theoretical. Based on these limitations and the available data, the effects of omega-3 fatty acid intake on the following risk factors are addressed in this report: total cholesterol; low density lipoprotein cholesterol (LDL); high density lipoprotein cholesterol (HDL); triglycerides (Tg); lipoprotein(a) [Lp(a)]; apolipoprotein (apo) A1; apo B; apo B-100 and LDL apo B; systolic and diastolic blood pressure (BP); hemoglobin (Hgb) A_{1c}; fasting blood sugar (FBS); fasting insulin; C-reactive protein (CRP); fibrinogen; factors VII, VIII, and von Willebrand factor (vWF); and platelet aggregation. In addition, we examine the following intermediate markers of CVD: coronary artery restenosis after

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angioplasty, carotid artery intima-media thickness (IMT), exercise tolerance testing (ETT), and heart rate (HR) variability.

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 that were requested and funded by the Office of Dietary Supplements, National Institutes of Health (NIH), 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 EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

Methods

Key Questions

Four general questions are addressed in this report:

1. What is the effect of omega-3 fatty acids on intermediate markers and risk factors of CVD?
2. What is the effect of different omega-3 fatty acids and different sources of the fatty acids?
3. How does the effect of omega-3 fatty acids differ in different sub-populations and in relation to various confounders?
4. What is the association between intake levels of omega-3 fatty acids and tissue levels?

Literature Search Strategy

We conducted comprehensive literature searches using six databases including MEDLINE®, PreMEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Biological Abstracts, and Commonwealth Agricultural Bureau (CAB) Health. Primary searches were performed between December 2002 and February 2003. General updated searches were conducted through April 2003 and highly focused updates were conducted through July 2003. Additional publications were identified from reference lists of review and primary articles, from domain experts, and the other two EPCs.

Selection Criteria and Screening Process

All abstracts identified through the literature search were screened using predetermined eligibility criteria. We identified all English language 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. We excluded abstracts that included only subjects who had a non-CVD-related condition (e.g., cancer, schizophrenia, or organ transplant), letters, and abstracts.

Upon review of full articles we excluded studies of children (under age 19 years), studies of daily omega-3 fatty acid doses of more than 6 g per day, studies of less than 4 weeks duration, crossover studies with less than 4 weeks washout between treatments, and studies that did not report complete data on outcomes of interest. We also excluded studies that did not report either the specific dose of omega-3 fatty acids or the amount of fish consumed and studies that reported only associations between omega-3 fatty acid tissue levels and risk factors. 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 the control.

Because of the large number of studies available for analysis, for most outcomes of interest we confined analysis to the largest randomized trials for each outcome evaluated. For outcomes with few studies, all studies were included regardless of study design or sample size (minimum of five subjects). We limited our review of studies examining the association between dietary omega-3 fatty acid intake and tissue levels of omega-3 fatty acids to the larger randomized trials that met eligibility criteria for either intermediate or clinical outcomes.

Data Extraction

Each eligible study was fully extracted by a single reviewer. 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: study design, blinding, randomization method, allocation concealment method, country, funding source, study duration, eligibility criteria, sample characteristics, number enrolled and analyzed, reasons for withdrawals, description of omega-3 fatty acid and control interventions or diets, intermediate and clinical outcomes, adverse events, results, and whether each study addressed each of the key questions. In addition, each study was categorized based on applicability and study quality.

Grading Study Quality

In order to improve consistency among omega-3 fatty acid reports by the three EPCs, we used three measures of study quality to evaluate the evidence:

- The Jadad Score, which captures items related to adequacy of randomization, double blinding, and dropouts on a scale of 0 to 5.[6]

- Adequacy of allocation concealment as either adequate, inadequate, or unclear using the definitions described by Schulz et al.[7]
- Generic quality grade of either A, B, or C.[8]

  A–Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality; no reporting errors; 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, above.

  C–Significant bias that may invalidate the results. A study with serious errors in design, analysis, or reporting.

Applicability

In this report, the focus is on the U.S. population. We categorized studies based on the study eligibility criteria into four populations: generally healthy people, people with CVD, people with diabetes, and people with dyslipidemia. A study could be categorized into multiple populations, as appropriate.

We further categorized studies within a target population into one of three levels of applicability.[8]

- 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 including baseline dietary intake broadly similar to that of the U.S. population.
- II–Sample is representative of a relevant sub-group of the target population, but not the entire population.
- III–Sample is representative of a narrow subgroup of subjects only, and is not applicable to other subgroups.

Qualitative and Statistical Analyses

Most outcomes evaluated were continuous variables. For these outcomes, summary tables report three sets of data pertaining to results: the mean (or median) baseline level in the omega-3 fatty acid arm, the net change of the outcome, and the reported *P* value of the difference between the omega-3 fatty acid arm and control. The net change of the outcome is the difference between the change in the omega-3 fatty acid arm and the change in the control arm. Coronary artery restenosis studies provided rate data on a dichotomous variable (restenosis or no restenosis). For these studies, we report three equivalent sets of data: the control rate, the relative risk of restenosis, and the 95 percent confidence interval of the relative risk. In addition, we performed a random effects model meta-analysis of the relative risk.[9]

To examine the association between the level of intake of omega-3 fatty acids and tissue levels, the change in omega-3 fatty acid and arachidonic acid compositions were calculated for each treatment arm. Data were extracted for fatty acid composition of plasma or serum phospholipids, platelet membrane phospholipids, and erythrocyte membrane phospholipids (and, from one study each, granulocyte and monocyte membrane phospholipids). For each tissue type, data from each treatment arm were combined in a meta-regression on the change of EPA+DHA composition compared to mean dose of EPA+DHA received in each treatment arm.[10] Changes in non-omega-3-fatty-acid arms or control groups were not included in meta-regression analyses.

Results

We screened over 7,464 abstracts. Based on this screen, we retrieved 807 full articles, 344 of which reported on CVD risk factors and intermediate markers of potential interest and met initial eligibility criteria. Within the 344 articles, there were 197 randomized trials that analyzed outcomes of interest in this report. We evaluated 123 articles that met final eligibility criteria regarding 23 potential risk factors and intermediate markers of CVD and tissue levels of omega-3 fatty acids. The majority of analyzed studies evaluated fish or other marine oils (EPA+DHA); few evaluated plant oils (EPA+DHA or ALA). Furthermore, few studies compared doses of similar omega-3 fatty acids, compared different omega-3 fatty acids, reported on potential covariates such as age and sex, analyzed effects based on duration of intake, or repeated measurements after subjects had stopped omega-3 fatty acid supplementation.

Lipids

Abnormal levels of serum lipids, primarily LDL, HDL, and Tg have long been recognized as independent risk factors for CVD. We analyzed the effect of omega-3 fatty acids on these and other serum lipids that have been associated with risk of CVD, including: Lp(a) which consists of an LDL core covalently bound to a plasminogen-like glycoprotein, apolipoprotein(a); apo AI, the major apolipoprotein of HDL; apo B, a ligand for the receptor that clears the lower density lipoprotein particles from the bloodstream; and two forms of one of its subtypes: total apo B-100, which is associated with lipoprotein particles of hepatic origin; and LDL apo B, which represents the portion of total blood apo B-100 that is associated with the LDL subfraction.

We found 182 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on cholesterol or Tg levels in at least 20 subjects. Of these, we analyzed the 25 randomized trials with lipid data for at least 60 subjects in parallel trials and 40 subjects in crossover trials who consumed omega-3 fatty acids. The strongest, most consistent effect of omega-3 fatty acids was found among the 19 studies of Tg. Most studies reported a net decrease in Tg of about 10 percent to 33 percent. The effect was dose-dependent and generally consistent among healthy subjects and patients with CVD, at elevated risk of CVD, or dyslipidemia. Across studies, the effect of omega-3 fatty acids on triglyceride levels was generally

greater in those studies with higher baseline mean triglyceride levels. However, the single study of a plant (rapeseed and linseed) oil found a non-significant but large net increase in Tg. Limited data suggest that the effect is not related to sex, age, baseline Tg level, weight, background diet, or lipid treatment. The effect of duration of intervention or exposure is unclear and there were no data regarding sustainment of effect. The effect of omega-3 fatty acids on other serum lipids was weaker. The 23 analyzed studies of total cholesterol and the 19 studies of HDL found heterogeneous results, but mostly found small, non-significant net increases in levels of both lipids. The 15 analyzed trials of LDL fairly uniformly found small net increases in LDL level. The effect of plant oils on these lipoproteins was possibly weaker, but was similar to the effect of marine oils. No differences in effect were seen by population across studies and in one study that performed a sub-analysis of diabetic subjects. One study found a larger net increase in total cholesterol among subjects on a higher fat diet compared to those on a lower fat diet, but this effect was not seen for other lipids. A single study reported a steady increase in HDL levels over time (from 6 weeks to 12 months) with fish oil. No other studies found an effect of time on lipids. No other covariates were reported to interact with fish oil effects on lipids.

No consistent effect was found across the 14 randomized studies of Lp(a) (among a total of 23 studies examined), although one study reported a small but significant effect in subjects with elevated baseline Lp(a) levels compared to those with lower levels. Among 61 studies of apo AI, we analyzed the 27 randomized studies of apo AI with data on at least 20 subjects in parallel trials and 15 subjects in crossover trials who consumed omega-3 fatty acids. The studies generally found no effect or a net decrease in level with omega-3 fatty acid consumption. Among 52 studies of total apo B there was little consistency of effect in the 25 randomized studies with data on at least 20 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids. The four available studies of apo B-100 and the six of LDL apo B came to opposite conclusions in that the former all found small net changes in apo B-100—mostly net decreases—but most of the latter found large, significant net increases in LDL apo B with omega-3 fatty acid consumption.

Blood Pressure

We reviewed a recent publication that performed a meta-regression of the effect of fish oils on blood pressure.[11] This study found a small but significant reduction in both systolic and diastolic blood pressure of about 2 mm Hg with fish oil consumption. The effect was stronger in older and hypertensive populations. Because the meta-regression excluded diabetic populations, we evaluated the six randomized studies of diabetics and found similar results. One study reported that neither sex nor Hgb A_{1c} levels were related to the fish oil effect on blood pressure. No study analyzed plant oils.

Glucose Tolerance

To evaluate the effect of omega-3 fatty acids on glucose tolerance, an important risk factor for CVD among people with diabetes or insulin resistance, we evaluated Hgb A_{1c}, an indicator of long-term serum glucose levels. We also evaluated fasting blood sugar (FBS) and fasting insulin levels, which are suggestive of insulin resistance in people with normal glucose levels. Overall, there was no consistent effect of omega-3 fatty acids on glucose tolerance. Among 32 studies of Hgb A1c there was no substantial significant effect of omega-3 fatty acid consumption, regardless of study population in the 18 randomized trials with data on at least 10 subjects who consumed omega-3 fatty acids in either parallel trials or crossover trials. Among the 57 studies of FBS, we found a wide range of net effects of omega-3 fatty acids on fasting blood sugars across the 17 randomized studies with data on at least 25 subjects in parallel trials and 15 subjects in crossover trials who consumed omega-3 fatty acids among the 57 studies with data on FBS. The heterogeneity was present regardless of the makeup of the study population, although the range of effect was widest among diabetic patients. The 15 randomized trials of fasting insulin levels were very heterogeneous. The heterogeneity found in the nine studies of generally euglycemic populations was similar to that found in the studies of diabetics and obese subjects.

Inflammation and Thrombosis

CRP is an acute phase reactant that is thought to represent an integrated assessment of the overall state of activation of the inflammatory system. A growing body of studies suggests that elevations in CRP levels detected by the high sensitivity assay predict a poor cardiovascular prognosis. The five available studies of CRP found no effect with fish oil supplementation or dietary fish.

Thrombosis plays an important role in atherosclerosis and CVD. There are numerous measurable factors to assess clotting potential. Of these, we analyzed fibrinogen, a liver protein necessary for clotting that has been found to be both increased in patients with ischemic heart disease and a predictor of cardiovascular events; factors VII, VIII, and vWF, important factors in the extrinsic coagulation system; and *in vitro* platelet aggregation. No consistent effect was found among the 24 randomized trials (among 59 available studies) of fibrinogen with data on at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids. Nor was a consistent effect found among the 19 randomized trials of factor VII with at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids, or the five available randomized trials of factor VIII. The nine available randomized trials of vWF mostly found a small, non-significant decrease in level with omega-3 fatty acid consumption. The results among the 11 analyzed studies of

platelet aggregation were heterogeneous depending on aggregating agent, dose of agent, and measurement metric used, however, in most studies no effect was found with omega-3 fatty acid intake. We found 84 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on platelet aggregation. Of these, we analyzed the randomized trials with data on at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids and that also reported platelet aggregation in tabular or text format. Studies that presented platelet aggregation data in graphical format only were not analyzed.

Coronary Artery Restenosis

We performed a meta-analysis of the 12 randomized trials that reported restenosis rates after coronary angioplasty. All 12 trials evaluated fish oils. We found heterogeneity of results across studies but an overall trend toward a net reduction of relative risk of 14 percent with fish oil intake. Two studies reported no significant difference in effect in men and women. Five additional non-randomized studies were not analyzed.

Carotid Artery Intima-Media Thickness

The four available studies of carotid IMT were heterogeneous. The randomized trial found no effect of fish oil, but two cross-sectional studies found that dietary omega-3 fatty acid was correlated with thinner IMT. The cohort study of plant oil margarine was inconclusive.

Exercise Tolerance Testing

The six available studies of exercise tolerance testing suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small.

Heart Rate Variability

Three analyses of two study populations of heart rate variability concluded that fish oil supplementation among patients with recent myocardial infarction and dietary fish consumption in healthy people improves heart rate variability, which may reduce the incidence of ventricular arrhythmias. However, fish oil supplementation did not improve heart rate variability in the same healthy population.

Correlation of Intake of Omega-3 Fatty Acids With Tissue Levels

Meta-regression revealed direct relationships between dose of consumed omega-3 fatty acids and changes in levels of EPA and DHA, either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membranes. Among the 60 studies analyzed for other outcomes that reported data on percent phospholipid levels, we analyzed the 30 randomized trials with data on at least 25 subjects in parallel trials and 20 subjects in crossover trials who consumed omega-3 fatty acids. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA corresponds to approximately a one percent increase in EPA+DHA level. Granulocyte and monocyte membrane phospholipid levels also increased after omega-3 fatty acid supplementation in individual studies.

Discussion

Overall, there is strong evidence that fish oils have a strong beneficial effect on Tg that is dose-dependent and similar in various populations. There is also evidence of a very small beneficial effect of fish oils on blood pressure and possible beneficial effects on coronary artery restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and possibly heart rate variability, particularly in patients with recent myocardial infarctions. No consistent beneficial effect is apparent for other analyzed CVD risk factors or intermediate markers. However, there is also no consistent evidence of a detrimental effect of omega-3 fatty acids on glucose tolerance. The correlation between intake of omega-3 fatty acids and tissue levels is fairly uniform in different measured tissues.

There are little available data, however, on how the effect of omega-3 fatty acids on CVD risk factors and intermediate markers may differ depending on people's underlying conditions and risk of CVD, amount of omega-3 fatty acid consumed, duration of consumption, or source or type of omega-3 fatty acids. In particular, few studies analyzed data based on CVD risk or compared doses or types of omega-3 fatty acids. Thus, conclusions regarding these areas are all weak and based on limited data. With the exceptions of studies confined to men or to specific populations of interest (e.g., diabetics), studies generally did not base eligibility criteria on factors of particular interest here. Most conclusions that we were able to draw were based on across-study comparisons (particularly for different populations), which cannot account for confounders. Furthermore, the potential effect of ALA is unknown.

Our analyses were further limited by factors inherent to evaluation of CVD risk factors and intermediate markers. While some of these markers have indeed been demonstrated to be important markers or risk factors for CVD, it is unclear whether all of the factors are. The measurement techniques for a number of the outcomes evaluated also have not been standardized, which complicates interpretation of individual study findings and limits the ability to compare studies. Thus, the meaning in terms of CVD risk of omega-3 fatty acids on various putative risk factors and intermediate outcomes is uncertain.

Given the limitations of the current evidence, we have several recommendations for future research. Future studies on CVD risk factors and intermediate outcomes should address the questions of possible different effects of omega-3 fatty acids

in different sub-populations and different effects related to different covariates, including dose and duration of intake. More multi-center trials are needed to assess the effect of ALA, independent of EPA+DHA, on CVD risk factors and intermediate outcomes. Additional research is needed to clarify the effect of omega-3 fatty acids on markers of glucose tolerance. The omega-6/omega-3 ratio of subjects' total diet (including supplements) should be estimated, reported, and analyzed for its effect on outcomes. 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 pay special attention to collecting data with regard to fish consumed, including the type of fish and method of preparation.

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. It 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. 93, *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of 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.

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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 (CVD). These reports are among several that address topics related to omega-3 fatty acids, and that were requested and funded 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 EPC-RAND, 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 (eicosapentaenoic acid [EPA; chemical abbreviation: 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], alpha-linolenic acid [ALA, 18:3 n-3], and docosapentaenoic acid [DPA, 22:5 n-3]) 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 risk factors and intermediate markers of CVD in humans. The other 2 reports by the Tufts-NEMC EPC focus on CVD outcomes in humans 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 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 — ALA 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, which have a higher number of carbon atoms and double bonds. These long-chain polyunsaturated fatty acids retain the omega type (n-3 or n-6) of the parent essential fatty acids.

ALA and LA comprise the bulk of the total polyunsaturated fatty acids consumed in a typical North American diet. Typically, LA comprises 89% of the total polyunsaturated fatty acids consumed, while ALA comprises 9%. Smaller amounts of other polyunsaturated fatty acids make up the remainder [1]. 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 [2]. 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 long-chain polyunsaturated fatty acids 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, grams, total energy intake — but also in quantity [3]. 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 extend ALA is converted to EPA and DHA in humans, and to what extend 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 long-chain polyunsaturated fatty acids. 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, EPA and DHA. However, the conversion from parent fatty acids into long-chain polyunsaturated fatty acids occurs slowly in humans, and conversion rates are not well understood. Because of the slow rate of conversion and the importance of long-chain polyunsaturated fatty acids to many physiological processes, humans must augment their level of long-chain polyunsaturated fatty acids 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.

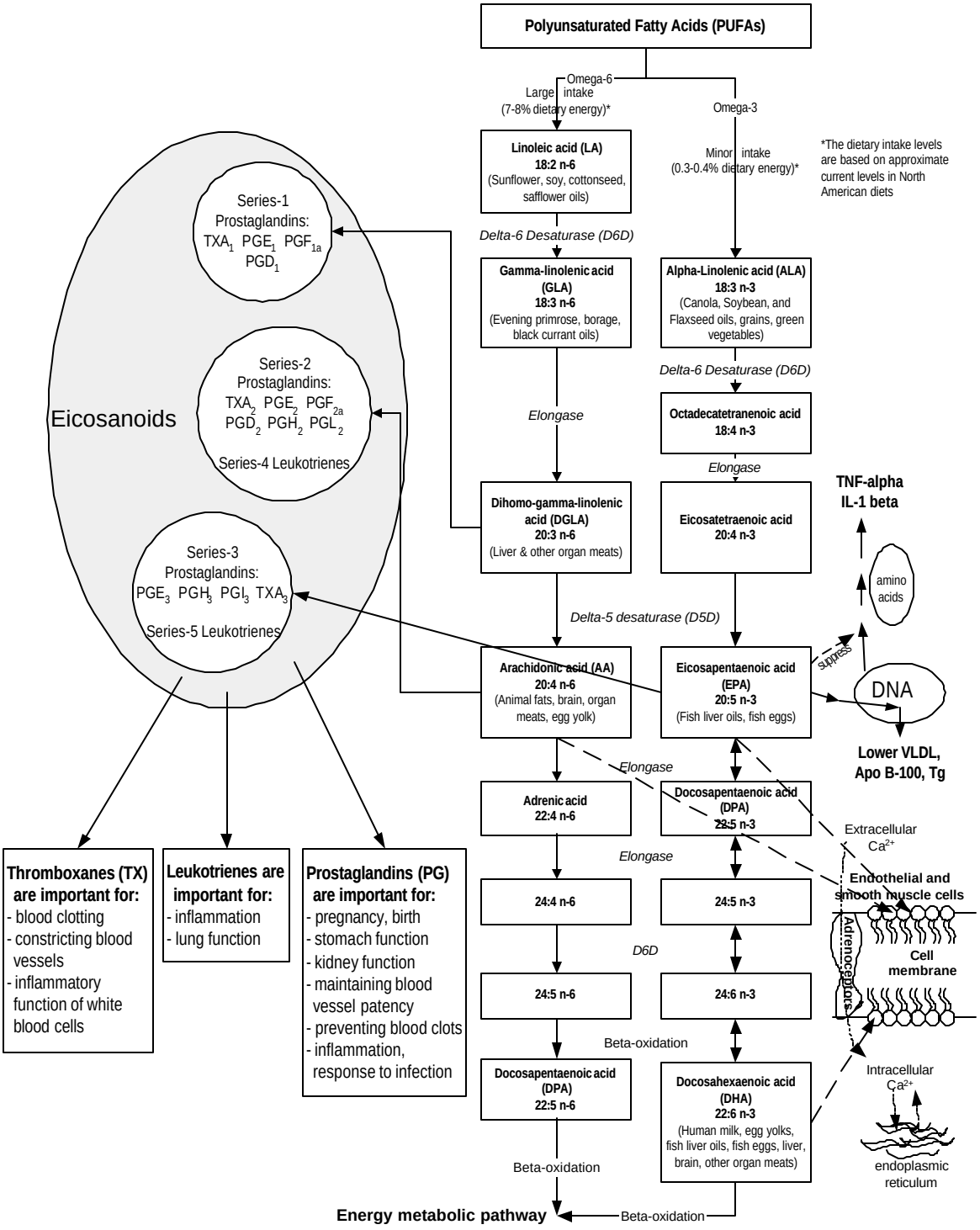
The specific biological functions of fatty acids depend on the number and position of double bonds and the length of the acyl chain. Both EPA and AA are 20-carbon fatty acids and are precursors for the formation of prostaglandins, thromboxane, and leukotrienes — hormone-like agents that are members of a larger family of substances called eicosanoids. Eicosanoids are localized tissue hormones that seem to be one of the fundamental regulatory classes of molecules in most higher forms of life. They do not travel in the blood, but are created in the cells to regulate a large number of processes, including the movement of calcium and other substances into and out of cells, dilation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division, and growth [4].

As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA, is the precursor of a group of eicosanoids including series-2 prostaglandins and series-4 leukotrienes. The omega-3 fatty acid, EPA, is the precursor to a group of eicosanoids including series-3 prostaglandins and series-5 leukotrienes. The series-2 prostaglandins and series-4 leukotrienes derived from AA are involved in intense actions (such as accelerating platelet aggregation and enhancing vasoconstriction and the synthesis of inflammatory mediators) in response to physiological stressors. The series-3 prostaglandins and series-5 leukotrienes that are derived from EPA are less physiologically potent than those derived from AA. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate excessive series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins, which are derived from the omega-3 fatty acid, EPA, may protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma [4]. In addition, animal studies, have demonstrated that omega-3 fatty acids, such as EPA and DHA, engage in multiple cytoprotective activities that may contribute to antiarrhythmic mechanisms [5]. Arrhythmias are a common 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 1ß (IL), and tumor necrosis factor a (TNF-a) - that have pro-inflammatory effects. These compounds exert pro-inflammatory cellular actions that include stimulating the production of collagenases and increasing the expression of adhesion molecules necessary for leukocyte extravasation [6]. The mechanism responsible for the suppression of cytokine production by omega-3 fatty acids 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 DPA, and then further elongated and oxygenated into DHA. EPA and DHA are frequently referred to as very long chain omega-3 fatty acids. DHA, which is thought to be important for brain development and functioning, is present in significant amounts in a variety of food products, including fish, fish liver oils, fish eggs, and organ meats. Similarly, AA can convert into an omega-6 form of DPA. Studies have reported that omega-3 fatty acids decrease triglycerides (Tg) and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, with a concomitant increase in high density lipoprotein (HDL). However, they appear to increase or have no effect on low density lipoprotein (LDL). Omega-3 fatty acids apparently lower Tg by inhibiting VLDL and apolipoprotein B-100 synthesis and decreasing post-prandial lipemia [7]. Omega-3 fatty acids, in conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular Tg production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for Tg production [8].

As noted earlier, omega-6 fatty acids are consumed in larger quantities (>10 times) than omega-3 fatty acids. Maintaining a sufficient intake of omega-3 fatty acids is particularly important since many of the body's physiologic properties depend upon their availability and metabolism.

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



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

The major source of omega-3 fatty acids is dietary intake of fish, fish oil, vegetable oils (principally canola and soybean), some nuts including walnuts, and dietary supplements. Two population-based surveys, the third National Health and Nutrition Examination (NHANES III) 1988-94 and the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) surveys, are the main source of dietary intake data for the U.S. population. NHANES III collected information on the U.S. population aged =2 months. Mexican Americans and non-Hispanic African-Americans, children =5 years old, and adults = 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall. Complete descriptions of the methods used and fuller analyses are available in the report *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, 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 [9]. In 1998, the Supplemental Children's Survey, a survey of food and nutrient intake by children under age of 10, was conducted as the supplement to the CSFII 1994-96. The CSFII 1994-96, 1998 surveyed 20,607 people of all ages with over-sampling of low-income population (<130% of the poverty threshold). Dietary intake data by individuals of all ages were collected over 2 nonconsecutive days by use of two 1-day dietary recalls.

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

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

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

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

Table 1.2 Mean, range, median, and standard error of the mean (SEM) of 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)

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

Dietary Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be found in many different sources of food, including fish, shellfish, some nuts, and various plant oils. Table 1.3 lists the amount of omega-3 fatty acids in some commonly consumed fish, shellfish, nuts, and edible oils, selected from the USDA website http://www.nal.usda.gov/fnic/foodcomp (accessed November 3, 2003; Finfish and Shellfish Products: sr16fg15.pdf; Fats and Oils: sr16fg04.pdf; and Nut and Seed Products: sr16fg12.pdf) [10]

Relationship of Dietary Fat and Cardiovascular Disease

Numerous studies have examined the relationship between dietary fat and CVD. Early epidemiology studies noted very low cardiovascular mortality among the Greenland Inuit as compared to mainland Danes, even though both had very high fat diets [11-13]. Studies in other populations with high fish intake, including South Pacific Islanders, Japanese, and people from the Mediterranean region, also generally found a low prevalence of CVD despite a prevalence of other risk factors, such as hypertension, similar to that found in other populations [14]. However, some epidemiological studies reached the opposite conclusion. The Seven Countries Study, for example, found that coronary heart disease mortality was highest in Eastern Finland, where average fish intake was 60 g per day [15]. This finding may in part be due to a positive association between fish consumption and both cigarette smoking and cholesterol levels in Finland; an association not seen in other countries.

The apparent paradox of low levels of CVD in people with high fat diets was explained by the high consumption of marine sources of very long chain, highly polyunsaturated omega-3 fatty acids [16]. Since these early studies, hundreds of observational and clinical trials have been conducted to analyze the effect of both marine and plant sources of omega-3 fatty acids on CVD and a wide range of CVD risk factors and intermediate markers of CVD, and to define and explain the potential benefits of increased intake of the omega-3 fatty acids.

Omega-3 Fatty Acids and Cardiovascular Disease Risk Factors

A large number of putative risk factors for and intermediate markers of CVD exist, including markers for different aspects of CVD, markers for risk factors of CVD, and markers for other factors related to cardiovascular health. However, the relationship between most of these laboratory measurements and diagnostic tests and aspects of atherosclerosis such as inflammation, are generally unproven. The relationships between these factors and actual clinical

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 (from USDA website http://www.nal.usda.gov/fnic/foodcomp, 2003).

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

disease and events are generally even more theoretical. Nevertheless, as the science of atherosclerosis advances, our understanding of these relationships is improving.

Several measurable factors are generally well accepted to be associated with risk of CVD. These include serum lipoproteins, blood pressure, diabetes mellitus, and related metabolic disorders. Improvement or suppression of these factors has been shown to reduce the risk of CVD. Inflammation is becoming accepted as a cause of atherogenesis, although potential treatments have yet to show reduction of cardiovascular events. Thrombosis and oxidation (free radicals) are also involved in atherogenesis, although their effect on the risk of CVD is less clear (except in people with specific hypercoagulable conditions). Several cardiovascular processes are also risk factors for cardiovascular events. These include atherogenesis, vascular dysfunction, arrhythmias, and cardiac dysfunction among others. These processes generally do not cause symptoms until they are fairly advanced. They may also be reversed, thus potentially reducing cardiovascular morbidity and mortality.

Both in trials and in patient care, surrogate markers for disease or risk of disease are useful measures for tracking people's health. Understanding how omega-3 fatty acids affect these various intermediate markers of CVD can help efforts to explain how omega-3 fatty acids affect clinical CVD. Understanding the relationship between omega-3 fatty acids and intermediate markers would also be helpful in determining who could most benefit (or could be most harmed) from adjusting omega-3 fatty acid intake, and would help efforts to track their effect on cardiovascular risk factors. The following sections briefly summarize the relationship between omega-3 fatty acids and selected risk factors for and intermediate markers of CVD.

Improvement of Lipoproteins

Elevated serum low density lipoprotein (LDL) and depressed high density lipoprotein (HDL), especially when accompanied by elevated triglycerides (Tg), are well-known risk factors for CVD. Studies have reported that omega-3 fatty acids decrease Tg and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, with a concomitant increase in HDL. However, they appear to increase or have no effect on LDL. Omega-3 fatty acids apparently lower Tg by inhibiting VLDL and apolipoprotein B-100 (apo B-100) synthesis and decreasing post-prandial lipemia [7]. Omega-3 fatty acids, in conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular Tg production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for Tg production [8].

Numerous other lipids and associated proteins are involved in lipid metabolism and thus possibly in atherogenesis and CVD; although they are less commonly measured. These include, among others, lipoprotein (a) [Lp(a)]; apolipoproteins (apo) A-I, B-48, B-100, C-III; and free fatty acids.

Reduction of Thrombosis

Blockage of coronary, cerebral and peripheral vessels due to thrombosis is a leading cause of CVD. Omega-3 fatty acids affect the clotting system in a number of ways. EPA competes with AA for the cyclo-oxygenase enzyme, thus reducing thromboxane A_2 (TX), a thrombotic agent. DHA may further inhibit cyclo-oxygenase [17]. Omega-3 fatty acids also inhibit TXB_2 production,

platelet aggregation, and platelet adhesion, although much less so than aspirin. Omega-3 fatty acids also lead to endothelial formation of prostaglandin I_3 (PG), PGI_2, and nitrous oxide, all of which reduce vasoconstriction [17,18]. However, knowledge about the role of omega-3 fatty acids on coagulation factors and fibrinolysis is incomplete.

Many markers of coagulability exist, including the numerous factors involved in the clotting cascade, homocysteine, bleeding time, and platelet aggregation. Except among people with specific hypercoagulable conditions, it is not clear that any of these measures, among others, are predictive of CVD or that modification of their levels modifies risk of CVD.

Reduction of Inflammation, Atherogenesis, and Leukocyte Activity

Awareness of the effect of inflammation on atherogenesis (atheromatous plaque formation) and the risk of cardiovascular events is increasing. Leukocytes (white blood cells) are the blood cells that respond to injury or infection with a protective inflammatory response and an immune response. However, leukocytes are prominent cells in the atheromatous plaque in major blood vessels, which suggests that early plaque formation has an inflammatory component. PGE_2 and leukotriene B_4 (LT) have pro-inflammatory biological actions, and together they can cause vascular leakage and extravasation of fluid. The omega-6 fatty acid, AA, is the progenitor of both PGE2 and LTB4 via the cyclo-oxygenase and 5-lipo-oxygenase enzymatic pathways, respectively. EPA is the omega-3 homologue of AA; the 2 fatty acids differ only in that EPA has 1 additional double bond at the third carbon. EPA can thus inhibit AA metabolism competitively via the enzymatic pathways and can suppress production of the omega-6 fatty acid eicosanoid inflammatory mediators. Although EPA promotes the formation of PGE3 and LTB5, these eicosanoids are far less active as pro-inflammatory agents than the corresponding derivatives of AA [8]. Furthermore, other pro-inflammatory factors, such as IL-1ß and TNF-a, can be suppressed by the effect of long-chain polyunsaturated fatty acids on lipoprotein metabolism [6].

C-reactive protein (CRP) is a well-described marker of inflammation and rises in response to injury, infection, and other inflammatory stimuli. In patients with either angina or risk factors for atherosclerosis, increased CRP has been associated with increased relative risk of nonfatal myocardial infarction and overall cardiovascular mortality [19]. It is unclear whether reduction in CRP would result in reduced risk of CVD. Trials commonly measure other inflammatory markers including IL-6 and vascular cell adhesion molecule 1 (VCAM-1). Less is known about their association with CVD.

Reduction of Arrhythmia

Cardiac arrhythmias can be fatal, causing sudden death, or can result in stroke, myocardial infarction, congestive heart failure, and peripheral embolisms, among other types of CVD. Animal studies have shown that fatal ventricular fibrillation could be essentially abolished by high-level feeding with omega-3 fatty acids [20]. Omega-3 fatty acids appear to act in multiple ways to prevent arrhythmias. Various animal and *in vitro* experiments have shown that omega-3 fatty acids directly modulate sodium, potassium, and calcium channels [21]. By incorporating into cell membrane phospholipids, the excitation-contraction coupling that can result in arrhythmia is reduced [22]. Omega-3 fatty acids also modulate various intracellular enzymes involved in controlling the contraction and relaxation cycles of myocytes [23]. EPA and DHA also affect adrenoceptors, membrane proteins whose function in the heart is to transmit the neuroendocrine

message of the catecholamines (adrenaline and its derivatives) [24]. The activity of DHA is thus similar in principle to that of ß-blockers, a group of key cardiovascular drugs used to decrease the cardiac effects of catecholamines. Omega-3 long-chain polyunsaturated fatty acids also appear to act similarly to another group of cardiovascular drugs, calcium channel blockers, by increasing intracellular calcium sequestration and interfering with receptor-operated calcium channels, thus lowering calcium influx [22]. The effect of omega-3 fatty acids on prostanoids and leukotrienes also theoretically reduces the arrhythmia potential of cardiac myocytes.

The risk of ventricular arrhythmia is most commonly measured by 24 hour ambulatory electrocardiography recordings, in which a continuous electrocardiogram (ECG) is taken for generally 24 hours. Various measures of heart rate variability are calculated, primarily based on the standard deviation (SD) of the duration of time between heart beats. Other common ECG measurements are also followed as indicators or risk of arrhythmia or cardiac ischemia.

Blood Pressure

Hypertension is well recognized as one of the leading causes of CVD. The recent Joint National Committee report (JNC 7) emphasizes the risks of blood pressure that is even slightly elevated above 120/80 mm Hg [25]. Lifestyle modification, including reduction of sodium and alcohol intake, weight loss, diets high in fruits and vegetables and low-fat dairy products, and exercise has been shown to reduce blood pressure, often as much as medication use. Early investigations into the way in which fatty fish consumption may lower CVD found that omega-3 fatty acids possibly reduce blood pressure [26]. While the mechanisms for such an effect remain uncertain, the most compelling hypothesis is that by altering the balance between vasoconstrictive TXA2 and vasodilatory PGI3, as described in the section on inflammation, overall blood vessel capacitance increases and thus blood pressure falls [27]. However, the baseline balance of vasoactive and regulatory hormones may be altered in people with frank hypertension or other types of CVD The question thus arises whether the effect of omega-3 intake on blood pressure is altered in people with hypertension.

Diabetes

Although long-chain omega-3 fatty acids appear to have an overall beneficial effect on CVD, their effect on glucose homeostasis is less clear. Omega-3 fatty acids may, in fact, have a detrimental effect on glucose tolerance [28]. Theoretical benefits of omega-3 fatty acids to diabetic management include reducing Tg, increasing HDL, increasing glucose-induced insulin secretion, and possibly lowering insulin resistance [28,29]. However, omega-3 fatty acids may worsen glucose tolerance in patients with clear cut diabetes and may, in fact, worsen insulin resistance [28].

Thus, important questions relate to the level of markers of glucose tolerance, such as fasting blood glucose (FBS), glycohemoglobin or hemoglobin A_{1c} (Hgb A_{1c}), and fasting insulin levels, in people with both diabetes and insulin resistance and people without glucose tolerance impairment.

Cardiovascular Diagnostic Tests

The metabolic effects of omega-3 fatty acids on lipoproteins, thrombosis, inflammation, arrhythmia and blood pressure all have potential effects on blood vessels and the heart, which

eventually can lead to clinical CVD. In addition, there are numerous diagnostic tests of cardiovascular health that are known to be predictive of future cardiovascular events both in people with and without a known history of CVD. Improvements in these diagnostic tests are commonly used as indicators of effective prophylaxis or treatment.

Among the tests of vascular health that have been assessed in omega-3 fatty acid trials are coronary arteriography (to measure coronary vessel stenosis), carotid intima-media thickness (IMT, which measures the thickness of the carotid artery wall, a measure of atherosclerosis), carotid Doppler ultrasonography or magnetic resonance arteriography (to measure carotid and extra-carotid stenosis), ankle brachial index (to measure peripheral blood flow), and endothelium-dependent vasorelaxation (an invasive or minimally invasive test of endothelial function). Other useful diagnostic tests measure heart function, including the exercise tolerance test (treadmill or stress test) and cardiac ultrasonography (which measures heart wall, chamber and valve structure and function).

Association of Omega-3 Fatty Acid Intake and Tissue Levels

The fatty acid composition of the cell membrane is a dynamic system, and the regulatory mechanisms are not fully understood. Since omega-3 fatty acids cannot be synthesized in the human body, the amount of total omega-3 fatty acids stored in adipose tissue is believed to be associated primarily with the amount of long-term omega-3 fatty acid dietary intake [30], while the amount incorporated into red blood cell membrane phospholipids is believed to be associated with short-term intake [31]. Studies have consistently shown that populations whose diets are rich in fish (and thus omega-3 fatty acids) have relatively high omega-3 fatty acid content in plasma phospholipids [32-35]. However, it remains less clear whether there is a reliable dose-response correlation between dietary omega-3 fatty acid intake and fatty acid profiles of plasma phospholipids, LDL fractions of serum phospholipids and cholesteryl esters, and blood cell phospholipids [36]. Further, the metabolism from ALA - the main source of dietary omega-3 fatty acids - to its longer chain metabolites and then to eicosanoids is not well understood. Thus, the association between fatty acid intake and measurable tissue levels is not straightforward. Further complicating measurement estimates of total body stores of omega-3 fatty acids is that there are numerous measurable levels, including cell membrane phospholipids and triglycerides from the 3 major blood cell lines (erythrocytes, leukocytes and platelets), plasma triglycerides, plasma free fatty acids, and adipose cells. In addition, there is continuous movement of fatty acids between compartments, and each compartment incorporates fatty acids differently. As discussed above, under Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids, omega-3 fatty acid metabolism is in part dependent on omega-6 fatty acid levels, further confounding associations between dietary intake and blood levels.

Chapter 2. Methods

Overview

This evidence report on omega-3 fatty acids and CVD risk factors and intermediate markers of cardiovascular disease (CVD) is based on a systematic review of the literature. To identify the specific issues central to this report, the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) held meetings and teleconferences with technical experts, including a Technical Expert Panel (TEP) and members of the other EPCs that are reviewing topics related to omega-3 fatty acids. A comprehensive search of the medical literature was conducted to identify studies addressing the 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.

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. It engaged technical experts, representatives from the Agency for Healthcare Research and Quality (AHRQ), and institutes at the National Institutes of Health (NIH) to work with the EPC staff to refine key questions, identify important issues, and define parameters to the report. Additional domain expertise was obtained through local nutritionists who joined the EPC.

The Tufts-NEMC EPC also worked in conjunction with EPCs at the University of Ottawa and at the Southern California EPC-RAND. Together, the 3 EPCs are mandated to 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. In addition, literature searches for all evidence reports were performed by the UO EPC, using identical search terms for studies of omega-3 fatty acids. The 3 EPCs agreed on a common definition of omega-3 fatty acids; however, some variation in definitions and study eligibility criteria were applied that reflected the different topics and key questions addressed. The studies included are described below, under Full Article Inclusion Criteria.

Accompanying reports on omega-3 fatty acids and cardiovascular outcomes, and on the animal and *in vitro* evidence for the effect of omega-3 fatty acids on cardiac electrogenesis, were generated using similar techniques.

Key Questions Addressed in this Report

Four key questions are addressed in this report. Questions 1 and 2 (and their sub-questions) both pertain to the effect of consumption of omega-3 fatty acids (either as treatment or in the diet) and both risk factors and intermediate outcomes. Question 3 pertains primarily to the effect of modifiers on any effects or associations. Question 4 pertains to the association between omega-3 fatty acid intake and tissue and plasma levels. The key questions and their related sub-questions are outlined in detail below.

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm

Question 1. What is the effect of omega-3 fatty acids (eicosapentaenoic acid [EPA; 20:5 n-3], docosahexaenoic acid [DHA; 22:6 n-3], and alpha-linolenic acid [ALA, 18:3 n-3], supplements, and fish consumption) on cardiovascular risk factors and intermediate markers of cardiovascular disease?

What is their effect on CVD risk factors and intermediate markers of CVD, specifically:

- *Serum lipids (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides [Tg])*
- *Other CVD risk factors and intermediate markers of CVD*

What is their effect on specific CVD risk factors, specifically:

- *new-onset Type II diabetes mellitus (DM*
- *new-onset insulin resistance/metabolic syndrome*
- *progression of insulin resistance*
- *new-onset hypertension*
- *blood pressure among hypertensive patients*

What is the relative effect of omega-3 fatty acids on different CVD risk factors and intermediate markers of CVD?

- *Can the intermediate markers and risk factors for CVD be ordered by strength of treatment effect of omega-3 fatty acids?*

Is there a threshold or dose-response relationship between omega-3 fatty acids and intermediate markers and risk factors for CVD?

How does the duration of intervention or exposure affect the treatment effect of omega-3 fatty acids on intermediate markers and risk factors of CVD?

Are treatment effects of omega-3 fatty acids on CVD intermediate markers and risk factors sustained after the intervention or exposure stops?

Question 2. Effect of different omega-3 fatty acids:

What is the effect of different specific omega-3 fatty acids (EPA, DHA, ALA), and different ratios of omega-3 fatty acid components in dietary supplements, on CVD intermediate markers and risk factors?

How does the effect of omega-3 fatty acids on CVD intermediate markers and risk factors differ by source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)?

Does the ratio of omega-6 fatty acid to omega-3 fatty acid intake affect the effect of omega-3 fatty acid intake on intermediate markers and risk factors of CVD?

Question 3. Sub-population analyses:

How does the effect of omega-3 fatty acids on intermediate markers and risk factors of CVD differ in sub-populations including men, pre-menopausal women, post-menopausal women, and different age groups?

How does baseline dietary intake of omega-3 fatty acids impact the effect of omega-3 fatty acid supplements on intermediate markers and risk factors of CVD?

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?

Does the use of medications for CVD and CVD risk factors (including lipid lowering agents and diabetes medications) impact the effect of omega-3 fatty acids?

Question 4. Omega-3 fatty acid metabolism:

What is the association between intake levels of EPA, DHA, and ALA and blood, tissue, and cell membrane levels?

What is the efficiency of conversion from ALA to EPA/ DHA, EPA/DHA to ALA, DHA to EPA, and EPA to DHA?

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 1.2) [37]. The framework graphically presents the key components of the 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?

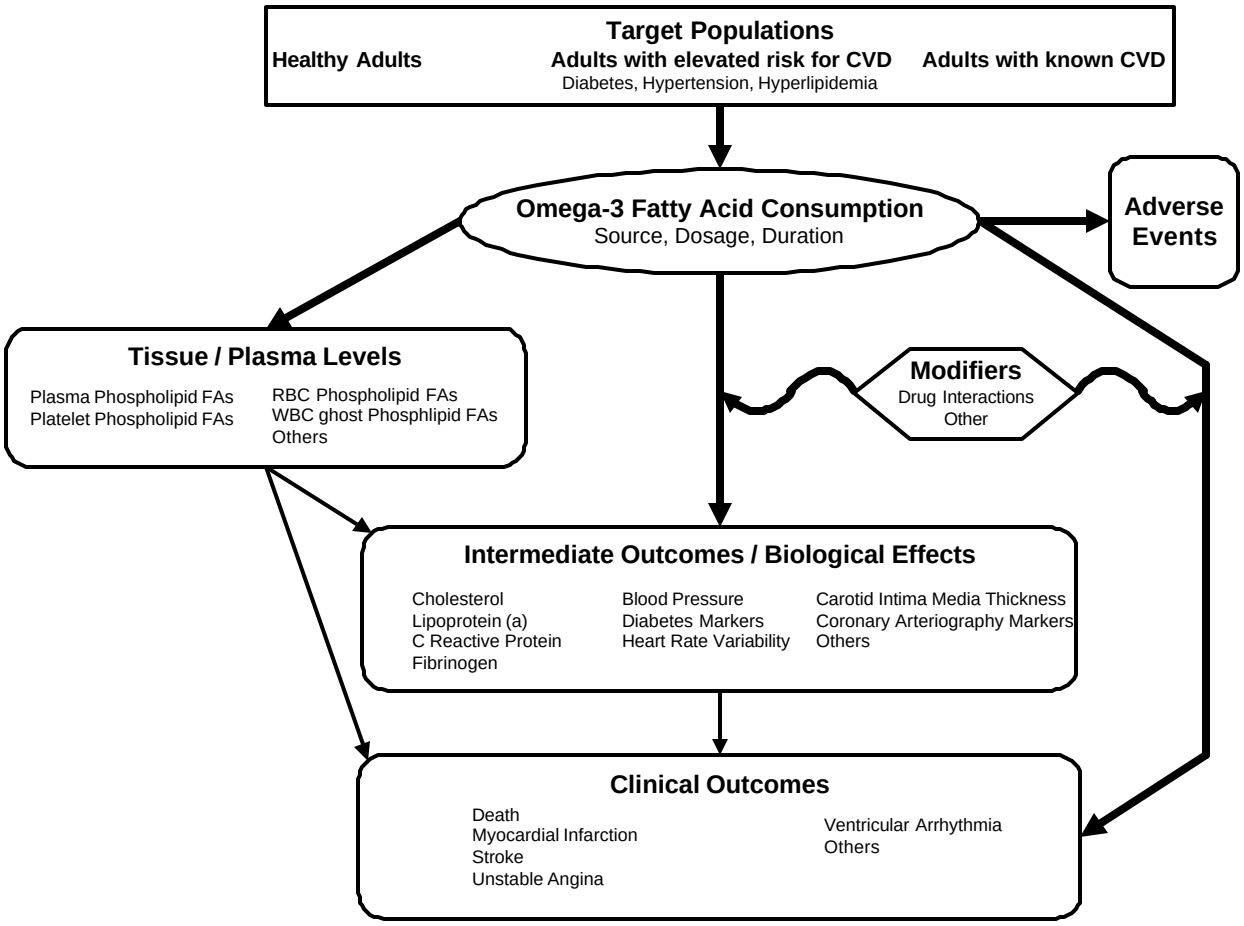
Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to omega-3 fatty acids) to improved health outcomes.

This report and the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, review the evidence addressing the associations or effects in humans. Specifically, this 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. The accompanying 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.

In both reports, the 3 specific populations of interest are healthy adults with no known CVD or risk factors; adults at increased risk of CVD due specifically to diabetes, hypertension, or hyperlipidemia; and 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.

Theoretically, the most immediate outcome related to omega-3 fatty acid intake is a change in tissue levels of the fatty acids. However, the measurement and interpretation of this effect is complicated by the variety of fatty acids, the different relative intake levels of fatty acids, metabolism of the fatty acids into other fatty acids, the different storage forms, and the wide range of cells into which the fatty acids are incorporated. The question of how omega-3 fatty acid intake relates to different measures of tissue and plasma fatty acid levels is addressed in this

Figure 1.2. 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).



report. Once it is understood how to best estimate body stores of omega-3 fatty acids, it will then be of interest in future reviews to understand how levels of body stores affect cardiovascular outcomes.

Although the most important questions relating to omega-3 fatty acids pertain to their effects on clinical outcomes (and potential adverse events), collecting data on long-term cardiovascular effects is relatively difficult. As a result, the bulk of the available evidence generally pertains to the efficacy in trials of interventions on intermediate outcomes and biological effects. This evidence is summarized in this report.

The effects of omega-3 fatty acids on CVD risk factors, intermediate markers of CVD and clinical outcomes can be related to one another in two ways. First, by reducing risk factors for CVD, such as blood pressure, or putative markers of the risk factors, such as C-reactive protein, omega-3 fatty acids can directly reduce the overall risk of cardiovascular events. Second, omega-3 fatty acids can have a direct or indirect beneficial effect on specific intermediate markers of

CVD, such as coronary stenosis, which would result in a lowered risk of cardiovascular events. In this report, we investigate 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, and subject characteristics (e.g., lipid levels, weight, blood pressure).

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). Crossover trials have the advantage of controlling fully for biases due to differences between study arms but may introduce bias due to incomplete washout of first treatment effect. In addition, they are generally small and have a narrow range of subjects. Uncontrolled trials and 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 other studies when data are relatively sparse.

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions related to CVD and to the metabolism of omega-3 fatty acids (Appendix A.1, available electronically at http://www.ahrq.gov/clinic/epcindex.htm). Relevant studies were identified primarily through search strategies conducted in collaboration with the UO EPC. The Tufts-NEMC EPC used the Ovid search engine to conduct preliminary searches on the Medline database. The final searches used 6 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.

Cardiovascular Search Strategy

The primary search strategy was designed to address both the clinical and intermediate outcomes of CVD in humans (Appendix A.1). 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.

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 (Appendix A.2).

Supplemental Searches

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 on July 30, 2003 using the term "nut" as a text word for studies of CVD (Appendix A.3). Furthermore, upon noting that a number of relevant articles were missing from our search strategy, we performed a supplemental search on July 1, 2003. This search included terms specific to the CVD risk factor and intermediate markers outcomes of interest (Appendix A.4).

Overall

The number of citations for the final results of 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 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 manually. At this stage, eligibility criteria were loosely defined to include all English language primary experimental or observational studies that evaluated any potential source of omega-3 fatty acids in at least 5 human subjects, irrespective of the study outcomes reported in the abstract. We excluded abstracts that clearly included only subjects who had a non-CVD-related condition (such as cancer, schizophrenia, or organ transplant), letters and abstracts.

Full Article Inclusion Criteria

Articles that passed the abstract screening process were retrieved and the full articles were screened for eligibility. Articles were rejected during this round based on the following criteria: review articles, inappropriate human population, pediatric studies and those conducted on

subjects less than 19 years old, no mention of omega-3 fatty acid 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, crossover studies with less than 4 week washout between treatments, 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. Studies that reported only lipid data among the outcomes of potential interest with fewer than 20 subjects were excluded during screening because of the large number of such studies and limited resources. In addition, with the exception of studies of Mediterranean diets and studies that reported fish servings, studies were excluded if no specific data were reported about omega-3 fatty acid consumption. Specific sources of omega-3 fatty acids 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.

The exclusion criterion of more than 6 g per day for non-adverse event clinical outcomes was based on discussions with the TEP, in which it was agreed that omega-3 fatty acid intake above this amount is impractical and has little relevance on health care recommendations. Therefore, the inclusion criterion for the maximum daily intake was set at 6 g per day. The definition of dose of omega-3 fatty acids varied greatly across studies. Thus, the maximal allowable dose may have applied to total daily omega-3 fatty acid, total EPA plus DHA, or a total of other combinations of omega-3 fatty acids. The total did not refer to total fish oil. Short duration studies (less than 4 weeks) and crossover studies with washout periods less than 4 weeks were excluded since, it was agreed, a metabolic steady-state of omega-3 fatty acids is likely not achieved for about 4 weeks.

Sometimes there were multiple publications of the same study reporting interim results or different outcomes. 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.

In addition, a list of approximately 100 potential markers of CVD (e.g., coronary intima media thickness) and risk factors (e.g., hypertension, C-reactive protein) was reviewed in detail. Because of limited time and resources, 22 factors were chosen from this list for definite inclusion. A second list of factors was evaluated for possible inclusion if time and resources allowed (see Table 3.1 in Results section). Studies that reported on none of these factors were rejected.

Because of the large number of studies available for analysis, for most outcomes of interest we decided to confine analysis to the largest randomized trials for each outcome evaluated. For outcomes with few studies, all studies were included regardless of study design or sample size (minimum of 5 subjects). We used a lower sample size threshold for crossover studies because these studies are more strongly powered for a given number of subjects than parallel studies. We generally aimed for approximately 20 to 25 studies for analysis. For studies of platelet aggregation, we used the additional inclusion criterion that platelet aggregation data must be presented in a numerical format; articles that reported platelet aggregation results only graphically were not analyzed. This additional criterion was used because of the particular difficulty in estimating data from graphs for this outcome and because of the large number of specific outcomes reported in each study. Specific criteria used are listed in Table 3.1 and

described in each outcome section in Chapter 3.

Incorporation of omega-3 fatty acids into phospholipids is very commonly reported by studies, often as proof of treatment compliance. Again because of limited time and resources, we limited our review of studies examining omega-3 fatty acid incorporation (or the association between dietary omega-3 fatty acid intake and tissue levels of omega-3 fatty acids) to the larger randomized trials that met eligibility criteria for either intermediate or clinical outcomes. We based this decision on the assumption that this sample of studies should not be biased. In addition, because the primary research question concerns correlation between dietary intake and blood levels of omega-3 fatty acids, for these analyses we have included only prospective, intervention trials to avoid biases and inaccuracies inherent to retrospective or survey-based studies. We have limited measurable levels to those most commonly reported and most practically measured, including erythrocyte, platelet cell membrane, and plasma phospholipids.

Data Extraction Process

An electronic data extraction form and database were created specifically for the evaluation of studies of omega-3 fatty acids and intermediate and clinical outcomes (Appendix B, available electronically at http://www.ahrq.gov/clinic/epcindex.htm). Data were entered into the form by selecting single or multiple choice buttons or as free text, as appropriate. The form allowed direct input of data into a Microsoft Access database and further manipulation of extracted data in both Microsoft Excel and Word.

As the data extraction form was being developed, all members of the EPC were trained to use the electronic form and software. In an iterative process, in which groups of studies were extracted by all trainees, the data entry form was improved, 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 researcher. During weekly meetings, data extraction problems were addressed. 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: study design, blinding, randomization method, allocation concealment method, country, funding source, study duration, eligibility criteria, sample characteristics (including comorbid conditions, concomitant medications, baseline diet, and demographics), number enrolled and analyzed, reasons for withdrawals, description of omega-3 fatty acid and control interventions or diets (including amount of specific fatty acids), risk factor, intermediate markers, and clinical outcomes, adverse events (which are discussed in the report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*), 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.

Meta-Regression

To examine the association between the level of intake of omega-3 fatty acids and tissue levels, the change in omega-3 fatty acid and arachidonic acid (AA 20:4 n-6) compositions were calculated for each study arm. Data were extracted for fatty acid composition of plasma or serum phospholipids, platelet membrane phospholipids, and erythrocyte membrane phospholipids, granulocyte membrane phospholipids, and monocyte membrane phospholipids. For each tissue type, data from each treatment arm were combined in a meta-regression on the change of EPA+DHA composition compared to mean dose of EPA+DHA received in each treatment arm.[38] Changes in non-omega-3-fatty-acid arms or control groups were not included in meta-regression analyses.

We performed simple linear regressions with the weighted least squares method, weighting each study arm by the square root of its sample size [39]. The equation of the meta-regression line is reported for each blood marker. R^2, or the goodness of fit, for the regression line is also reported. Data are presented both in summary tables and graphically in scatter plots in which the sources of the omega-3 fatty acid treatments are distinguished by different symbols.

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 to inform the reader of these reports about the degree of potential bias, the grading of the quality of evidence is not straightforward. Despite many attempts, even for a single type of study design, most factors commonly used in quality assessment of randomized controlled trials have not been found to be consistently related to the direction or magnitude of the reported effect size [40]. There is still no uniform approach to reliably grade published studies based on the information reported in the literature. Different EPCs have used a variety of approaches to grade study quality in past evidence reports.

Common Elements for Grading the Methodological Quality of Randomized Controlled Trials in Evidence Reports

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 [41,42]. 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 [43].

The Jadad Score assesses the quality of randomized controlled trials using 3 criteria: adequacy of randomization, double blinding, and drop outs [41]. A study that fully meets all 3 criteria gets a maximum score of 5 points. Adequacy of allocation concealment was assessed using the criteria described by Schulz et al., as adequate, inadequate, or unclear [42].

Generic Summary Quality Grade for Studies

The Jadad and Schulz scores address only some aspects of the methodological quality of randomized controlled trials. Potential biases due to reporting and analytic problems in the study are ignored. In this evidence report, we applied a 3-category grading system (A, B, C) to each randomized trial. We have used this grading system in most of our previous EPC evidence reports, as well as in several evidence based clinical practice guidelines [44]. This scheme defines a generic grading system for study quality that is applicable to each type of study design (i.e., randomized controlled trial, cohort study, case-control study):

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.

Studies that reported multiple results of interest to this report could receive different quality grades for different outcomes if there were reporting or methodological issues with specific outcomes but not others. We did not grade the few non-randomized studies that were analyzed.

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 (i.e., 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, as specified in the Scope of Work for this series of evidence reports. We also address specific subgroups within that population (i.e., healthy Americans, Americans with CVD, and Americans with diabetes or dyslipidemia), as specified. 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, diabetes or dyslipidemia.

CVD — Cardiovascular disease population. Subjects with a history of or currently with cardiac, peripheral vascular, or cerebrovascular disease, as defined by the author. In addition studies of hypertensive patients were included.

DM — Diabetic population. Subjects with any type of diabetes, including type I (DM I), type II (DM II), insulin dependent (IDDM) and non-insulin dependent (NIDDM), as defined by the authors.

DysLip — Population with dyslipidemia, either elevated total cholesterol, LDL, or Tg, or low levels of HDL, as defined by the authors.

One study was classified as CVD Risk because it included a combination of subjects with known CVD, diabetes, dyslipidemia and other potential CVD risk factors. In addition, some studies received multiple classifications (CVD/DM or DM/DysLip), when inclusion criteria included multiple conditions.

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 capture this parameter, we categorize studies within a target population into 1 of 3 levels of applicability [44]:

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 including baseline dietary intake broadly similar to that of the US population.

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, would also fall into this category.

III — Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups. For example, a study of male college students 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, CVD, DM, and DysLip) and the 3-level grade (I, II, III).

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 effect and associations. In addition, large studies are more likely to be generalizable; however, large size alone does not guarantee broad applicability.

Reporting Results

Most outcomes evaluated were continuous variables, such as lipid level or intima-media thickness. For these outcomes, summary tables report 3 sets of data: the mean (or median) baseline level in the omega-3 fatty acid arm; the net change of the outcome, and the reported *P* value of the difference between the omega-3 fatty acid arm and control. The net change of the outcome is the difference between the change in the omega-3 fatty acid arm and the change in the control arm, or:

$$\text{Net change} = (\text{Omega } 3_{\text{Final}} - \text{Omega } 3_{\text{Initial}}) - (\text{Control}_{\text{Final}} - \text{Control}_{\text{Initial}}).$$

The great majority of articles reported these 4 values and *P* values. While some studies reported adjusted and unadjusted within-arm and between-arm (net) differences, to maintain consistency across studies we calculated the unadjusted net change using the above formula for all studies when the data were available. To provide a rough estimate of the effect of omega-3 fatty acids when median values were reported (as for lipoprotein (a)), we used the above formula with the median values, recognizing that the resultant net change is not mathematically valid. When data were available at multiple time points, we extracted data on only the time point at the end of omega-3 fatty acid intervention. Data from other time points are discussed in the text.

We included only the reported *P* values for the net differences. We did not calculate any *P* values, but, when necessary, used provided information on the 95% confidence interval or standard error of the net difference to determine whether the *P* value was less than .05. We included any reported *P* value less than .10. Reported *P* values above .10 and values reported as "non-significant" were included as NS, non-significant.

Coronary artery restenosis studies provided rate data on a dichotomous variable (restenosis or no restenosis). For these studies, we report 3 equivalent sets of data: the control rate (the rate of restenosis in the control group, a standard measure of the underlying severity of illness in the study population), the relative risk of restenosis, and the 95% confidence interval. In addition we performed a random effects model meta-analysis [45].

All exceptions and caveats are described in footnotes.

Evidence and Summary Tables

We report the evidence in 2 complementary forms:

Evidence tables offer a detailed description of studies we analyzed that address each of the key questions. These tables provide detailed information about the study design, patient characteristics, inclusion and exclusion criteria, interventions and comparison groups evaluated, and outcomes. Baseline and follow-up data for each analyzed outcome are reported in the Results column. A study, regardless of how many interventions or outcomes were reported, appears once in the evidence tables. The studies are ordered alphabetically by the first author's last name and study year.

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. Studies are grouped by omega-3 fatty acid source (EPA/DHA oils, plant oils, fish and Mediterranean diets, and combinations – comparisons – of different sources). Then studies are ordered first by omega-3 fatty acid dose and second by omega-3 fatty acid study arm size (both largest to smallest). A study with outcomes may appear multiple times in different summary tables.

Methodological Limitations

Due to practical limitations of time and resources, many constraints were applied to the available data, as described above. In consultation with the TEP and NIH representatives, we prioritized the original list of questions to focus on those of greatest interest to the scientific and medical communities and for which data were likely to be available. Likewise, the list of specific CVD risk factors that we examined was reduced to those that members of the TEP agreed have the greatest clinical relevance and are most clearly related to CVD. Therefore, a large number of commonly evaluated markers were not included. For example, tissue plasminogen activator (TPA), plasminogen activator inhibitor (PAI), and LDL oxidation were not included because their levels are not clearly associated with clinical CVD outcomes, or the meaning of a change in their levels is not well understood, or there is much variability in how the factor is measured and interpreted, among other reasons. In addition, the TEP attempted to focus on those factors which are most relevant to clinical practice.

The decision about which specific outcomes to evaluate from the list of potential outcomes was based on an evaluation of the available evidence. CVD risk factors and intermediate markers with more limited evidence, possibly due to publication bias, or that were primarily evaluated in small or non-randomized or uncontrolled trials were generally omitted; although data on particular outcomes of interest, such as C-reactive protein and exercise tolerance testing, were included despite limited data.

Finally, because of the large number of studies, only the highest quality, larger studies were analyzed. While we attempted to find data to answer all the key questions, only those studies included in the main analyses were evaluated in thorough detail. This has implications for questions regarding populations, covariates, comparison of omega-3 fatty acid sources, and other sub-questions. However, it is unlikely that any of the missed studies were critical to our understanding of the key questions, since only the smaller, lower quality studies would have been missed.

It is also important to note that for almost all analyzed outcomes, the available data are biased toward positive results. Many articles reported that omega-3 fatty acid treatment did not affect levels of various outcomes, but did not report supporting data. These studies were not evaluated for the reported outcomes.

Chapter 3. Results

In this chapter, we review the results of our literature search and summarize findings from studies that passed our screening and selection process. Studies examining the relationship between omega-3 fatty acids - eicosapentaenoic acid (EPA, 20:5 n-3), docosahexaenoic acid (DHA, 22:6 n-3), and alpha linolenic acid (ALA, 18:3 n-3) - and selected risk factors of cardiovascular disease (CVD) are summarized first, followed by studies that examine the correlation between omega-3 fatty acid intake and tissue levels of fatty acids.

Summary of Studies Found

Through the literature search we identified and screened over 7,464 abstracts indexed as English language articles concerning humans. We retrieved and screened 807 full text articles for potentially relevant human data. Of these, we rejected 463 articles for the reasons listed in the section "Listing of Excluded Studies" under "Rejected Studies". Of the remaining 344 articles, we analyzed risk factor and other outcome data from 123 (Table 3.1, "References and Included Studies" under "Included Studies"). The 221 non-rejected studies that were not analyzed are listed in the section "Listing of Excluded Studies" under "Studies Not Analyzed Because of Non-Randomized Design or Small Size". For most outcomes, we analyzed only the approximately 20 to 30 largest randomized trials. These trials were selected based on criteria described both in Table 3.1 and in the sections describing each risk factor included in this chapter.

We compiled an Evidence Table that provides detailed information about each study we analyzed (Appendix C, available electronically at http://www.ahrq.gov/clinic/epcindex.htm). The summary tables present specific information about each of the studies that we analyzed for a given risk factor or outcome. Information presented in the summary tables include: study design and size, amount of omega-3 fatty acid consumption, baseline level of the relevant risk factor, net change of risk factor level (change in omega-3 fatty acid arm less change in control arm), reported statistical significance of the net change, study quality, study population, and applicability for each study.

Most studies that we analyzed evaluated fish or other marine oils (as supplements, dietary fish, or oil spreads); few evaluated plant oils (as supplements, dietary oils, or oil spreads). Furthermore, few studies compared doses of similar omega-3 fatty acids, compared different omega-3 fatty acids, reported on potential covariates such as age and sex, analyzed effects based on duration of intake, or repeated measurements after subjects had stopped omega-3 fatty acid supplementation. Only 13 articles (reporting on 12 trials) reported any data related to either baseline dietary or experimental dietary intake of both omega-3 fatty acid and omega-6 fatty acid intake to allow an estimate of mean daily omega-6 to omega-3 fatty acid ratio [46-58]. However, no study analyzed the relationship between evaluated outcomes and either omega-6 to omega-3 fatty acid consumption ratio or combined omega-6 and omega-3 fatty acid consumption amounts. Any available data relating to relative amounts of omega-6 fatty acid consumption could not be evaluated separately from different doses or types of omega-3 fatty acids.

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/epcindex.htm

Each risk factor is discussed separately in the following, largely arbitrary, order:

- Lipids (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides, lipoprotein (a) [Lp(a)], apolipoproteins [apo] AI, B, B-100, and LDL apo B)

- Blood pressure

- Measures of glucose metabolism (hemoglobin A_{1c} [Hgb A_{1c}], fasting blood sugar [FBS], and fasting insulin)

- C-reactive protein (CRP)

- Measures of hemostasis (fibrinogen, factors VII and VIII, von Willebrand factor [vWF], and platelet aggregation)

- Non-serum diagnostic tests (coronary artery restenosis [following angioplasty], carotid intima-media thickness [IMT], exercise tolerance testing [ETT], and heart rate variability).

The final section of this chapter summarizes studies that examine the correlation between omega-3 fatty acid intake and tissue levels, including plasma or serum phospholipid levels, platelet phospholipids, erythrocyte membrane phospholipids, granulocyte membrane phospholipids, and monocyte membrane phospholipids.

Table 3.1 Numbers of studies of omega-3 fatty acids and cardiovascular risk factors

CVD Risk Factor	Total Studies Meeting Minimum Eligibility Criteria	Total Randomized Studies	Eligibility Criteria for Analysis [a]		Analyzed Studies
Lipids	182 [b]	108	RCT ≥ 60	Xover ≥ 40	**25**
Total Cholesterol	169	98	RCT ≥ 60	Xover ≥ 40	**23**
Low Density Lipoprotein	119	70	RCT ≥ 60	Xover ≥ 40	**15**
High Density Lipoprotein	141	81	RCT ≥ 60	Xover ≥ 40	**19**
Triglycerides	164	100	RCT ≥ 60	Xover ≥ 40	**19**
Lipoprotein (a)	23	14	RCT ≥ 5	Xover ≥ 5	**14**
Apolipoprotein A-1	61	37	RCT ≥ 20	Xover ≥ 15	**27**
Apolipoprotein B	52	29	RCT ≥ 20	Xover ≥ 10	**25**
Apolipoprotein B-100	11	10	RCT ≥ 5	Xover ≥ 5	**10**
Blood pressure	103	71	RCT ≥ 15 DM	Xover ≥ 10 DM	**6** [c]
Hemoglobin A_{1c}	32	22	RCT ≥ 10	Xover ≥ 10	**18**
Blood sugar, fasting	57	34	RCT ≥ 25	Xover ≥ 15	**17**
Fasting insulin	21	15	RCT ≥ 5	Xover ≥ 5	**15**
C-reactive protein	5	4	All		**5**
Fibrinogen	59	34	RCT ≥ 15	Xover ≥ 10	**24**
Factor VII	40	25	RCT ≥ 15	Xover ≥ 10	**19**
Factor VIII	13	5	RCT ≥ 5	Xover ≥ 5	**5**
von Willebrand factor	20	9	RCT ≥ 5	Xover ≥ 5	**9**
Platelet aggregation	84	39	RCT ≥ 15	Xover ≥ 10	**11** [d]
Coronary arteriography	17	14	RCT ≥ 5	Xover ≥ 5	**12** [e]
Carotid intima-media thickness	4	1	All		**4**
Exercise tolerance test	6	3	All		**6**
Heart rate variability	3	2	All		**3**
Sub-Total [f]	327	197			**123**
Risk Factors Not Analyzed					
Apolipoprotein C-III	3	1			
Remnant-like particles	2	0			
Free fatty acids or Non-esterified fatty acids	7	5			
Diabetes incidence	1	0			
Microalbuminuria	4	3			
Homocysteine	4	2			
Factor XII	4	1			
Bleeding time	48	21			
Interleukin 6	2	1			
VCAM-1 [g]	2	1			
Creatine kinase	5	4			
Echocardiography	1	1			
Endothelial function	11	8			
ECG parameters	4	3			
Heart rate, resting	23	16			
Ankle brachial index	1	1			
Total (Analyzed and not analyzed)	346				

a RCT ≥, minimum number of subjects in a parallel randomized controlled trial; Xover ≥, minimum number of subjects in a cross-over study; DM = diabetes mellitus.

b Minimum of 20 subjects consuming omega-3 fatty acids.

c We analyzed only studies of diabetic patients.

d We analyzed only studies with platelet aggregation data reported in text or table. We did not analyze studies that reported outcomes only in figures.

e We analyzed only studies that reported the number (or percent) of patients who had restenosis.

f Individual study numbers do not add up to totals because many articles reported more than 1 outcome.

g Vascular cell adhesion molecule 1

Lipids: Total Cholesterol

(Table 3.2)

Abnormal levels of serum lipids, primarily low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (Tg) have long been recognized as risk factors for CVD. Of interest is whether consuming omega-3 fatty acids as part of a therapeutic lifestyle change would improve lipid levels, or at least would not be detrimental. Recent National Cholesterol Education Program (NCEP) guidelines recommend a goal for fasting total cholesterol of less than 200 mg/dL in all adults, with lower levels recommended for people at elevated risk for CVD, including diabetics, smokers, people with hypertension or a family history of premature CVD, or who are beyond middle age [59].

Lipid levels are the most commonly measured CVD risk factor in trials of omega-3 fatty acid consumption. We found 182 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on lipid levels in at least 20 subjects (See Table 3.1). Of these, we analyzed the 25 randomized trials with lipid data for at least 60 subjects in parallel trials and 40 subjects in crossover trials who consumed omega-3 fatty acids. It is important to note that because we analyzed only the largest randomized trials, we did not capture many smaller studies of diabetic patients.

Among these studies, 169 reported data on total cholesterol levels. We analyzed the 23 largest randomized trials.

Table 3.2 Effects of omega-3 fatty acids on total cholesterol (mg/dL) in randomized trials (6 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source	g/d		N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils													
Cairns, 1996	325	Fish oil	ED	5.4	328	Corn oil	227	-3	NS	B	3	Un	CVD	II
Bonaa, 1992	71	Fish oil	ED	5.1	74	Corn oil	251	+2	NS	B	4	Un	DysLip	I
Lungershausen, 1994	42 [e]	Fish oil	ED	4.9	42 [e]	Corn oil	221	+2	NS	B	3	Un	CVD	II
Bairati, 1992b	66	Fish oil	ED	4.5	59	Olive oil	240	-1	NS	B	5	Un	CVD	II
Grimsgaard, 1997	75	Purified EPA	E	3.8	77	Corn oil	231	-10	.004 [f]	A	5	Un	GEN	I
	72	Purified DHA	D	3.7			232	-3	NS [f]					
Nilsen, 2001 [g]	75	Fish oil	ED	3.4	75	Corn oil	214	+9	NS	B	3	Un	CVD	II
Eritsland, 1995b	260	Fish oil	ED	3.3	251	No oil	252	-2	NS	B	2	Ad	CVD	II
Brox, 2001 [h]	38	Cod liver oil	ED	3.3	37	No oil	319	-19	NS	C	1	Un	DysLip	I
	37	Seal oil	ED	2.6			308	0	NS					
Franzen, 1993	92 [i]	Fish oil	ED	3.1	83 [i]	Olive	219	+2	nd	C	5	Ad	CVD	II
Osterud, 1995	26	Cod liver oil	ED	3.1	28	No oil	203	+1	NS	B	2	Un	GEN	I
	27	Seal/Cod oil	ED	2.8			204	+9	NS					
	27	Seal oil	ED	2.4			199	+2	NS					
	26	Whale oil	ED	1.7			197	+10	NS					
Leigh-Firbank, 2002	55 [e]	Fish oil	ED	3.0	55 [e]	Olive oil	255	-2	NS	B	3	Un	DysLip	I
Sacks, 1994	60 [j]	Fish oil	ED	2.4	66 [j]	Olive oil	190	+4	NS	C	3	Un	GEN	I

Continued

Table 3.2 Effects of omega-3 fatty acids on total cholesterol (mg/dL) in randomized trials (continued)

Author, Year	Omega-3 Fatty Acid Arm [a] N	Source		g/d	Control N	Source	Results [b] Base	Net Δ	*P*	Quality [c] Summary	Jadad	Allocation Conceal	Applicability [d]	
	DHA/EPA Oils (continued)													
Sirtori, 1998	459	Fish oil	ED	1.7 [k]	450	Olive oil	234 [L]	-1 [L]	NS	B	4	Ad	CVD risk [m]	I
von Schacky, 1999	89 [n]	Fish oil	ED	1.7 [o]	86 [p]	Plant oil	237	+6	NS	C	5	Ad	CVD	II
GISSI, 1999	2836	Fish oil	ED	0.9	2828	No oil	210	+2	NS	B	3	Un	CVD	II
	2830	Fish oil [q]			2830	Vitamin E	211	+4						
Leng, 1998	37 [r]	Fish oil	ED	0.045 [s]	36 [t]	Sunflower oil	233	+2	NS	C	4	Ad	CVD	II
	Plant Oils													
Natvig, 1968	289 [u]	Linseed oil	A	~5	316 [u]	Sunflower oil	246	+1	NS	C	2	Un	GEN	III
	47 [v]				51 [v]		250	+5	NS				DM [w]	III
Borchgrevink, 1966	100	Linseed oil	A	~5	100	Corn oil	289	+13	nd	C	2	Un	CVD	III
	Fish and Mediterranean Diets													
Singh, 2002	499	Indo-Mediterranean	T	1.8	501	NCEP I [x]	221	-20	<.0001	C	2	Un	CVD risk [y]	III
Hanninen, 1989	19	Fish (3.8/week)	ED	0.9	18	0.4 Fish/week	176	-8	nd	B	2	Un	GEN	III
	22	Fish (2.3/week)	ED	0.5			157	+2	nd					
	21	Fish (1.5/week)	ED	0.4			158	-7	nd					
	20	Fish (0.9/week)	ED	0.2			170	+3	nd					
de Lorgeril, 1994	171 [z]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [aa]	Regular	240	-1	NS	C	2	Un	CVD	II
	Combinations													
Mori, 1994	17	Fish oil & Fish diet [bb]	ED	5.2	18	Olive/Palm/ Safflower 40% fat diet	235 [cc]	+7 [dd]	NS	B	2	Un	CVD	II
	16	Fish oil	ED	4.2				+19 [dd]	NS					
	17	Fish diet [bb] & Placebo oil	ED	3.0				+13 [dd]	NS					
	17	Fish oil	ED	2.1				+21 [dd]	<.05					
	18	Fish diet [bb] & Placebo oil	ED	3.0	17	Oil 30% fat		+1 [dd]	NS					
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED	1.7	30	Sunflower margarine	212	+14	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED	0.8			211	+4	NS					
	30	Rapeseed/Linseed margarine	A	4.5			217	+2	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f *P*=.04 for difference in effect of EPA and DHA.

g Only subjects who did not change statin treatment are included here.
h Data missing from article provided by study author.
i Maximum. Total analyzed was 172, not 175 (92+83).
j 84 at baseline.
k 2.6 g/day for first 2 months, then 1.7 g/day for 4 months.
L Estimate from graph.
m Dyslipidemia and one or more of: hypertension, diabetes, or glucose intolerance.
n 111 at baseline.
o 3.4 g/day for first 3 months, then 1.7 g/day for 21 months.
p 112 at baseline.
q Plus vitamin E 300 mg.
r Baseline data based on N=52.
s Plus 280 mg gamma linolenic acid (omega-6 fatty acid).
t Baseline data based on N=50.
u 33 missing data for one or both tests.
v 7 missing data for one or both tests.
w Sub-analysis.
x National Cholesterol Education Program step I prudent diet.
y One or more of: hypercholesterolemia, hypertension, diabetes, angina pectoris or myocardial infarction.
z Baseline data based on 289 subjects.
aa Baseline data based on 295 subjects.
bb Omega-3 fatty acid from fish diet is approximate, assuming that each of 4 different fish was consumed equally.
cc Mean baseline value for all subjects combined.
dd Estimated from graph.

Overall Effect [48,49,52,53,60-78]

Across the 23 studies there was a wide range of effects of omega-3 fatty acids on total cholesterol, although in most studies the net effect was small and generally of an increase in total cholesterol. Most studies found net increases of between 0% and 6% (approximately 0 to 14 mg/dL). Only 3 studies found that the changes in total cholesterol in subjects on omega-3 fatty acids were significantly different than control. Notably, the directions of the treatment effects were not consistent across these studies.

Sub-populations

Only 5 of the studies included generally healthy subjects, 3 of which were all male[66,67,72]. Net effects were generally small but inconsistent in direction. Most of the studies included subjects with a variety of types of CVD. There was no clear consistent effect among the 12 studies. Two studies evaluated subjects at increased risk of CVD with different sets of treatments and came to different conclusions. Sirtori et al. found no effect with fish oil in approximately 900 individuals with dyslipidemia and either hypertension, diabetes or glucose intolerance [77]. Singh et al. reported a large, highly significant reduction in total cholesterol with an Indo-Mediterranean diet in approximately 1,000 people with either hypercholesterolemia, hypertension, diabetes, angina or myocardial infarction [76]. However, this study found that subjects on the Indo-Mediterranean diet lost significantly more weight (3 kg) than those on the control diet. In addition, they reported uniform highly significant effects on all serum markers despite widely ranging effects. A number of statistical calculation errors were also found.

While no study evaluated a population of all diabetic subjects, Natvig et al., in an early Norwegian trial of linseed oil supplements, reported a sub-analysis of the 98 diabetic subjects and found that the effect of linseed oil was similar in both all subjects and specifically in diabetic

subjects, but that total cholesterol decreased by a small amount more in the diabetic subjects [72]. The difference was not significant.

Covariates

No subgroup analyses based on covariates were reported. Two studies performed regressions. Bairati et al. reported no change in total cholesterol effect after adjusting for age, sex, baseline lipid level, lipid treatment, body mass index and alcohol use [60]. Mori et al. performed a regression adjusting for change in weight and found a highly significant "group effect" increase in total cholesterol with omega-3 fatty acids ($P < .001$) [71]. This study also found larger relative net increases in total cholesterol among subjects on a 40% fat diet, but no net effect (and a decrease in absolute change) in subjects on a 30% fat diet. No clear difference was seen between the 5 studies that included only men and the remaining studies [61,66,67,71,72].

Dose and Source Effect

Three studies compared different sources – and doses – of marine oil supplements [62,66,74]. Grimsgaard et al. found a significantly greater decrease in total cholesterol with purified EPA than DHA in healthy, middle-aged men [66]. Brox et al. found a substantially greater decrease in total cholesterol with higher omega-3 fatty acid dose cod liver oil supplement than seal oil supplement in healthy subjects with elevated total cholesterol; although they imply that the difference was not statistically significant [62]. Osterud et al. found varying degrees of net increases of total cholesterol with different marine oil supplements in healthy subjects [74]. No clear pattern was evident among different doses of omega-3 fatty acids and dose effect of marine oil supplements was evident across the studies.

Hanninen et al. compared 5 fish diets [67]. No significant effect on total cholesterol was seen with any diet and there was no dose effect based on frequency of fish consumption.

Among subjects on a higher fat diet, there was no clear difference in effect based on source of EPA+DHA among men studied by Mori et al. [71]. Despite an apparent larger net increase in total cholesterol among subjects consuming both fish oil margarine and fish oil supplements compared to those consuming only fish oil margarine or rapeseed and linseed margarine, Finnegan et al. found no differences in effect among the treatments [53].

The 4 studies of ALA all reported net increases in total cholesterol, but there was no apparent difference compared to fish and fish oil studies.

Exposure Duration

In 7 studies, total cholesterol levels varied by similar amounts in treatment and control arms at multiple time points [49,53,67,69,73,75,77]. No differences in effect were seen at times ranging from 5 weeks to 2 years. No effect across studies is evident based on duration of intervention or exposure.

Sustainment of Effect

No study reported data on an effect after ceasing omega-3 fatty acid treatment.

Lipids: Low Density Lipoprotein

(Table 3.3)

Among the lipids commonly measured, the level of low density lipoprotein (LDL) is generally of most concern when determining CVD risk and whether to initiate therapy. The NCEP guidelines note that the relationship between LDL levels and CVD risk is continuous over a broad range of LDL levels from low to high [59]. Recommended goals for LDL level depend on an individual's CVD risk factors. Risk factors include diabetes, smoking, hypertension, family history of premature CVD, and being beyond middle age. With no or one risk factor, LDL goal is less than 160 mg/dL; with 2 or more risk factors, LDL goal is less than 130 mg/dL. People who already have CVD or who have diabetes are recommended to achieve an LDL of less than 100 mg/dL. As with total cholesterol, of interest is whether consuming omega-3 fatty acids as part of a therapeutic lifestyle change would improve LDL levels, or at least would not be detrimental.

Of the 25 randomized trials with lipid data for at least 60 subjects in parallel trials and 40 subjects in crossover trials who consumed omega-3 fatty acids 15 reported data on LDL (See Table 3.1).

Overall Effect [48,49,52,53,60,63-66,68-71,76,79]

The effect of omega-3 fatty acid consumption was fairly uniform across studies. Most found a net increase in LDL with treatment, although the range of effects varied substantially. Most studies found net increases of LDL of 10 mg/dL or less, although the complete range of mean net effects was a decrease of 19 mg/dL to an increase of 21 mg/dL. As with a number of other outcomes, Singh et al. found a discordant result [76]. In this case, they reported a large, highly significant reduction in LDL with an Indo-Mediterranean diet in subjects at risk for CVD. However, as previously noted, this study found a difference in weight loss between the 2 interventions and reported uniform highly significant effects on all serum markers despite widely ranging effects; also, a number of statistical calculation errors were found.

Sub-populations

Only a single study included generally healthy subjects and no study included exclusively diabetics. Most of the studies included subjects with CVD. There was no clear difference among the 10 studies of CVD populations compared to the 3 dyslipidemia studies or single study of healthy subjects.

Covariates

No subgroup analyses based on covariates were reported. Two studies performed regressions. Bairati et al. reported that the effect of fish oil supplements on LDL (a net increase) was reduced and became borderline non-significant ($P = .06$) after adjusting for age, sex, baseline lipid level, lipid treatment, body mass index and alcohol use [60]. Mori et al. performed a regression adjusting for change in weight and found a highly significant "group effect" increase in LDL with omega-3 fatty acids ($P < .001$) [71]. In contrast to their findings for total cholesterol, they reported similar effects on LDL among subjects on a 40% fat diet and on a 30% fat diet.

Table 3.3 Effects of omega-3 fatty acids on low density lipoprotein (mg/dL) in randomized trials (6 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils													
Cairns, 1996	325	Fish oil	ED	5.4	328	Corn oil	148	+3	NS	B	3	Un	CVD	II
Bonaa, 1992	70	Fish oil	ED	5.1	68	Corn oil	177	+7	NS	B	4	Un	DysLip	I
Lungers-hausen, 1994	42 [e]	Fish oil	ED	4.9	42 [e]	Corn oil	156	+7	NS	B	3	Un	CVD	II
Bairati, 1992b	66	Fish oil	ED	4.5	59	Olive oil	158	+12	<.05	B	5	Un	CVD	II
Grimsgaard, 1997	75	Purified EPA	E	3.8	77	Corn oil	157	-5	NS	A	5	Un	GEN	I
	72	Purified DHA	D	3.7			157	0	NS					
Eritsland, 1995b	260	Fish oil	ED	3.3	251	No oil	177	+4	NS	B	2	Ad	CVD	II
Franzen, 1993	92 [f]	Fish oil	ED	3.1	83 [f]	Olive	151	+9	nd	C	5	Ad	CVD	II
Leigh-Firbank, 2002	55 [e]	Fish oil	ED	3.0	55 [e]	Olive oil	175	+13	.03	B	3	Un	DysLip	I
Angerer, 2002	87	Fish oil	ED	1.7	84	Fatty acid	157	+6	NS	B	4	Ad	CVD	II
GISSI, 1999	2836	Fish oil	ED	0.9	2828	No oil	137	+3	NS	B	3	Un	CVD	II
	2830	Fish oil [g]			2830	Vitamin E	138	+5						
Leng, 1998	37 [h]	Fish oil	ED	0.045 [i]	36 [j]	Sunflower oil	107	+6	NS	C	4	Ad	CVD	II
	Fish and Mediterranean Diets													
Singh, 2002	499	Indo-Mediterranean	T	1.8	501	NCEP I [k]	141	-19	<.0001	C	2	Un	CVD risk [L]	III
de Lorgeril, 1994	171 [m]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [n]	Regular	175	+3	NS	C	2	Un	CVD	II
	Combinations													
Mori, 1994	17	Fish oil & Fish diet [o]	ED	5.2	18	Olive/Palm/ Safflower 40% fat diet	157 [p]	+11 [q]	NS	B	2	Un	CVD	II
	16	Fish oil	ED	4.2				+21 [q]	<.01					
	17	Fish diet [o] & Placebo oil	ED	3.0				+10 [q]	NS					
	17	Fish oil	ED	2.1				+16 [q]	<.05					
	18	Fish diet [o] & Placebo oil	ED	3.0	17	Oil 30% fat		+12 [q]	<.05					
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED	1.7	30	Sunflower margarine	132	+13	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED	0.8			132	0	NS					
	30	Rapeseed/Linseed margarine	A	4.5			137	-2	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Maximum. Total analyzed was 172, not 175 (92+83).

g Plus vitamin E 300 mg.
h Baseline data based on N=52.
i Plus 280 mg gamma linolenic acid (omega-6 fatty acid).
j Baseline data based on N=50.
k National Cholesterol Education Program step I prudent diet.
L One or more of: hypercholesterolemia, hypertension, diabetes, angina pectoris or myocardial infarction.
m Baseline data based on 289 subjects.
n Baseline data based on 295 subjects.
o Omega-3 fatty acid from fish diet is approximate, assuming that each of 4 different fish was consumed equally.
p Mean baseline value for all subjects combined.
q Estimated from graph.

Dose and Source Effect

Mori et al. found no difference in effect among men consuming various doses of EPA+DHA either as supplements or as dietary fish [71]. Finnegan et al. noted a particularly large increase in LDL in the fish oil margarine/fish oil supplement arm compared to other arms, but the differences were not statistically significant [53]. Grimsgaard found no difference in effect on LDL level between purified EPA and purified DHA [66].

The 2 studies of ALA reported smaller net changes in LDL, but it is not clear that this represents a real difference in effect.

Exposure Duration

In 3 studies, LDL levels varied by similar amounts in treatment and control arms at multiple time points [49,53,69]. No differences in effect were seen at times ranging from 8 weeks to 2 years. No effect across studies is evident based on duration of intervention or exposure.

Sustainment of Effect

No study reported data on an effect after ceasing omega-3 fatty acid treatment.

Lipids: High Density Lipoprotein

(Table 3.4)

High density lipoprotein (HDL) plays a primary function in removing lipids from the bloodstream to be processed in the liver. Therefore, people with reduced levels of HDL are at increased risk of CVD independent of LDL or Tg levels. The new NCEP guidelines categorize an HDL level of less than 40 mg/dL as low, implying an increased risk of CVD [59]. Commonly used and well-tolerated drugs for dyslipidemia generally have at most a modest effect on HDL levels. Lifestyle changes, including physical exercise and low saturated fat diets are generally recommended to help increase HDL. Of interest is whether consuming omega-3 fatty acids as part of a therapeutic lifestyle change would help improve HDL levels, or at least that it would not be detrimental.

Of the 25 randomized trials with lipid data for at least 60 subjects in parallel trials and 40 subjects in crossover trials who consumed omega-3 fatty acids 19 reported data on HDL (See Table 3.1).

Table 3.4 Effects of omega-3 fatty acids on high density lipoprotein (mg/dL) in randomized trials (6 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]				Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	P	Summary	Jadad	Allocation Conceal			
		DHA/EPA Oils													
Cairns, 1996	325	Fish oil	ED	5.4	328	Corn oil	40	0	NS	B	3	Un		CVD	II
Bonaa, 1992	70	Fish oil	ED	5.1	69	Corn oil	51	-1	NS	B	4	Un		DysLip	I
Lungers-hausen, 1994	42 [e]	Fish oil	ED	4.9	42 [e]	Corn oil	40	+1	NS	B	3	Un		CVD	II
Grimsgaard, 1997	75	Purified EPA	E	3.8	77	Corn oil	51	+1	NS [f]	A	5	Un		GEN	I
	72	Purified DHA	D	3.7			53	+3	.0005 [f]						
Bairati, 1992b	66	Fish oil	ED	4.5	59	Olive oil	40	+4	<.05	B	5	Un		CVD	II
Nilsen, 2001 [g]	119	Fish oil	ED	3.4	120	Corn oil	42	+5	<.05	B	3	Un		CVD	II
Eritsland, 1995b	260	Fish oil	ED	3.3	251	No oil	41	+1	NS	B	2	Ad		CVD	II
Brox, 2001 [h]	38	Cod liver oil	ED	3.3	37	No oil	50	0	NS	C	1	Un		DysLip	I
	37	Seal oil	ED	2.6			50	+4	NS						
Franzen, 1993	92 [i]	Fish oil	ED	3.1	83 [i]	Olive	43	+2	nd	C	5	Ad		CVD	II
Osterud, 1995	26	Cod liver oil	ED	3.1	28	No oil	48	+3	NS	B	2	Un		GEN	I
	27	Seal/Cod oil	ED	2.8			53	+4	<.05						
	27	Seal oil	ED	2.4			51	+2	NS						
	26	Whale oil	ED	1.7			49	+5	<.005						
Leigh-Firbank, 2002	55 [e]	Fish oil	ED	3.0	55 [e]	Olive oil	37	0	NS	B	3	Un		DysLip	I
Sacks, 1994	60 [j]	Fish oil	ED	2.4	66 [j]	Olive oil	46	+2	NS	C	3	Un		GEN	I
Angerer, 2002	87	Fish oil	ED	1.7	84	Fatty acid	51	-3	NS	B	4	Ad		CVD	II
GISSI, 1999	2836	Fish oil	ED	0.9	2828	No oil	42	0	NS	B	3	Un		CVD	II
	2830	Fish oil [k]			2830	Vitamin E	42	0							
Leng, 1998	37 [L]	Fish oil	ED	0.045 [m]	36 [n]	Sunflower oil	45	+1	NS	C	4	Ad		CVD	II
		Fish and Mediterranean Diets													
Singh, 2002	499	Indo-Mediterranean	T	1.8	501	NCEP I [o]	45	+2	<.0001	C	2	Un		CVD risk [p]	III
de Lorgeril, 1994	171 [q]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [r]	Regular	45	-1	NS	C	2	Un		CVD	II
		Combinations													
Mori, 1994	17	Fish oil & Fish diet [s]	ED	5.2	18	Olive/Palm/ Safflower 40% fat diet	48 [t]	+3 [u]	<.01	B	2	Un		CVD	II
	16	Fish oil	ED	4.2				+2 [u]	<.05						
	17	Fish diet [s] & Placebo oil	ED	3.0				+3 [u]	<.001						
	17	Fish oil	ED	2.1				+4 [u]	<.01						
	18	Fish diet [s] & Placebo oil	ED	3.0	17	Oil 30% fat		+3 [u]	<.05						
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED	1.7	30	Sunflower margarine	52	+2	NS	A	4	Un		DysLip	I
	30	Fish oil margarine	ED	0.8			53	+3	NS						
	30	Rapeseed/Linseed margarine	A	4.5			50	+1	NS						

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.
c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
e Cross-over study.
f *P*=.009 for difference in effect of EPA and DHA.
g All subjects regardless of whether statin treatment changed during study.
h Data missing from article provided by study author.
i Maximum. Total analyzed was 172, not 175 (92+83).
j 84 at baseline.
k Plus vitamin E 300 mg.
L Baseline data based on N=52.
m Plus 280 mg gamma linolenic acid (omega-6 fatty acid).
n Baseline data based on N=50.
o National Cholesterol Education Program step I prudent diet.
p One or more of: hypercholesterolemia, hypertension, diabetes, angina pectoris or myocardial infarction.
q Baseline data based on 289 subjects.
r Baseline data based on 295 subjects.
s Omega-3 fatty acid from fish diet is approximate, assuming that each of 4 different fish was consumed equally.
t Mean baseline value for all subjects combined.
u Estimated from graph.

Overall Effect [48,49,52,53,60,62-66,68-71,73-76,79]

The effect of omega-3 fatty acid consumption was generally consistent across the 19 studies. Most found a small net increase in HDL with treatment of up to 3 to 5 mg/dL, although 7 found a small net decrease or no effect in at least one tested study arm. Six of the studies reported that the net increase in HDL was statistically significant.

Sub-populations

Across studies, there is no clear difference in effect among the 11 studies of CVD populations, the 4 studies of dyslipidemic patients, the 3 studies of healthy subjects, or the study of Indians at increased risk of CVD. No study included only diabetic patients.

Covariates

No subgroup analyses based on covariates were reported. Two studies performed regressions. Bairati et al. reported that the effect of fish oil supplements on HDL (a net increase) was reduced and became borderline non-significant ($P = .06$) after adjusting for age, sex, baseline lipid level, lipid treatment, body mass index and alcohol use [60]. Mori et al. performed a regression adjusting for change in weight and found a highly significant "group effect" increase in HDL with omega-3 fatty acids ($P < .001$) [71]. In contrast with their findings for total cholesterol, they reported similar effects on HDL among subjects on a 40% fat diet and those on a 30% fat diet.

Dose and Source Effect

Three studies compared different sources – and doses – of marine oil supplements [62,66,74]. Grimsgaard et al. found a small difference in effect between purified EPA and DHA, but the net increase in HDL was significantly larger in men consuming DHA than those consuming EPA [66]. In studies by Brox et al. and Osterud et al., somewhat different net effects were seen with the different types of oils; however, neither study reported on whether the oils differed from each other on their effect on HDL [62,74]. No dose effect of marine oil supplements was evident across the studies.

Mori et al. found no difference in effect among men consuming various doses of EPA+DHA either as supplements or as dietary fish [71]. All doses and sources of omega-3 fatty acids resulted in significant increases in HDL. Finnegan et al. reported no difference in effect with different omega-3 fatty acid treatments [53].

Only 2 studies tested ALA supplementation, with minimal effect.

Exposure Duration

Five studies reported data on time trends of HDL levels. Leng et al., de Lorgeril et al. and Finnegan et al. reported no difference in HDL levels at multiple time periods between 8 weeks and 2 years. [49,53,69]. In contrast, Nilsen et al. reported a steady increase in HDL in patients with recent myocardial infarctions who started fish oil supplements at 6 weeks (+8%), 6 months (+14%), and 12 months (+19%); patients on corn oil had variable HDL levels (-0.3%, +4%, and +7%, respectively). Sacks et al. reported that HDL levels were unchanged at 3 months in healthy subjects taking fish oil supplements compared to control – decreasing by about 1.5 mg/dL in both – but that HDL returned to baseline at 6 months, resulting in a small net difference compared to control. No clear effect across studies is evident based on duration of intervention or exposure.

Sustainment of Effect

No study reported data on an effect after ceasing omega-3 fatty acid treatment.

Lipids: Triglycerides

(Table 3.5, Figures 3.1 and 3.2)

Elevated levels of triglycerides (Tg) are increasingly being recognized as a risk factor for CVD, independent of other serum lipids. Elevated Tg are most frequently seen in patients with the metabolic syndrome, although various secondary and genetic factors can raise Tg. The recent NCEP guidelines recommend a goal for fasting Tg of less than 150 mg/dL [59]. Fish oil's ability to lower Tg is considered one of the leading mechanisms by which omega-3 fatty acid consumption lowers CVD risk [80].

Of the 25 randomized trials with lipid data for at least 60 subjects in parallel trials and 40 subjects in crossover trials who consumed omega-3 fatty acids 19 reported data on Tg (See Table 3.1).

Overall Effect [48,49,52,53,60,63-68,70,71,73,74,76,77,79,81]

With few exceptions, Tg levels in the 19 studies decreased by substantial amounts in subjects taking omega-3 fatty acids, both in absolute amount and compared to control groups. The changes in Tg were generally highly significant.

Table 3.5 Effects of omega-3 fatty acids on triglycerides (mg/dL) in randomized trials (6 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			
	N	Source		g/d	N	Source	Base	Net Δ	P	Summary	Jadad	Allocation Conceal	Applicability [d]
	DHA/EPA Oils												
Cairns, 1996	325	Fish oil	ED	5.4	328	Corn oil	235	-64	<.05	B	3	Un	CVD II
Bonaa, 1992	72	Fish oil	ED	5.1	72	Corn oil	124	-23	<.01	B	4	Un	DysLip I
Lungershausen, 1994	42 [e]	Fish oil	ED	4.9	42 [e]	Corn oil	150	-19	<.01	B	3	Un	CVD II
Bairati, 1992b	66	Fish oil	ED	4.5	59	Olive oil	204	-80	<.0001	B	5	Un	CVD II
Grimsgaard, 1997	75	Purified EPA	E	3.8	77	Corn oil	109	-23	.0001 [f]	A	5	Un	GEN I
	72	Purified DHA	D	3.7			110	-29	.0001 [f]				
Nilsen, 2001 [g]	61	Fish oil (men)	ED	3.4	61	Corn oil	140	-50	.001	B	3	Un	CVD II
	12	Fish oil (women)			13		123	-71	.07				
Eritsland, 1995b	260	Fish oil	ED	3.3	251	No oil	172	-32	<.0001	B	2	Ad	CVD II
Franzen, 1993	92 [h]	Fish oil	ED	3.1	83 [h]	Olive	158	-34	nd	C	5	Ad	CVD II
Osterud, 1995	26	Cod liver oil	ED	3.1	28	No oil	113	-28	<.05	B	2	Un	GEN I
	27	Seal/Cod oil	ED	2.8			114	-21	NS				
	27	Seal oil	ED	2.4			106	-14	NS				
	26	Whale oil	ED	1.7			97	-9	NS				
Leigh-Firbank, 2002	55 [e]	Fish oil	ED	3.0	55 [e]	Olive oil	221	-74	<.001	B	3	Un	DysLip I
Maresta, 2002	125	Fish oil	ED	2.6 [i]	132	Olive oil	160	+5	NS	B	3	Un	CVD II
Sirtori, 1998	459	Fish oil	ED	1.7 [j]	450	Olive oil	294 [k]	-63	<.0001	B	4	Ad	CVD risk [L] I
Angerer, 2002	87	Fish oil	ED	1.7	84	Fatty acid	194	-22	NS	B	4	Ad	CVD II
GISSI, 1999	2836	Fish oil	ED	0.9	2828	No oil	163	-8	<.05	B	3	Un	CVD II
	2830	Fish oil [m]			2830	Vitamin E	160	-6					
	Fish and Mediterranean Diets												
Singh, 2002	499	Indo-Mediterranean	T	1.8	501	NCEP I [n]	163	-22	<.0001	C	2	Un	CVD risk [o] III
Hanninen, 1989	19	Fish (3.8/week)	ED	0.9	18	0.4 Fish/week	81	-14	nd [p]	B	2	Un	GEN III
	22	Fish (2.3/week)	ED	0.5			81	-12	nd [q]				
	21	Fish (1.5/week)	ED	0.4			60	-8	nd [q]				
	20	Fish (0.9/week)	ED	0.2			69	+4	NS				
de Lorgeril, 1994	171 [r]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [s]	Regular	190	-19	NS	C	2	Un	CVD II
	Combinations												
Mori, 1994	17	Fish oil & Fish diet [t]	ED	5.2	18	Olive/Palm/ Safflower	154 [u]	-65 [k]	<.001	B	2	Un	CVD II

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]				Applicability [d]
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	16	Fish oil	ED	4.2		40% fat diet		-56 [k]	<.01					
	17	Fish diet [t] & Placebo oil	ED	3.0				-32 [k]	<.001					
	17	Fish oil	ED	2.1				-21 [k]	<.05					
	18	Fish diet [t] & Placebo oil	ED	3.0	17	Oil 30% fat		-37 [k]	<.01					
Finnegan, 2003	31	Fish oil margarine / Fish oil	ED	1.7	30	Sunflower margarine	142	-10	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED	0.8			146	+6	NS					
	30	Rapeseed/Linseed margarine	A	4.5			147	+23	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Non-significant difference in effect between EPA and DHA.

g Only subjects who did not change statin treatment are included here.

h Maximum. Total analyzed was 172, not 175 (92+83).

i 5.1 g for 1 month before and 1 month after PTCA, then reduced to 2.6 g for an additional 5 months.

j 2.6 g/day for first 2 months, then 1.7 g/day for 4 months.

k Estimate from graph.

L Dyslipidemia and one or more of: hypertension, diabetes, or glucose intolerance.

m Plus vitamin E 300 mg.

n National Cholesterol Education Program step I prudent diet.

o One or more of: hypercholesterolemia, hypertension, diabetes, angina pectoris or myocardial infarction.

p *P*<.02 change from baseline.

q *P*<.10 change from baseline.

r Baseline data based on 289 subjects.

s Baseline data based on 295 subjects.

t Omega-3 fatty acid from fish diet is approximate, assuming that each of 4 different fish was consumed equally.

u Mean baseline value for all subjects combined.

Sub-populations

The 3 studies of healthy subjects, whose mean Tg levels were normal, generally found net decreases in Tg levels of about 10% to 25%. Eleven studies included subjects with a variety of types of CVD, all with mean Tg levels above 150 mg/dL. With the exception of Maresta et al., the 11 studies reported net decreases in Tg of between about 10% to 30%, most of which were statistically significant [81]. There was no obvious difference between the study by Maresta et al. of patients undergoing PTCA and other studies to explain the discordant finding.

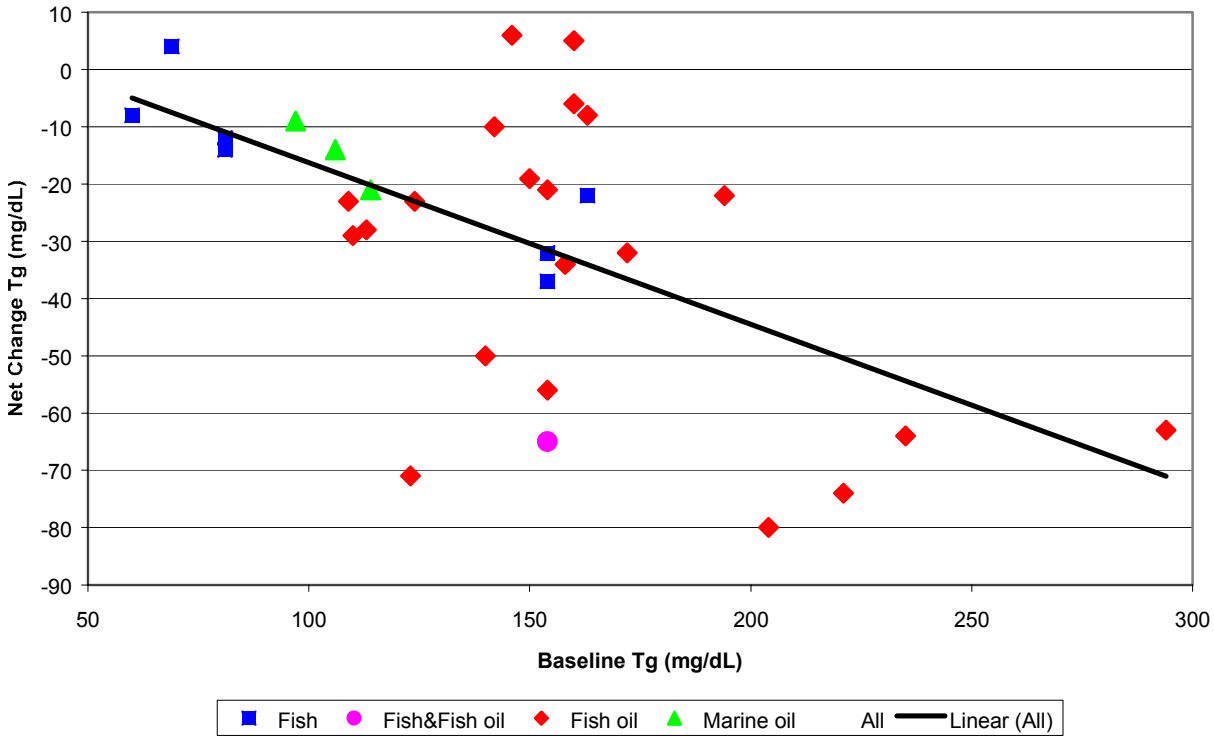
Two studies evaluated subjects at increased risk of CVD with different sets of treatments. Both of these studies found large, significant reductions in Tg. Two of 3 studies of dyslipidemic

patients reported large net decreases in Tg of 20% or 33%. Finnegan et al., in a study of moderately hyperlipidemic patients, found different effects of omega-3 fatty acid consumption on Tg depending on dose and source [53]. No study evaluated a population of only diabetic subjects.

Covariates

Nilsen et al. found similar decreases in Tg among men and women, where the difference in significance level can be ascribed mostly to sample size [73]. Two studies that performed regressions both found no substantial change in the significant Tg reduction after adjusting for age, sex, baseline lipid level, lipid treatment, body mass index and alcohol use [60] or change in weight [71]. Grimsgaard et al. reported the effect of purified EPA and DHA on Tg in quartiles of baseline Tg [66]. While the authors did not discuss whether the effect of omega-3 fatty acids was associated with baseline Tg level, there does appear to be a trend toward greater reduction of Tg in subjects with higher baseline Tg. Those in the lowest quartile had a net reduction of approximately 7 mg/dL (10 – 14%); those in the middle two quartiles had net reductions of between 15 mg/dL and 27 mg/dL (14 – 30%); and those in the highest quartile (128 mg/dL – 319 mg/dL) had net decreases in Tg of about 50 mg/dL (about 28%). Across studies, the average net decrease in Tg level was larger in studies with higher mean baseline levels, as indicated by Figure 3.1, in which the meta-regression is not adjusted for dose of omega-3 fatty acid or study size. After adjusting for dose and the study variance, the association across studies remains statistically significant. In a separate analysis comparing different percentages of fat in the diet, Mori et al. also found nearly identical effects in subjects on 30% or 40% fat diets who were consuming similar amounts of omega-3 fatty acids [71].

Figure 3.1 Meta-regression of baseline triglyceride (Tg) level versus net change in Tg. Each point represents an individual study or study arm. Marine oils include non-fish animal sources including Minke whale and seal. Regression not adjusted for dose of omega-3 fatty acid or study size.

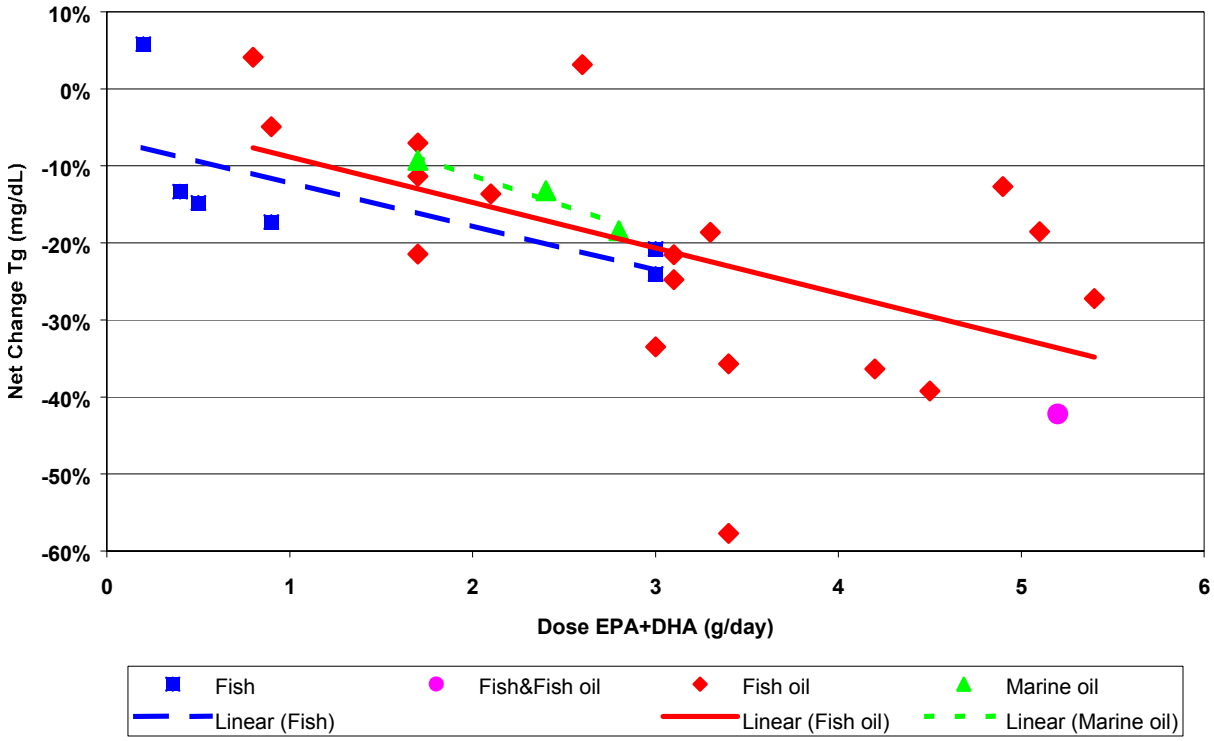


Dose and Source Effect

The 4 studies that compared different doses of marine oil supplements found that the greatest net decrease in Tg level occurred in study arms receiving the highest dose of EPA+DHA, although none of the articles reported whether there was a significant trend within the study. Across studies there was a clear trend toward greater percent decrease in Tg with higher doses, regardless of source (Figure 3.2). At least a 10% reduction in Tg was found in most studies with doses of at least 1.7 g per day of marine oil supplementation. Most study arms with doses of at least 3 g per day of marine oil supplements resulted in at least a 20% reduction in Tg. Among the studies of dietary fish, only the 2 arms with high omega-3 fatty acid fish diets in Mori, et al. achieved at least a 20% reduction of Tg [71].

Grimsgaard et al., overall, found no difference in effect between purified EPA and purified DHA, although the net decreases in Tg were consistently greater in the DHA group than in the EPA group across quartiles of baseline Tg [66]. Across studies, and within the Mori et al. study [71], the source of the EPA+DHA, whether as a supplement or from dietary fish, does not appear to make a difference. In contrast, the effect of ALA is uncertain. The single study that evaluated pure ALA supplementation, Finnegan et al., found increases in Tg levels in subjects on both 4.5 g and 9.5 g per day of ALA margarine (the latter dose is not included in the summary table) [53]. Both Singh et al. and de Lorgeril et al. provided ALA in the context of a Mediterranean diet, which also included higher dietary fish intake [49,76].

Figure 3.2 Meta-regression of dose of EPA+DHA intake versus net change in triglycerides (Tg). Each point represents an individual study or study arm. Separate simple regressions were performed for each oil source type (except for the individual study arm of combined fish and fish oil). Marine oils include non-fish animal sources including Minke whale and seal. Regression not adjusted for baseline Tg or study size.



Exposure Duration

The effect of duration of intervention or exposure was somewhat inconsistent among the 4 studies that reported data on Tg levels at different time points in studies of omega-3 fatty acids. Hanninen et al. found progressive decreases of Tg at 5 and 12 weeks in group of subjects consuming higher amounts of fish [67]. Similarly, Nilsen et al found progressive decreases in men, but not in a small group of women, at 6 weeks, 6 months and 12 months [73]. Sirtori et al. found that the effect of lower dose fish oil supplementation to reduce Tg occurred by 2 months and remained stable at 4 and 6 months [77]. In contrast, Finnegan et al. reported a significant decrease (15%) in mean Tg levels after 2 months which was not sustained at 6 months in the EPA+DHA arms [53]. Across studies, there is no apparent correlation between study duration and fish oil supplement effect, even after grouping studies by fish oil dosage.

Sustainment of Effect

No study reported data on an effect after ceasing omega-3 fatty acid treatment.

Lipoprotein(a)

(Table 3.6)

Lipoprotein(a) [Lp(a)] consists of an LDL core covalently bound to a plasminogen-like glycoprotein, apolipoprotein(a) [82]. Elevated levels of Lp(a) are an independent risk factor for atherosclerotic disease, possibly by promoting thrombosis. Lp(a) levels are largely determined by genetic polymorphism, specifically the number of K-IV repeats. Steroid hormones, and thus menopause, affect levels. There is a very large range of Lp(a) levels, from less than 0.1 mg/dL to more than 300 mg/dL and the distribution can be highly skewed. Treatments available to lower Lp(a) levels include niacin and hormone replacement therapy (in post-menopausal women).

We found 23 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on Lp(a) levels (See Table 3.1). Of these, we analyzed the 14 randomized trials. All but 2 were parallel trials. The source of fatty acids was marine oil supplements in 12 studies, dietary fish in 1 study and Mediterranean diet in 1 study.

Overall Effect [49,55,58,62,83-92]

Across the 14 studies there is no consistent effect on Lp(a) levels of omega-3 fatty acid consumption compared to control. In approximately one-third of the studies the omega-3 fatty acid study arms had a net increase in Lp(a) level compared to control; in the remaining studies the net decrease in Lp(a) level was generally small and non-significant. Only 2 studies reported a statistically significant difference between the effect of omega-3 fatty acid and control, both of which found a net decrease in Lp(a). However, the variability of Lp(a) levels among subjects within all the studies resulted in wide confidence intervals which limited the likelihood of statistically significant findings.

Sub-populations

The 5 studies that evaluated generally healthy subjects found no consistent effect of omega-3 fatty acids on Lp(a). Marckmann et al. found a large net increase of Lp(a) with fish oil supplement use and Deslypere et al. found a large net increase of Lp(a) in 1 of 3 treatment arms [85,89]. The remaining studies (and study arms) reported generally small effects, which were not uniform in direction. Five studies evaluated subjects with known CVD, one of which included only patients with hypertriglyceridemia on simvastatin. The apparent large decrease in Lp(a) in the latter study, Durrington et al., occurred because the median Lp(a) level rose by less in the fish oil supplement group than the corn oil group [86]. Again no consistent effect was seen. In the only study of diabetic subjects, Luo et al. found a statistically significant net reduction of Lp(a) of about 20% with fish oil supplementation [88]. The 4 studies of subjects with dyslipidemia (including the one with subjects with CVD on simvastatin) all found that subjects on marine oil supplements had a net decrease in Lp(a) compared to control; however, none of the changes was significant.

Table 3.6 Effects of omega-3 fatty acids on lipoprotein (a) (mg/dL) in randomized trials (4 weeks to 14 months)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
		DHA/EPA Oils												
Deslypere, 1992	14	Fish oil	T	3.4	14	Olive oil	22.5	+10.3	NS	B	2	Un	GEN	I
	15	Fish oil	T	2.2			27.2	+2.3	NS					
	15	Fish oil	T	1.1			22.1	+4.9	NS					
Alaswad, 1999	11	Fish oil	ED	3.4	12	Calcium gluconate	7.8	-1.1	NS	B	2	Un	DysLip	II
Prisco, 1994	10	Fish oil	ED	3.4	10	Olive oil	10.2	-0.9	NS	B	3	Un	GEN	II
Eritsland, 1995a	214 [e]	Fish oil	ED	3.3	219 [e]	No oil	[5.5]	[0]	NS	B	2	Ad	CVD	II
	66 [f]				50 [f]		[29.7]	[-1.5]	.02					
Brox, 2001 [g]	38	Cod liver oil	ED	3.3	37	No oil	18.5	-1.7	NS	C	1	Un	DysLip	I
	37	Seal oil	ED	2.6			16.3	-1.9	NS					
Durrington, 2001	30	Fish oil	ED	3.2	29	Corn oil	[10.5]	[-6.8]	NS	A	4	Un	CVD DysLip	II
Conquer, 1999	9	Seal oil	ED	3.0	10	Evening primrose	1.6	+0.1	NS	A	4	Un	GEN	II
Swahn, 1998	26	Fish oil	ED	2.9	27	Corn oil	30.8	-0.7	NS	B	5	Un	CVD	II
Hamazaki, 1996	13	DHA-rich Fish oil	ED	1.7-2.0 [h]	11	Corn oil	120	0	NS	B	4	Un	GEN	II
Luo, 1998	10 [i]	Fish oil	ED	1.8	10 [i]	Sunflower	17	-3	<.02	B	3	Un	DM II	II
Marckmann, 1997	22	Fish oil margarine	T	0.9	24	Sunflower margarine	[3.6]	[+3.0]	NS	B	3	Un	GEN	II
Nenseter, 2000	34	Fish powder	ED	0.2	36	Cellulose	[13.5]	[-0.8]	NS	B	3	Un	DysLip	I
		Fish and Mediterranean Diets												
de Lorgeril, 1994	171 [j]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [k]	Regular	28	+6	NS	C	2	Un	CVD	II
Schaefer, 1996	11	High fish	ED	0.7% Kcal	11	Low fish	38	-3	NS	C	1	Un	GEN	I

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm. Numbers in brackets are median values.; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm; for studies with numbers in brackets, the net difference was estimated by subtracting the final median value from the baseline median value; see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Baseline Lp(a) < 20 mg/dL.

f Baseline Lp(a) >= 20 mg/dL.

g Data missing from article provided by study author.

h Depending on body weight.

i Cross-over study.

j Baseline data based on 289 subjects.

k Baseline data based on 295 subjects.

Eritsland et al. found that the effect on Lp(a) was not related to age or sex [87]. The 2 studies that excluded pre-menopausal women both found small, non-significant, net reductions in mean Lp(a) with fish oil supplements or fish diet [58,83]. The 4 studies of men generally found small, non-significant, net increases in Lp(a) [84,85,89,91]. No study included only women.

Covariates

As shown in the summary table, Eritsland et al. found a differential effect of omega-3 fatty acids based on baseline Lp(a) level in patients referred for coronary artery bypass graft surgery [87]. Those with Lp(a) in the upper quintile (≥ 20 mg/dL) had a small but significant absolute and net reduction in Lp(a), while the remaining subjects did not. A similar comparison between subjects with elevated baseline Tg (≥ 245 mg/dL) and those with lower Tg found no difference in effect.

Dose and Source Effect

Only 2 studies directly compared different doses of fish oil supplements or different oils. Deslypere et al. reported no effect on Lp(a) at any of 3 doses of fish oil supplements, although the mean Lp(a) level rose by almost 50% after 1 year in subjects on the highest dose [85]. Brox et al. found no difference between similar doses of cod liver oil and seal oil supplements [62]. Across studies no differences could be discerned based on marine oil dose or omega-3 fatty acid-rich diet.

Exposure Duration

Two studies reported Lp(a) data at different time periods. de Lorgeril et al. found no difference in effect on Lp(a) at 8, 52, and 104 weeks in a study of Mediterranean diet [49]. Prisco et al. also found no difference in effect at 2 and 4 months in a study of fish oil supplements [91]. Across studies there is no apparent relationship between effect and duration of intervention or exposure.

Sustainment of Effect

Both Prisco et al. and Deslypere et al. reported no difference between Lp(a) levels while subjects were on fish oil supplements and at multiple time points up to 6 months after stopping supplementation [85,91].

Apolipoprotein A-I

(Table 3.7)

Apolipoprotein A-I (apo A-I) is the major apolipoprotein of HDL. It serves as a cofactor for enzymes that metabolize HDL in plasma. Apo A-I levels are strongly correlated with HDL cholesterol levels, but ratios of HDL to apo A-I do vary. While the effect of omega-3 fatty acids on lipoprotein-associated cholesterol and apolipoprotein assays are of interest, unlike cholesterol

levels, apolipoprotein assays, which are antibody specific and are not standardized, are not as amenable to cross-study comparisons. Furthermore, there are no data to suggest that apolipoprotein levels are more predictive of CVD risk than lipoprotein cholesterol levels.

We found 61 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on apo A-I levels (See Table 3.1). Of these, we analyzed the 27 randomized trials with data on at least 20 subjects in parallel trials and 15 subjects in crossover trials who consumed omega-3 fatty acids.

Table 3.7 Effects of omega-3 fatty Acids on apolipoprotein A-I (mg/dL) in randomized trials (4 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]			Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source	g/d	N	Source	Base	Net Δ	P	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils												
Wilt, 1989	38 [e]	Fish oil	ED 6.0	38 [e]	Safflower	151	-4	NS	B	4	Un	DysLip	III
Green, 1990	27 [e]	Fish oil	ED 5.2	27 [e]	Corn/Olive	113	-10	NS	B	4	Un	DysLip	II
Bonaa, 1992	71	Fish oil	ED 5.1	74	Corn oil	155	-7	<.05	B	4	Un	DysLip	I
Balestrieri, 1996	14 [e]	Fish oil	ED 5.1	38 [e]	Olive oil	116	-2	NS	B	3	Un	DysLip	III
Jensen, 1989	18 [e]	Cod liver oil	ED 4.6	18 [e]	Olive oil	134	-6	NS	B	4	Un	IDDM	II
Sirtori, 1992	12 [e]	Fish oil	ED 4.5	12 [e]	No oil	132	-4	nd	C	2	Un	DysLip	II
Schectman, 1989 [f]	18 [e]	Fish oil	ED 4.0	18 [e]	Safflower	117	-5	NS	B	2	Un	DysLip	II
Schectman, 1988 [f]	13 [e]	Fish oil	ED 4.0	13 [e]	Safflower	114	-10	NS	B	2	Un	NIDDM	II
Grimsgaard, 1997	75	Purified EPA	E 3.8	77	Corn oil	138	-4	.02 [g]	A	5	Un	GEN	I
	72	Purified DHA	D 3.7			138	+2	NS [g]					
Harris, 1997	22	Fish oil	ED 3.4	20	Corn oil	132	+1	NS	B	3	Un	DysLip	II
Nordoy, 1998	21	Fish oil	ED 3.4	20	Corn oil	142	+1	NS	B	4	Un	DysLip	I
Deslypere, 1992	14	Fish oil	T 3.4	14	Olive oil	137	-17	NS	B	2	Un	GEN	III
	15	Fish oil	T 2.2			139	-7	NS					
	15	Fish oil	T 1.1			137	-9	NS					
Chan, 2002	12	Fish oil	ED 3.4	12	Corn oil	118	+5	NS [h]	B	3	Un	DysLip	II
	11	Fish oil & Atorvastatin		12	Corn oil & Atorvastatin	128	+3						
Eritsland, 1995b	178	Fish oil	ED 3.3	174	No oil	124	+2	NS	B	2	Ad	CVD	II
Brox, 2001 [i]	38	Cod liver oil	ED 3.3	37	No oil	160	0	NS	C	1	Un	DysLip	I
	37	Seal oil	ED 2.6			160	+10 [j]	NS					
Durrington, 2001	30	Fish oil	ED 3.2	29	Corn oil	90	-6	NS	A	4	Un	CVD DysLip	II
McGrath, 1996	23 [e]	Fish oil	ED 3.0	23 [e]	Olive oil	119	+2	NS	A	4	Un	DM II	II
Nikkila, 1991	32 [e]	Fish oil	ED 2.4	32 [e]	Corn oil	109	-2	NS	B	3	Un	CVD DysLip	II
Luo, 1998	10 [e]	Fish oil	ED 1.8	10 [e]	Sunflower	148	+1	NS	B	3	Un	DM II	II
Marckmann, 1997	23	Fish oil margarine	T 0.9	24	Sunflower margarine	149	-2	NS	B	3	Un	GEN	II

Continued

Table 3.7 Effects of omega-3 fatty Acids on apolipoprotein A-I (mg/dL) in randomized trials (continued)

Author, Year	Omega-3 Fatty Acid Arm [a] N	Source		g/d	Control N	Source	Results [b] Base	Net Δ	P	Quality [c] Summary	Jadad	Allocation Conceal	Applicability [d]	
	Fish and Mediterranean Diets													
Hanninen, 1989	19	Fish (3.8/week)	ED	0.9	18	0.4 Fish/week	113	0	NS	B	2	Un	GEN	III
	22	Fish (2.3/week)	ED	0.5			117	+2	NS					
	21	Fish (1.5/week)	ED	0.4			121	-9	NS					
	20	Fish (0.9/week)	ED	0.2			118	0	NS					
Agren, 1988	14	Fish (3.7/week)	ED	0.8	12	0.25 Fish/week	126	-14	<.01	B	3	Un	GEN	III
	15	Fish & low SFA					123	-3	NS					
Agren, 1991	20	Fish (5/week)	ED	0.75	15	Regular	149	+8	NS	B	2	Un	GEN	III
	20	Fish (5/week) [k]			23	Regular [k]	159	0	NS					
de Lorgeril, 1994	171 [L]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [m]	Regular	124	-12	NS	C	2	Un	CVD	II
	Combinations													
Cobiac, 1991	13	Fish oil	ED	4.6	6	Olive, Palm, Safflower oil	117 [n]	+1	NS	B	2	Un	GEN	II
	12	Fatty Fish diet	ED	4.5			120 [n]	0	NS					
Silva, 1996	20	Fish oil	ED	3.6	--	--	159	-28 [o]	nd [p]	B	3	Un	DysLip	II
	15	Soya oil	A	0.8 [q]			184	-33 [o]	nd [p]					
Agren, 1996	14	Fish oil	ED	2.3	14	No oil	125	-8	NS	B	3	Un	GEN	III
	14	Algae DHA oil	D	1.7			128	+1	NS					
	13	Fatty Fish diet	ED	1.1			120	+1	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to subgroup; III = narrow applicability. See Methods.

e Cross-over study.

f Unclear if 2 studies by Schectman et al. [93,94] are independent of each other. Possible overlap of up to 6 subjects with NIDDM and hypertriglyceridemia.

g *P*=.0008 for difference in effect of EPA and DHA.

h Main effect.

i Data missing from article provided by study author.

j Only 2 significant digits reported. 10 mg/dL is smallest unit of change possible.

k Recommended aerobic exercise for 30 minutes 3 times a week.

L Baseline data based on 289 subjects.

m Baseline data based on 295 subjects.

n Units were not reported

o Pre-post difference (not compared to control).

p NS between treatments.

q No data on ALA amount. We assumed 7 g ALA per 100 g oil. 12 g oil.

Overall Effect [48,49,52,62,66,67,85,86,88,89,93-109]

Across the 27 studies, effects of omega-3 fatty acids on apo A-I levels were generally heterogeneous but small. Most studies found a small net change in apo A-I with omega-3 fatty acid consumption. Three-quarters of studies found net changes between –5% and +5% (–7 to

+10 mg/dL). No study found a large net increase in apo A-I level. A small number of studies found larger net decreases of up to 18% reductions (–33 mg/dL).

Sub-populations

Eight studies evaluated healthy people, all single-sex groups (7 male[66,85,89,95,97,100,110], 1 female[96]), mostly of university students. Four studies evaluated diabetic patients. Thirteen studies evaluated patients with dyslipidemia, 2 of which were also of patients with CVD. There was one additional study of patients with CVD. There were no clear patterns of treatment effect or differences in effect among the sub-populations.

Covariates

Silva et al. reported that sex, body mass index, hypertension, and non-insulin dependent diabetes did not affect the fish oil or soya oil supplement effect on lipid parameters including apo A-I in hyperlipidemic subjects [107]. No other study evaluated correlations or sub-analyses based on apo A-I. Agren et al. (1988) compared the effect of daily fish with daily fish with a low saturated fat diet in male university students [95]. Among subjects on a fish and low saturated fat diet, apo A-I levels remained essentially unchanged compared to those on a regular diet. In contrast, subjects on a fish diet who were not told to lower their saturated fat intake had a significant net decrease in apo A-I that was among the largest net decreases across studies. However, no comparison was made between the 2 treatment groups, nor were any explanations for the difference examined or discussed. Three studies compared fish oil to placebo oil supplements in dyslipidemic patients who were all taking either atorvastatin or simvastatin [98,99,106]. The effects of fish oil supplementation on apo A-I were small in all 3 studies. The effects were not uniform in direction.

Dose and Source Effect

Neither Deslypere et al. nor Hanninen et al. reported a dose dependent effect on apo A-I of either fish oil supplements or different frequencies of fish meals [67,85]. No dose effect was seen across studies of EPA+DHA either.

Five studies compared different sources of omega-3 fatty acids. Grimsgaard et al. found a small but significant net decrease in apo A-I with purified EPA compared to a smaller, non-significant, net increase with purified DHA; the difference between the 2 omega-3 fatty acids was statistically significant ($P = .008$) [66]. Brox et al. compared 2 sources of marine oil supplements: cod liver and seal oil [62]. No effect was found with either treatment. Cobiac et al. found no treatment effect with either fish oil supplementation or with a fatty fish diet [100]. Silva et al. found similarly large, significant reductions in apo A-I level in subjects taking either fish oil or soya oil supplements; however, no non-omega-3 fatty acid was used as a control [107]. Agren et al. (1996) compared fish oil supplementation, algae DHA oil supplementation, and fatty fish diet and also found no difference in effect on apo A-I among the groups [97].

Exposure Duration

Two studies reported apo A-I levels at multiple time points. Neither Hanninen et al. nor de Lorgeril et al. found any time-related effects of omega-3 fatty acids on apo A-I, at 5 and 12 weeks, and 8, 52, and 104 weeks, respectively [49,67].

Sustainment of Effect

Three studies followed subjects after stopping the intervention. Jensen et al. and Deslypere et al. found no change in apo A-I levels 8 weeks and 6 months, respectively, after stopping fish oil supplements [85,103]. In contrast, Agren et al. (1988) reported that 5 months after a 15 week trial of dietary fish apo A-I levels remained at lowered levels in the fish diet group who had no limitation of saturated fat; however, they do not indicate what these students' diets were at subsequent follow-up [95].

Apolipoprotein B, Apolipoprotein B-100, and LDL Apolipoprotein B

(Tables 3.8 and 3.9)

Apolipoprotein (apo) B has 2 major subtypes, B-100 and B-48. Apo B-100 is associated with lipoprotein particles of hepatic origin, specifically very low, intermediate, and low density lipoproteins (VLDL, IDL, LDL). Its major function is to serve as a ligand for the receptor that clears these particles from the bloodstream. During the conversion of VLDL to LDL in the circulation, only apo B-100 remains on LDL. Measures of LDL apo B represent the portion of total blood apoB-100 that is associated with the LDL subfraction. There is 1 apo B-100 molecule per LDL particle. A discordance in LDL apoB-100 and LDL cholesterol levels implies a change in the composition of the LDL particle. Total apo B is thus indicative of VLDL, IDL and LDL levels, while apo B-100 and LDL apo B are indicative specifically of LDL levels. While the effect of omega-3 fatty acids on lipoprotein-associated cholesterol and apolipoprotein assays are of interest, unlike cholesterol levels, apolipoprotein assays, which are antibody specific and are not standardized, are not as amenable to cross-study comparisons. Furthermore, there are no data to suggest that apolipoprotein levels are more predictive of CVD risk than lipoprotein cholesterol levels.

We found 52 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on total apo B levels, and 11 studies that reported data on either apo B-100 or LDL apo B (See Table 3.1). Of these, we analyzed the 25 randomized trials of apo B that had data on at least 20 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids. We also analyzed the 10 studies of apo B-100 or LDL apo B, all of which were randomized.

Overall Effect

Total apo B (Table 3.8) [48,49,53,66,67,71,85,86,88-90,93,95-101,103-106,108,109]**.** Across the 25 studies, we found little consistency in the effect of omega-3 fatty acids on apo B levels. About half the

studies found a small net increase and half a small net decrease in apo B levels. Only 2 studies found significant changes in individual study arms, but Deslypere et al. found a significant decrease and Mori et al. found a significant increase [71,85].

Table 3.8 Effects of omega-3 fatty acids on apolipoprotein B (mg/dL) in randomized trials (4 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source	g/d		N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils													
Wilt, 1989	38 [e]	Fish oil	ED	6.0	38 [e]	Safflower	112	+5	NS	B	4	Un	DysLip	III
Green, 1990	27 [e]	Fish oil	ED	5.2	27 [e]	Corn/Olive	122	-5	NS	B	4	Un	DysLip	II
Bonaa, 1992	71	Fish oil	ED	5.1	74	Corn oil	153	-1	NS	B	4	Un	DysLip	I
Balestrieri, 1996	14 [e]	Fish oil	ED	5.1	14 [e]	Olive oil	205	+1	NS	B	3	Un	DysLip	III
Jensen, 1989	18 [e]	Cod liver oil	ED	4.6	18 [e]	Olive oil	109	+6	NS	B	4	Un	IDDM	II
Sirtori, 1992	12 [e]	Fish oil	ED	4.5	12 [e]	No oil	167	0	NS	C	2	Un	DysLip	II
Schectman, 1988	13 [e]	Fish oil	ED	4.0	13 [e]	Safflower	99	+7	NS	B	2	Un	NIDDM	II
Grimsgaard, 1997	75	Purified EPA	E	3.8	77	Corn oil	101	-5	NS	A	5	Un	GEN	I
	72	Purified DHA	D	3.7			100	-3	NS					
Nordoy, 1998	21	Fish oil	ED	3.4	20	Corn oil	108	+1	NS	B	4	Un	DysLip	I
Deslypere, 1992	14	Fish oil	T	3.4	14	Olive oil	89	-8	<.05	B	2	Un	GEN	III
	15	Fish oil	T	2.2			85	-1	NS					
	15	Fish oil	T	1.1			91	-2	NS					
Chan, 2002	12	Fish oil	ED	3.4	12	Corn oil	128	-4	NS [f]	B	3	Un	DysLip	II
	11	Fish oil & Atorvastatin			12	Corn oil & Atorvastatin	134	-8						
Durrington, 2001	30	Fish oil	ED	3.2	29	Corn oil	96	+5	NS	A	4	Un	CVD DysLip	II
McGrath, 1996	23 [e]	Fish oil	ED	3.0	23 [e]	Olive oil	95	+1	NS	A	4	Un	DM II	II
Nikkila, 1991	32 [e]	Fish oil	ED	2.4	32 [e]	Corn oil	122	+3	NS	B	3	Un	CVD DysLip	II
Luo, 1998	10 [e]	Fish oil	ED	1.8	10 [e]	Sunflower	138	+10	NS	B	3	Un	DM II	II
Marckmann, 1997	23	Fish oil margarine	T	0.9	24	Sunflower margarine	113	+1	NS	B	3	Un	GEN	II
Nenseter, 2000	34	Fish powder	ED	0.2	36	Cellulose	133	+2	NS	B	3	Un	GEN	II
	Fish and Mediterranean Diets													
Hanninen, 1989	19	Fish (3.8/week)	ED	0.9	18	0.4 Fish/week	93	-9	nd	B	2	Un	GEN	III
	22	Fish (2.3/week)	ED	0.5			78	-2	nd					
	21	Fish (1.5/week)	ED	0.4			80	-5	nd					
	20	Fish (0.9/week)	ED	0.2			78	0	nd					
Agren, 1988	14	Fish (3.7/week)	ED	0.8	12	0.25 Fish/week	70	-2	NS	B	3	Un	GEN	III
	15	Fish & low SFA					63	-3	NS					
Agren, 1991	20	Fish (5/week)	ED	0.75	15	Regular	64	+2	NS	B	2	Un	GEN	III
	20	Fish (5/week) [g]			23	Regular [g]	67	+5	NS					
de Lorgeril, 1994	171 [h]	Mediterranean/ Canola margarine	A	0.8% Kcal	168 [i]	Regular	152	-1	NS	C	2	Un	CVD	II

Table 3.8 Effects of omega-3 fatty acids on apolipoprotein B (mg/dL) in randomized trials (continued)

Author, Year	Omega-3 Fatty Acid Arm [a] N	Source	g/d	Control N	Source	Results [b] Base	Net Δ	P	Quality [c] Summary	Jadad	Allocation Conceal	Applicability [d]	
	Combinations												
Mori, 1994	17	Fish oil & Fish diet [j]	ED 5.2	18	Olive/Palm/ Safflower 40% fat diet	143 [k]	+5 [L]	NS	B	2	Un	GEN	II
	16	Fish oil	ED 4.2				+9 [L]	<.05					
	17	Fish oil	ED 2.1				+12 [L]	<.05					
	17	Fish diet [j] & Placebo oil	ED 3.0				+6 [L]	NS					
	18	Fish diet [j] & Placebo oil	ED 3.0	17	Oil 30% fat diet		+1 [L]	NS					
Cobiac, 1991	13	Fish oil	ED 4.6	6	Olive, Palm, Safflower oil	99 [m]	+6	NS	B	2	Un	GEN	II
	12	Fatty Fish diet	ED 4.5			100 [m]	-1	NS					
Agren, 1996	14	Fish oil	ED 2.3	14	No oil	72	-3	NS	B	3	Un	GEN	III
	14	Algae DHA oil	D 1.7			71	-3	NS					
	13	Fatty Fish diet	ED 1.1			75	0	NS					
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED 1.7	30	Sunflower margarine	176 [n]	+1	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED 0.8			174 [o]	+3	NS					
	30	Rapeseed/Linseed margarine	A 4.5			178 [p]	+1	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Main effect.

g Recommended aerobic exercise for 30 minutes 3 times a week.

h Baseline data based on 289 subjects.

i Baseline data based on 295 subjects.

j Omega-3 fatty acid from fish diet is approximate, assuming that each of 4 different fish was consumed equally.

k Mean baseline value for all subjects combined.

L Estimated from graph.

m Units were not reported.

n Reported as 1.76 mmol/L.

o Reported as 1.74 mmol/L.

p Reported as 1.78 mmol/L.

Apo B-100 (Table 3.9, top) [50,52,62,107] and LDL apo B (Table 3.9, bottom) [93,94,108,111-113]. The 4 studies of apo B-100 found a range of effects with omega-3 fatty acid consumption. Two found a decreases in level of less than 5%; the other 2 studies found net increases of 2% and 15%. In contrast, large, significant net increases in LDL apo B were found in 4 of 6 studies (20 to 45 mg/dL).

Table 3.9 Effects of omega-3 fatty acids on apolipoprotein B-100 and LDL apolipoprotein B (mg/dL) in randomized trials (1 month to 14 months)

Author, Year	Omega-3 Fatty Acid Arm [a]			Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source	g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
Apo B-100													
	DHA/EPA Oils												
Eritsland, 1995b	178	Fish oil	ED 3.3	174	No oil	182	+3	NS	B	2	Ad	CVD	II
Brox, 2001 [e]	38	Cod liver oil	ED 3.3	37	No oil	200	-10 [f]	NS	C	1	Un	DysLip	I
	37	Seal oil	ED 2.6			200	-10 [f]	NS					
DeLany, 1990 [g]	5	Fish oil	ED 2	5	No oil	62	+9	NS	C	1	Un	GEN	III
	Combinations												
Silva, 1996	20	Fish oil	ED 3.6	--	--	188	-3 [h]	nd [i]	B	3	Un	DysLip	II
	15	Soya oil	A 0.8 [j]			222	-5 [h]	nd [i]					
LDL Apo B													
	DHA/EPA Oils												
Deck, 1989	8 [k]	Fish oil	ED 4.6	8 [k]	Corn oil	96	+25	<.05	B	5	Un	DysLip	II
Sirtori, 1992	12 [k]	Fish oil	ED 4.5	12 [k]	No oil	157	+2	NS	C	2	Un	DysLip	II
Schectman, 1989 [L]	15 [k]	Fish oil	ED 4.0	15 [k]	Safflower	92	+20	nd [m]	C	2	Un	DysLip	II
Schectman, 1988 [L]	13 [k]	Fish oil	ED 4.0	13 [k]	Safflower	82	+9	<.05	B	2	Un	NIDDM	II
Radack, 1990	10	Fish oil	ED 2.2	8	Olive oil	100	+45	<.05	B	5	Un	DysLip	II
	7	Fish oil	ED 1.1			95	+29	<.05					
Radack, 1991	33 [k]	Fish oil	ED 2.0	33 [k]	Safflower oil	249	-6	NS	B	5	Ad	CVD	II

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Data missing from article provided by study author.

f Only 2 significant digits reported. 10 mg/dL is smallest unit of change possible.

g Possibly not randomized ("[S]ubjects were divided into… treatment groups so that initial mean cholesterol concentration of each group was similar.").

h Pre-post difference (not compared to control).

i NS between treatments.

j No data on ALA amount. Assume 7 g ALA per 100 g oil. 12 g oil.

k Cross-over study.

L Unclear if 2 studies by Schectman et al. [93,94] are independent of each other. Possible overlap of up to 6 subjects with NIDDM and hypertriglyceridemia.

m Increase in LDL apo B within fish oil arm was significant compared to baseline (*P*<.05).

Sub-populations

Total apo B. The heterogeneity of effects seen across all studies is apparent among the 10 studies of healthy populations (8 of which were in men[66,67,71,85,89,95,97,100] and one of which was in women[96]), the 10 studies of dyslipidemic populations (subjects in 2 of which also had CVD), and

the 3 studies of CVD populations (including those studies with subjects with dyslipidemia). The 4 studies of diabetics, one of which included insulin-dependent diabetics, all found small, non-significant, net increases in total apo B.

Apo B-100 and LDL apo B. The 2 apo B-100 studies of dyslipidemic patients reported small net decreases in apo B-100, while the study of patients undergoing coronary bypass surgery showed a small net increase and the study of healthy, male college students found a larger net increase in apo B-100. The 5 LDL apo B studies of dyslipidemic or diabetic subjects found generally large increases in LDL apo B, while the single study of hypertensive subjects showed a small net decrease.

Covariates

Total apo B. Nenseter et al. performed a subanalysis based on age of the effect of a low-omega-3 fatty acid fish powder [90]. Subjects between ages 30 and 52 years had a significantly greater rise in apo B level compared to subjects 53 to 70 years old; furthermore age negatively correlated with the rise in apo B ($r = –0.40$, $P < .04$). The authors also imply that the effect was not correlated with sex. Mori et al. performed a regression adjusting for change in weight and found a highly significant "group effect" increase in apo B with omega-3 fatty acids ($P < .01$) [71]. Agren et al. (1988), in a study of male university students, found no difference in effect between 2 fish diets that differed in the amount of low saturated fats [95]. Three studies compared fish oil to placebo oil supplements in dyslipidemic patients who were all taking either atorvastatin or simvastatin [98,99,106]. The effects of fish oil supplements on apo B were small in all. They were not uniform in direction.

Apo B-100 and LDL apo B. Silva et al. reported that any effect of fish oil and soya oil supplements on apo B was not correlated with sex, BMI, hypertension, or diabetes in hyperlipidemic patients [107]. Schectman et al. found that changes in LDL apo B did not correlate with baseline differences in diet or with individual changes in diet or body weight [93]. Other studies did not correlate findings with possible covariates. The small number of studies limits hypothesis generating of possible effect mediators across studies.

Dose and Source Effect

Total apo B. Among studies of fish oil supplements, Deslypere et al. found a significant net decrease in apo B in subjects on the highest dose of omega-3 fatty acids but smaller non-significant net decreases with smaller doses [85]. Among the individual study arms, apo B levels fell in the arm with a higher dose of fish oil but rose in the lower dose arms (and the olive oil arm). No dose effect was seen across fish oil supplement studies. Among studies of dietary fish, Hanninen et al. reported a trend in effect related to different frequencies of fish meals [67]. Subjects most frequently consuming fish had the largest, significant reduction in apo B (compared to baseline). Subjects with intermediate frequencies of fish consumptions (average of 1.5 and 2.3 meals per week) had smaller reductions in apo B with *P* values (compared to baseline) of less than .10. Subjects on only about 1 fish meal per week had a non-significant increase in apo B.

Five studies compared different sources of omega-3 fatty acids. Grimsgaard et al. found no difference in effect between purified EPA and purified DHA [66]. Mori et al. compared a variety of doses of fish oil supplements and combinations of dietary fish and supplemental fish oil, along with higher and lower percentage fat diets [71]. Overall, significant net increases in apo B were

seen in the subjects who consumed fish oil supplements and were on non-fish diets, but smaller, non-significant increases were seen in the subjects who were on fish diets, regardless of fish oil supplementation or percent fat in the diet. Cobiac et al. similarly found that subjects on fish oil supplement had a net increase in apo B while those on dietary fish had almost no change [100]. While neither change was statistically significant, there was a trend toward a difference between the 2 treatments ($P = .10$). In contrast, Agren et al. (1996) reported small non-significant net reductions in apo B with fish oil and algae DHA oil supplementation and no effect with fatty fish diet; although they do not comment on potential differences between groups [97]. Finally, Finnegan et al. reported no effects on apo B and no differences among people consuming different omega-3 fatty acids from margarine and/or supplements [53].

Apo B-100 and LDL apo B. Neither Brox et al. nor Silva et al. found a difference in effect of different omega-3 fatty acids on apo B-100 levels [62,107]. Radack et al. (1990) found a similar large increase in LDL apo B in 2 groups of hypertriglyceridemic patients consuming different doses of fish oil supplements [113]. While the increase was greater in the group consuming a higher dose of fish oil, no analysis was done to compare the effect in the 2 arms.

Exposure Duration

Total apo B. While the authors do not describe an effect of duration of fish consumption, the data at 5 and 12 weeks in Hanninen et al. may suggest that any effects of dietary fish on apo B do not occur until after 5 weeks [67]. At 5 weeks there were essentially no changes in apo B in any of the study arms, compared to significant and near significant reductions in arms with more frequent fish consumption. In de Lorgeril et al. a Mediterranean and ALA margarine diet had no effect on apo B at 8 weeks, 1 year, and 2 years.

Apo B-100 and LDL apo B. In their study of apo B-100, DeLany et al. found that while there was no difference in effect between 5 g fish oil supplementation and no oil at 5 weeks, there was a significant increase over time at 0, 2, and 5 weeks in subjects on fish oil supplements [50]. However, this analysis included 5 subjects who took 20 g fish oil supplements. There was also a small increase in apo B-100 levels in subjects not consuming oil supplements. Radack et al. (1990) reported no change in LDL apo B level between measurements at 8, 12, and 20 weeks [113].

Sustainment of Effect

Total apo B. Three studies followed subjects after stopping the intervention. Both Jensen et al. and Agren et al. (1988) found no change in apo B levels 8 weeks and 5 months, respectively, after stopping fish oil supplements [95,103]. Deslypere et al. found that 6 months after stopping supplements apo B levels rose to similar levels in all groups except those who had been on the lowest dose fish oil, although no analysis was performed on follow-up data [85].

Apo B-100 and LDL apo B. Although Radack et al. (1990) measured LDL apo B levels 4 weeks after stopping treatment [113], no study reported whether changes in apo B-100 or LDL apo B levels were sustained.

Blood Pressure

(Tables 3.10 and 3.11)

Hypertension is a well-known risk factor for atherosclerosis and cardiovascular disease. Recently the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) noted that the relationship between blood pressure and risk of cardiovascular events is continuous, consistent and independent of other factors.[25] The benefits to lowering blood pressure are evident even in people with "pre-hypertension" (blood pressure of 120-139/80-89).

We found 103 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on blood pressure (See Table 3.1). In addition, we found a recent systematic review with a meta-regression of the blood pressure response to fish oil supplementation [114]. This thorough review touched on most of the major questions addressed by the current report, therefore this section relies primarily on the findings of Geleijnse et al. However, they explicitly excluded studies of diabetic patients. Therefore, we analyzed the 6 randomized trials with data on blood pressure in diabetic patients that had a minimum of 15 patients in parallel trials and 10 patients in crossover trials who consumed omega-3 fatty acids.

Meta-Regression [114]

Geleijnse et al. collected trials of fish oil supplementation and blood pressure through March 2001. Eligibility criteria were: (1) randomized design, (2) adult study population, and (3) publication after 1966. Trials were excluded if they included sick or hospitalized patients, including kidney disease and diabetic patients, or if the intervention was shorter than 2 weeks duration. A total of 36 trials with 50 omega-3 fatty acid study arms were analyzed. Of note, 6 of these studies did not meet our eligibility due to high omega-3 fatty acid dose (3), short washout period in crossover trial (2), or short study duration (1).

The range of trial duration was 3 to 52 weeks and doses of omega-3 fatty acids were less than 1.0 g/day in 1 trial, 1.0 to 1.9 g/day in 5 trials, 2.0 to 2.9 g/day in 4 trials, and 3.0 to 15.0 g/day in 26 trials.

The mean net reduction (controlling for placebo arms) in systolic and diastolic blood pressure, weighted for study size, was –2.1 mm Hg (95% confidence interval –3.2, –1.0) and –1.6 mm Hg (–2.2, –1.0), respectively. The mean reductions in systolic and diastolic blood pressures were somewhat smaller in the 22 double blinded studies. Data on univariate and multivariate weighted meta-regression analyses performed on study subgroups based on mean age, sex, mean baseline blood pressure, and mean body mass index are reported. Briefly, systolic and diastolic blood pressure reductions were significantly larger in older (mean age ≥ 45 years) than younger populations, and in hypertensive (blood pressure ≥ 140/90 mm Hg) compared to normotensive populations. A lack of studies in women precluded adequate analysis based on sex. Body mass index was not associated with blood pressure response to fish oil supplementation. In addition, trial duration and fish oil dose were not associated with effect.

Overall Effect in Diabetes Studies [115-120]

Across the 6 studies of diabetic patients, there were generally small, non-significant effects of fish oil supplements on systolic (Table 3.10) and diastolic (Table 3.11) blood pressure. Overall, these study results were similar to the findings of the meta-regression among non-diabetic populations in their small, but generally inconsistent net effects. One study reported a small significant reduction in mean diastolic pressure (–2 mm Hg) and 2 reported significant reductions in mean systolic pressure (–3 and –6 mm Hg).

Covariates

Haines et al., who found non-significant small net increases in blood pressure, reported that neither sex nor Hgb A_{1c} levels were related to the effect of fish oil supplements on blood pressure [115]. No study analyzed data based on age. Across studies there was no clear difference

Table 3.10 Effects of omega-3 fatty acids on systolic blood pressure (mm Hg) in randomized trials of diabetic subjects (6 weeks to 1 year)

Author, Year	Omega-3 Fatty Acid Arm [a]			Control		Results [b]			Quality [c]			Applicability [d]
	N	Source	g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal	
		DHA/EPA Oils										
Haines, 1986	19	Fish oil	ED 4.6	22	Olive oil	135	+1	NS	B	2	Ad	IDDM II
Rossing, 1996 [e]	14	Cod liver oil	ED 4.6	15	Olive oil	141	-3	NS	A	3	Un	IDDM II
Woodman, 2002 [e]	17	Purified EPA	E 3.8	16	Olive oil	137	0	NS	B	3	Un	DM II II
	17	Purified DHA	D 3.7			139	+7	NS				
Lungershausen, 1997	16	Fish oil	ED 3.4	16	Corn oil	139	-6	.04	B	4	Un	DM I&II II
Hendra, 1990	37	Fish oil	ED 3.0	37	Olive oil	145	+1	NS	B	4	Un	DM II I
Jain, 2002	25	Fish oil	ED 0.6	15	"Placebo"	127	-3	.0003	C	2	Un	DM II II

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Mean 24 hour ambulatory blood pressure.

Table 3.11 Effects of omega-3 fatty acids on diastolic blood pressure (mm Hg) in randomized trials of diabetic subjects (6 weeks to 1 year)

Author, Year	Omega-3 Fatty Acid Arm [a]			Control		Results [b]			Quality [c]			Applicability [d]
	N	Source	g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal	
		DHA/EPA Oils										
Haines, 1986	19	Fish oil	ED 4.6	22	Olive oil	81	+2	NS	B	2	Ad	IDDM II

Rossing, 1996 [e]	14	Cod liver oil	ED	4.6	15	Olive oil	82	-1	NS	A	3	Un	IDDM II
Woodman, 2002 [e]	17	Purified EPA	E	3.8	16	Olive oil	76	0	NS	B	3	Un	DM II II
	17	Purified DHA	D	3.7			72	+1	NS				
Lungershausen, 1997	16	Fish oil	ED	3.4	16	Corn oil	81	+1	NS	B	4	Un	DM I&II II
Hendra, 1990	37	Fish oil	ED	3.0	37	Olive oil	85	-3	NS	B	4	Un	DM II I
Jain, 2002	25	Fish oil	ED	0.6	15	"Placebo"	82	-2	.0003	C	2	Un	DM II II

a-e See Table 3.10

among populations with type I or type II diabetes, and there were insufficient data to comment on age, sex, menopausal status, race, weight or other variables.

Dose and Source Effect

No study compared different doses of omega-3 fatty acids. Woodman et al. compared purified EPA and purified DHA and found a net fall in mean 24 hour ambulatory systolic blood pressure in subjects on EPA and a net increase in diastolic pressure; however, there was no statistical difference between the 2 treatments [120]. Across studies, there is no apparent difference in effect on systolic blood pressure based on fish oil supplement dose. However, the largest, and significant, reductions in diastolic pressure were found in the 2 studies with the smallest fish oil supplementation doses.

Exposure Duration

In 3 studies no differences in effect are noted based on duration of intervention or exposure at 3 and 6 weeks [115], 6 and 12 weeks [118], or 6 and 12 months [119].

Sustainment of Effect

No study reported blood pressures after subjects stopped treatment.

Hemoglobin A_{1c}

(Table 3.12)

Chronically elevated serum glucose levels, which occur in diabetes, result in elevated levels of glucose binding to hemoglobin. This bound product, hemoglobin A_{1c} (Hgb A_{1c}), or glycohemoglobin, is used to measure long-term control of diabetes.

We found 32 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on Hgb A_{1c} levels (See Table 3.1). Of these, we analyzed the 18 randomized trials with data on at least 10 subjects in either parallel trials or crossover trials who consumed omega-3 fatty acids.

Overall Effect [77,85,88,93,102,103,106,115,117-126]

Across the 18 studies, omega-3 fatty acids had a very small, if any, effect on Hgb A_{1c} levels compared to control. The range of net effects across the studies was –0.4% to +1.0%. Only 1

study reported a statistically significant reduction in Hgb A_{1c}; however, this study by Jain et al. found one of the smaller net changes of all studies [117].

Sub-populations

As expected, the large majority of studies evaluating Hgb A_{1c} included diabetic patients. Fourteen studies analyzed diabetic populations, 3 of which were also dyslipidemic. An additional 2 studies analyzed dyslipidemic patients; 1 included patients with untreated hypertension; and 1 evaluated healthy monks.

While none of the 4 studies of dyslipidemic patients had net reductions in Hgb A_{1c} levels, given the small differences in almost all studies, there are no clear difference in effect in the different populations, including diabetic patients.

Covariates

Schectman et al. found that the effect of fish oil supplements on Hgb A_{1c} did not correlate with baseline differences in diet or with individual changes in diet or body weight [93]. Toft et al. and Westerveld et al. reported no change in effect of fish oil supplements on Hgb A_{1c} after adjustment for body weight [125,126]. Likewise, Haines et al reported no relationship between effect on Hgb A_{1c} and sex [115]. Three studies were notable for including only men [85,88], or because all subjects were taking simvastatin [106]. The effect found in these studies was not clearly different than that found in studies.

Table 3.12 Effects of omega-3 fatty acids on hemoglobin A_{1c} (%) in randomized trials (4 weeks to 1 year)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
		DHA/EPA Oils												
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	11.1	+0.2	NS	B	2	Ad	IDDM	II
Jensen, 1989	18 [e]	Cod liver oil	ED	4.6	18 [e]	Olive oil	9.5	+0.1	NS	B	4	Un	IDDM	II
Rossing, 1996	14	Cod liver oil	ED	4.6	15	Olive oil	8.8	-0.3	NS	A	3	Un	IDDM	II
Schectman, 1988	11 [e]	Fish oil	ED	4.0	11 [e]	Safflower	7.9	+0.1	NS	B	2	Un	NIDDM	II
Woodman, 2002	17	Purified EPA	E	3.8	16	Olive oil	7.1	+0.2	NS	B	3	Un	DM II	II
	18	Purified DHA	D	3.7			7.5	0	NS					
Toft, 1995	38	Fish oil	ED	3.4	40	Corn oil	5.7	+0.1	NS	A	5	Ad	CVD	II
Harris, 1997	22	Fish oil	ED	3.4	18	Corn oil	5.3	0	NS	B	3	Un	DysLip	II
Nordoy, 1998	21	Fish oil	ED	3.4	20	Corn oil	5.8	+0.2	NS	B	4	Un	DysLip	I
Lungershausen, 1997	16	Fish oil	ED	3.4	16	Corn oil	8.5	+0.2	NS	B	4	Un	DM	II
Deslypere, 1992	14	Fish oil	T	3.4	14	Olive oil	4.8	+0.2	NS	B	2	Un	GEN	III
	15	Fish oil	T	2.2			4.9	-0.1	NS					
	15	Fish oil	T	1.1			5.0	-0.1	NS					
Bonnema, 1995	14	Fish oil	ED	3.3	14	Olive oil	8.0	+1.0	NS	A	3	Ad	IDDM	II
McVeigh, 1993	23 [e]	Fish oil	ED	3.0	23 [e]	Olive oil	9.6	+0.2	NS	A	4	Un	DM II	II
Pedersen, 2003	23	Fish oil	ED	2.6	21	Corn oil	8.2	0.0	NS	A	3	Un	DysLip DM II	II
Luo, 1998	10 [e]	Fish oil	ED	1.8	10 [e]	Sunflower	8.8	-0.4	NS	B	3	Un	DM II	II
Westerveld, 1993	8	Purified EPA	E	1.8	8	Olive oil	8.2 [f]	-0.4 [g]	NS	C	3	Un	NIDDM	II

	8	Purified EPA	E	0.9			7.6	+0.4	NS					
Sirtori, 1998	203	Fish oil	ED	1.7 [h]	211	Olive oil	7.3	+0.6	NS	B	4	Ad	DysLip NIDDM	I
Jain, 2002	25	Fish oil	ED	0.6	15	"Placebo"	8.0	-0.1	.009	C	2	Un	DM II	II
	Fish and Mediterranean Diets													
Dunstan, 1997	26	Fatty Fish	T	3.6	23	No fish	8.2	+0.3	.06	B	2	Un	DysLip NIDDM	I

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f According to text. In table, baseline Hgb A_{1c}=8.6%

g Per data in text. Per data in table, net change = -0.8%

h 2.6 g/day for first 2 months, then 1.7 g/day for 4 months.

Dose and Source Effect

Two studies compared different doses of fish oil supplements. Deslypere et al., in a 1 year study of healthy Belgian monks, reported no difference in the effect of 3 doses of fish oil or olive oil [85]. Westerveld et al. also reported no difference in the effect of 2 different doses of fish oil, purified EPA, or olive oil in non-insulin dependent diabetics [126]. Across studies, there was no apparent dose effect of fish oil supplements. The only study of dietary fish found a lack of effect similar to the fish oil supplement studies. Woodman et al. compared purified EPA to DHA in type II diabetics [120]. No difference was noted between the 2 treatments.

Exposure Duration

Two studies reported treatment effect at multiple time points. In Haines et al. there was a transient drop in Hgb A_{1c} by 0.6% (0.5% net) at 3 weeks which reverted to baseline at 6 weeks [115]. The change was not statistically significant. Rossing et al. found no difference in effect between 6 and 12 months [119]. Across studies there was no apparent effect of treatment duration.

Sustainment of Effect

Jensen et al., in a crossover study, found that Hgb A_{1c} remained unchanged 8 weeks after stopping oil supplementation.

Fasting Blood Sugar (Table 3.13)

Elevated fasting blood sugar (FBS) is a risk factor or indicator of diabetes. People with diabetes or with altered glucose tolerance have a highly elevated risk of CVD. As discussed in the introduction, the effect of omega-3 fatty acids on diabetic control is unclear.

We found 57 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on FBS levels (See Table 3.1). Of these, we analyzed the 17 randomized trials with data on at least 25 subjects in parallel trials and 15 subjects in crossover trials who consumed omega-3 fatty acids.

Overall Effect [52,53,68,76,77,103,116,117,120,123,125,127-132]

The effect of omega-3 fatty acids on FBS was inconsistent across the 17 studies. Four studies found large and/or near-significant net increases in FBS compared to control; 3 found large and/or significant net decreases in FBS and the rest found small non-significant changes. Across the studies, the net effect ranged between a decrease of 29 mg/dL over 8 weeks and an increase of 25 mg/dL over 6 weeks. Interpretation of the overall data is further complicated by inconsistent patterns of effect within individual study arms. In omega-3 fatty acid arms and in control arms, FBS increased from baseline in half the arms and either decreased or remained unchanged in the other half.

Sub-populations

Seven studies evaluated diabetic populations, 2 of which also had dyslipidemia; an additional 5 studies evaluated patients with dyslipidemia. Three studies included subjects who had CVD or were at increased risk for CVD (due to either diabetes or dyslipidemia). Two studies were of healthy populations.

The findings within the diabetic populations were inconsistent. The largest net decrease in FBS was found by Jensen et al. in the only study of insulin-dependent diabetics [103], while the largest net increase in FBS with omega-3 fatty acids was seen in Woodman et al. in one of the studies of type II diabetics [120]. Furthermore in each of the 3 groups of subjects on fish oil supplements in these 2 studies, FBS rose by approximately 10 or 20 mg/dL; the large difference

Table 3.13 Effects of omega-3 fatty acids on fasting blood sugar (mg/dL) in randomized trials (4 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
		DHA/EPA Oils												
Jensen, 1989	18 [e]	Cod liver oil	ED	4.6	18 [e]	Olive oil	178	-29	NS	B	4	Un	IDDM	II
Mori, 2000	19	Purified EPA	E	3.8	20	Olive oil	91	+2	.06	B	4	Un	DysLip	II
	17	Purified DHA	D	3.7			92	-3	NS					
Woodman, 2002	17	Purified EPA	E	3.8	16	Olive oil	134	+25	.002	B	3	Un	DM II	II
	18	Purified DHA	D	3.7			149	+18	.002					
Mackness, 1994	41	Fish oil	ED	3.4	38	Corn oil	91	+2	NS	A	3	Un	DysLip	I
Toft, 1995	38	Fish oil	ED	3.4	40	Corn oil	99	+2	.06	A	5	Ad	CVD	II
Grundt, 1995	28	Fish oil	ED	3.4	28	Corn oil	85	0	NS	B	2	Un	DysLip	II
Eritsland, 1995b	255	Fish oil	ED	3.3	245	No oil	86	+1	NS	B	2	Ad	CVD	II

Leigh-Firbank, 2002	55 [e]	Fish oil	ED	3.0	55 [e]	Olive oil	99	+3	NS	B	3	Un	DysLip	I
Hendra, 1990	37	Fish oil	ED	3.0	37	Olive oil	202	+14	NS	B	4	Un	DM II	I
McVeigh, 1993	23 [e]	Fish oil	ED	3.0	23 [e]	Olive oil	184	+7	NS	A	4	Un	DM II	II
Sirtori, 1998	203	Fish oil	ED	1.7 [f]	211	Olive oil	149	+2	NS	B	4	Ad	DysLip NIDDM	I
Jain, 2002	25	Fish oil	ED	0.6	15	"Placebo"	139	-10	.004	C	2	Un	DM II	II
		Fish and Mediterranean Diets												
Mori, 1999	17	Fatty Fish [g]	T	3.7	16	No fish [g]	95	+4 [h]	NS	B	2	Un	CVD	II
	14	Fatty Fish [i]			16	No fish [i]	94	-1 [h]	NS					
Dunstan, 1998	14	Fatty Fish [j]	T	3.6	11	No fish [j]	180	-4	NS	B	2	Un	DysLip NIDDM	I
	12	Fatty Fish [k]			12	No fish [k]	160	+5	NS					
Singh, 2002	499	Indo-Mediterranean	T	1.8	501	NCEP I [L]	108	-5	<.0001	C	2	Un	CVD risk [m]	III
		Combinations												
Freese, 1997a	16	Fish oil	ED	5.2	--	--	85	+5 [n]	nd [o]	C	3	Un	GEN	II
	22	Linseed oil	A	5.9			86	-1 [p]	nd [o]					
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED	1.7	30	Sunflower margarine	97	-3	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED	0.8			97	-3	NS					
	30	Rapeseed/Linseed margarine	A	4.5			99	-5	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f 2.6 g/day for first 2 months, then 1.7 g/day for 4 months.

g Weight-maintaining diet.

h Estimate from graph.

i Weight-loss diet.

j Moderate exercise.

k Light exercise.

L National Cholesterol Education Program step I prudent diet.

m One or more of: hypercholesterolemia, hypertension, diabetes, angina pectoris or myocardial infarction.

n Pre-post difference (not compared to control); *P*<.05 compared to baseline.

o NS between treatments.

p Pre-post difference (not compared to control); not significantly different than baseline.

in net effect is due to the difference in effect of the olive oil control (+49 mg/dL and –7 mg/dL, respectively). In the remaining studies of diabetics, the change in FBS was in the same direction in omega-3 fatty acid arms and control arms; in 6 omega-3 study arms FBS rose from 10 mg/dL to 23 mg/dL; in 4 arms FBS fell from –2 mg/dL to –16 mg/dL. In studies of diabetics, factors other than omega-3 fatty acid consumption – such as those related to population characteristics, other treatments, or study design – appear to have had a greater effect on change in FBS than the omega-3 fatty acid treatment itself.

Among the 7 studies of dyslipidemic populations, 2 of which were also diabetic, all found a small non-significant net effect of omega-3 fatty acids on FBS that ranged from –4 to +5 mg/dL. Only Dunstan et al. found large changes in individual omega-3 fatty acid arms, which were related primarily to exercise level and were similar to the changes in the no fish control arms [127].

The 4 studies of CVD patients or people with an elevated risk of CVD all found small absolute and net changes in FBS with omega-3 fatty acid consumption. Only Singh et al. found a significant net change and had a relatively large absolute change (-8 mg/dL) in FBS, although notably about 20% of the subjects were diabetic, two-thirds were vegetarian, and those subjects on the Indo-Mediterranean diet on average lost 3 kg more weight than controls [76]. In addition, this study reported uniform, highly significant effects on all serum markers despite widely ranging effects. A number of statistical calculation errors were also found.

The single study of a healthy population, by Freese et al., found small differences in FBS with 2 different omega-3 fatty acid treatments (in opposite directions) [128].

Covariates

Schectman et al. found that changes in FBS did not correlate with baseline differences in diet or with individual changes in diet or body weight [93]. Two studies of diabetics reported data on associations between effect and other variables. Hendra et al. reported that the change in FBS was unrelated to change in weight [116]. Woodman et al. reported that the significant effect compared to olive oil was unchanged after adjusting for age, sex, and BMI [120]. In Mori, et al. (1999), a study of obese hypertensive subjects, the direction of the absolute and net changes in FBS appear related to whether subjects were on a weight-reduction diet or not (those on a weight maintaining diet had increases in FBS, while those on a weight-reduction diet had reductions in FBS); however, they reported no interaction between fish diet and weight loss on FBS [131]. No patterns across studies are evident based on reported data on covariates.

Dose and Source Effect

No study directly compared doses of the same source of omega-3 fatty acids. In comparisons of EPA and DHA, Woodman et al. reported no difference in effect on FBS [120]; however, Mori et al. (2000) reported a trend toward increasing FBS with EPA, but no change with DHA [132]. Freese et al. reported a significant increase from baseline in FBS with fish oil supplementation compared to no change with linseed oil; however the difference between the 2 treatments was reported to be non-significant [128]. In a comparison of multiple sources of omega-3 fatty acids, Finnegan et al. found no significant differences in effect between various doses of either fish oils or plant oils [53]. Across studies, there was no discernable difference in effect based on either fish oil dose or omega-3 fatty acid source among diabetic or dyslipidemic populations.

Exposure Duration

Two studies measured FBS levels at multiple time points. Hendra et al. found that FBS rose with fish oil supplements at both 3 and 6 weeks, although the net difference with control was significant only at 3 weeks [116]. In a longer study that measured FBS at 2, 4, and 6 months, Finnegan et al. found no treatment effect at any time period [53]. The heterogeneity does not appear to be related to study duration.

Sustainment of Effect

Jensen et al., in a crossover study which found that FBS rose by large amounts in both the high-dose cod liver oil and olive oil supplement arms, found that FBS fell back near baseline levels 8 weeks after stopping oil supplementation, although none of the levels were significantly different from each other [103]. Freese et al., who compared fish oil to linseed oil supplements, reported that FBS, which had risen in the fish oil arm, returned to baseline during a 12 week follow-up period [128].

Fasting Insulin

(Table 3.14)

In people with normal glucose levels (euglycemia), elevated fasting insulin levels are suggestive of insulin resistance, a precursor to type II diabetes and an independent risk factor for CVD. The value of insulin levels in those with insulin resistance, including insulin resistance related to obesity, and diabetes ("hyperglycemia"), is questionable. The effect of omega-3 fatty acids on insulin resistance and fasting insulin levels is also unclear.

We found 21 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on fasting insulin levels (See Table 3.1). Of these, we analyzed the 15 randomized trials. All but 3 of the trials were also analyzed for data on FBS or Hgb A_{1c}.

Overall Effect [52,53,68,77,88,89,106,120,122,125,129,131-134]

Baseline levels of fasting insulin varied broadly across studies. In general, studies of non-insulin-dependent diabetics and obese subjects (under "Studies of "Hyperglycemic" Subjects") had higher mean insulin levels than dyslipidemic, hypertensive, or healthy patients (under Studies of "Euglycemic" Subjects). However, within each population grouping the range of insulin levels remained broad. Mean insulin levels varied within studies also. In 6 studies, baseline insulin levels differed between omega-3 fatty acid arms and control arms by 20% to 60%. Among these, Toft et al. reported a significant difference at baseline and Chan et al. reported no significant difference; the remaining studies did not comment [125,133]. In an attempt to standardize across studies, given the large variation in insulin levels, we calculated net differences in terms of percent change from baseline instead of absolute changes.

Table 3.14 Effects of omega-3 fatty acids on fasting insulin (pmol/L) in randomized trials (4 weeks to 9 months)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base [e]	Net % Δ	*P*	Summary	Jadad	Allocation Conceal		
Studies of "Euglycemic" Subjects														
		DHA/EPA Oils												
Mori, 2000	19	Purified EPA	E	3.8	20	Olive oil	9	+28%	.04	B	4	Un	DysLip	II
	17	Purified DHA	D	3.7			10	+29%	.001					
Toft, 1995	38	Fish oil	ED	3.4	40	Corn oil	52 [f]	-1%	NS	A	5	Ad	CVD	II
Grundt, 1995	28	Fish oil	ED	3.4	28	Corn oil	66	-15%	NS	B	2	Un	DysLip	II
Nordoy, 1998	21	Fish oil	ED	3.4	20	Corn oil	12 [g]	-28%	NS	B	4	Un	DysLip	I
Eritsland, 1995b	255	Fish oil	ED	3.3	245	No oil	125	-1%	NS	B	2	Ad	CVD	II
Leigh-Firbank, 2002	55 [h]	Fish oil	ED	3.0	55 [h]	Olive oil	72	-1%	NS	B	3	Un	DysLip	I
Marckmann, 1997	23	Fish oil margarine	T	0.9	24	Sunflower margarine	64 [i]	-8%	NS	B	3	Un	GEN	II
		Fish and Mediterranean Diets												
Mori, 1999	17	Fatty fish [j]	T	3.7	16	No fish [j]	12	+14%	NS	B	2	Un	CVD [k]	II
	14	Fatty fish [L]			16	No fish [L]	13	-18%	NS					
		Combinations												
Finnegan, 2003	31	Fish oil margarine/ Fish oil	ED	1.7	30	Sunflower margarine	42	0%	NS	A	4	Un	DysLip	I
	30	Fish oil margarine	ED	0.8			57 [m]	-16%	NS					
	30	Rapeseed/Linseed margarine	A	4.5			49 [m]	-19%	NS					
Studies of "Hyperglycemic" Subjects														
		DHA/EPA Oils												
Woodman, 2002	17	Purified EPA	E	3.8	16	Olive oil	98	+4%	NS	B	3	Un	DM II	II
	18	Purified DHA	D	3.7			115	+3%	NS					
Chan, 2003	12	Fish oil	ED	3.1	12	Corn oil	285 [n]	+12%	NS	A	4	Un	GEN [o]	III
Rivellese, 1996	8	Fish oil	ED	2.6 [p]	8	Olive oil	75 [q]	+29%	NS	A	3	Un	DysLip NIDDM	II
Luo, 1998	10 [h]	Fish oil	ED	1.8	10 [h]	Sunflower	84	+15%	NS	B	3	Un	DM II	II
Sirtori, 1998	203	Fish oil	ED	1.7 [r]	211	Olive oil	116	-11%	NS	B	4	Ad	DysLip NIDDM	I
		Fish and Mediterranean Diets												
Dunstan, 1997	14	Fatty fish [s]	T	3.6	11	No fish [s]	78	-25% [t]	.08	B	2	Un	DysLip NIDDM	I
	12	Fatty fish [u]			12	No fish [u]	78	-28% [t]	.05					

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net % Δ = net percent difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Studies with a greater than 20% difference between treatment and control are noted.
f Mean insulin in control arm = 64 pmol/L. Reported to be significantly different than treatment arm.
g Mean insulin in control arm = 9 pmol/L. No data on whether significantly different than treatment arm.
h Cross-over study.
i Mean insulin in control arm = 53 pmol/L. No data on whether significantly different than treatment arm.
j Weight-maintaining diet.
k Overweight.
L Weight-loss diet.
m Mean insulin in control arm = 37 pmol/L. No data on whether significantly different than treatment arm.
n Mean insulin in control arm = 215 pmol/L. Reported as not significantly different from treatment arm.
o Obese men.
p 2.6 g/day for first 2 months, then 1.7 g/day for 1 month.
q Mean insulin in control arm = 121 pmol/L. No data on whether significantly different than treatment arm.
r 2.6 g/day for first 2 months, then 1.7 g/day for 4 months.
s Moderate exercise.
t Percent decrease based on baseline level in fish diet arm, derived from regression analysis.
u Light exercise.

Across the 15 studies there were a wide range of apparent treatment effects ranging from net changes of –28% to +29% (or –22 pmol/L in Dunstan et al. [122] to +34 pmol/L in Chan et al. [133]). Approximately one-third of the omega-3 fatty acid study arms had net percent changes of either greater than +10%, between –10% and +10%, or less than –10%.

Sub-populations

Nine of the studies reported data on essentially euglycemic populations. The remaining 6 studies evaluated diabetic or obese populations in which the fasting insulin level may be of less value. While the studies with hyperglycemic subjects all had elevated mean fasting insulin levels, there was a wide range of mean insulin levels in the studies of euglycemic subjects.

Among the studies of euglycemic subjects, the heterogeneity of effect was similar to the heterogeneity seen across all studies. The heterogeneity was particularly apparent among the studies of dyslipidemic patients.

Covariates

Among the studies of euglycemic subjects, Mori et al. (1999) reported no interaction between dietary fish intake and weight loss on insulin levels [131]. However, a weight loss diet resulted in a reduction of insulin levels, regardless of fish consumption. In addition, there was a net decrease in insulin levels in subjects who were on a weight loss diet with fish compared to a net increase in insulin in subjects who were on a weight-maintaining diet. Otherwise, studies did not attempt to correlate the effect on insulin of covariates. The 3 studies that either included only euglycemic men [89,132] or excluded pre-menopausal women [131] had a wide range of effects on insulin levels. Thus, no potential sex effect could be seen.

No study of hyperglycemic subjects reported a correlation between insulin and covariates. As in studies of euglycemic subjects the effects on insulin found among the 2 studies of hyperglycemic men [88,133] and the study that excluded pre-menopausal women [120] were heterogeneous.

Dose and Source Effect

Finnegan et al. compared plant oil margarine to 2 doses of fish oil (as margarine and as both margarine and supplement) and to omega-6 fatty acid margarine [53]. None of the differences in insulin levels was statistically significant and the article does not comment on the relative effects of different treatments. However, dyslipidemic subjects on ALA margarine had an absolute and net decrease in fasting insulin, while subjects on low dose fish oil had a small absolute increase in insulin that was less than the increase in the control group, and subjects on high dose fish oil had an increase in insulin similar to controls. Across the studies, the effect on insulin does not appear to be associated with fish oil dose.

Both Mori et al. (2000) and Woodman et al. compared purified EPA to DHA, although in different populations [120,132]. No difference was noted between the 2 treatments in both studies.

Exposure Duration and Sustainment of Effect

Only Finnegan et al. measured insulin levels at multiple time points [53]. They reported no treatment-time interaction with insulin levels at 2, 4, and 6 months. No study measured insulin levels after ceasing omega-3 fatty acid consumption.

C-Reactive Protein

(Table 3.15)

C-reactive protein (CRP) is an acute phase reactant produced in the liver. It is thought to represent an integrated assessment of the overall state of activation of the inflammatory system. Recently, a high sensitivity assay for measuring CRP has been developed that can detect levels of CRP below what was previously considered the 'normal' range. A growing body of studies suggest that elevations in CRP levels detected by the high sensitivity assay predict a poor cardiovascular prognosis [135].

All eligible studies that reported on the effect of omega-3 fatty acids on CRP levels were included; 5 studies qualified. Four were randomized trials of oil supplements or diet; 1 was a retrospective cross-sectional analysis of usual diet.

Overall Effect [56,99,136-138]

No study found a significant effect of omega-3 fatty acid consumption on CRP level. However, CRP levels increased relative to subjects who were on control oils in most study arms among the 4 randomized trials. In contrast, the cross-sectional study did find that CRP levels were lower among subjects who ate fish regularly (fish score >4) but the difference was not statistically significant.

Sub-populations and Covariates

No study directly compared the effect of omega-3 fatty acids with placebo in different populations. There was no clear difference in effect across studies based on population. Baseline CRP levels varied across studies; although the reason for the different CRP levels is not apparent. Madsen et al. reported that when the 11 subjects with baseline CRP greater than 2 mg/L were analyzed separately, no difference in effect was seen with fish oil supplementation (as in all subjects) [137]. Likewise, the effect of omega-3 fatty acids does not appear to differ across studies based on average baseline CRP.

The trial by Chan et al. was a factorial study with fish oil supplements and atorvastatin (40 mg/day) in obese men who had a substantially higher baseline CRP than a separate group of 10 lean men (0.49 mg/L) [139]. While atorvastatin did significantly reduce CRP levels (by 0.73 mg/L) there was no interaction with fish oil.

Table 3.15 Effects of omega-3 fatty acids on C-reactive protein (mg/L) in studies (4 wk to 3 mo or cross-sectional)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
RCTs														
		DHA/EPA Oils												
Madsen, 2003	20	Fish oil	ED	5.9	20	Olive oil	[1.07]	[-0.15]	NS	B	3	Un	GEN	I
	20	Fish oil	ED	1.7			[0.69]	[+0.02]	NS					
Chan, 2002	12	Fish oil	ED	3.4	12	Corn oil	2.11	+0.05	NS [e]	B	3	Un	DysLip	II
		Plant oils												
Junker, 2001	18	Rapeseed oil diet	T	2.5% [f]	40	Olive or Sunflower	0.5 [g]	+0.11 [h]	NS	C	1	Un	GEN	I
		Fish and Mediterranean Diets												
Mezzano, 2001	21	Mediterranean	T	1.6	21	Red meat	4.9	+1.7	NS	C	1	In	GEN	III
Cross-Sectional							**Cohort Δ**							
		Diets												
Madsen, 2001	43	Fish Score 5-6			24	Fish Score 2-4	2.3	-0.1 [i]	NS	--	--	--	CVD	II
	83	Fish Score 7-8					1.9	-0.5 [i]						
	102	Fish Score 9-10					2.1	-0.3 [i]						
	127	Fish Score 11-12					2.2	-0.1 [i]						

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm (numbers in square brackets are median values or net differences of median values); Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Cohort Δ = difference in CRP between cohort and reference cohort (cross-sectional); *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Statistical significance based on 23 subjects on Omacor and 25 on placebo, half of whom were also on atorvastatin.

f Kcal.
g Median.
h Net difference of median values of rapeseed compared to average change in 2 control groups.
i Difference between cohort and low-fish cohort (fish score 2-4). Back-calculated from reported ln(CRP).

Dose and Source Effect

No study compared different sources of omega-3 fatty acids. Any differences in effect due to differing sources across studies could not be appreciated among the few studies. The cross-sectional study did not find an association between fish score (amount of fish in diet) and CRP level.

Exposure Duration

Junker et al. evaluated CRP levels at both 2 and 4 weeks. No differences were noted between baseline and either 2 or 4 weeks [56]. Mezzano et al. evaluated CRP levels at 30 days and 90 days (and also at 60 days after 30 days of added red wine). CRP was unchanged at all observation points.

Sustainment of Effect

No study re-examined CRP after subjects stopped taking omega-3 fatty acids.

Fibrinogen

(Table 3.16)

Fibrinogen, a liver protein necessary for clotting, has been found to be both increased in patients with ischemic heart disease and a predictor of cardiovascular events. It is unknown whether reducing fibrinogen levels would alter cardiovascular risk. In addition, there is currently no standardized measurement technique.

We found 59 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on fibrinogen levels (See Table 3.1). Of these, we analyzed the 24 randomized trials with data on at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids.

Overall Effect [46,56,69,74,85,89,90,100,115,116,138,140-152]

Across the 24 studies there was no consistent effect on fibrinogen levels of omega-3 fatty acid consumption compared to control. Approximately half the omega-3 fatty acid study arms resulted in a net increase in fibrinogen level compared to control; in the other half there was either a net decrease or no effect on fibrinogen level. Only 4 studies reported a statistically significant difference between the effect of omega-3 fatty acid and control. In 3 of these, the net decrease of fibrinogen ranged from approximately 5% to 20%. One study reported a significant net increase of fibrinogen of 11%.

Sub-populations

Thirteen of the studies evaluated generally healthy subjects. No consistent effect was found specifically in this population. Four studies evaluated subjects with known CVD: 2 studies of patients with stable claudication (Gans et al. and Leng et al.) [69,144], one of patients who were undergoing coronary bypass (Eritsland et al.) [142], and one of subjects with hypertension (Toft et al.) [152]. All 4 studies found no effect of omega-3 fatty acids on fibrinogen levels. Seven studies included subjects with diabetes and/or dyslipidemia. Again, there was no consistent effect. However, the largest (significant) net decrease in fibrinogen was found by Radack et al. in a group of 10 subjects with hyperlipoproteinemia types IIb or IV on a moderate dose of fish oil supplement [151]. A significant net increase in fibrinogen was seen by Haines et al. among 19 subjects with insulin-dependent diabetes on a high dose of fish oil supplement, although the effect was not related to Hgb A1c level. [115].

In the study of patients undergoing coronary bypass, Eritsland et al. found that the (lack of) effect of omega-3 fatty acids on fibrinogen was unchanged after adjusting for multiple factors including age and sex [142]. Seven studies included only men [46,85,100,138,140,147,149]. The distribution of effects was similar in this subset of studies as in the whole set. Three of these studies of men and an one additional study included only younger adults (generally less than 30 or 40 years old) [46,138,140,146]. These studies had results similar to studies of broader age ranges or of older subjects. Overall, the studies provided insufficient data on race or ethnicity to allow analysis of these subpopulations. Almost half the studies were performed in Scandinavia and Finland; most of the remaining are from northern Europe and Australia. Notably the study by Radack et al., which

Table 3.16 Effects of omega-3 fatty acids on fibrinogen (g/L) in randomized trials (4 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils													
Hansen, 1989	40 [e]	Cod liver oil	ED	5.8	40 [e]	No oil	2.4	-0.1	NS	C	1	Un	GEN	I
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	2.7	+0.3	<.05	B	2	Ad	IDDM	II
Misso, 1995	12 [e]	Fish oil	ED	3.6	12 [e]	Olive oil	3.0	+0.2	NS	C	2	Un	GEN	II
Hansen, 1993a	11	Fish oil Tg [f]	ED	3.6	10	Corn oil	2.4	+0.3 [g]	nd	B	4	Un	GEN	II
	10	Fish oil EE [h]	ED	3.4			2.4	-0.1 [g]	nd					
Toft, 1997	38	Fish oil	ED	3.4	38	Corn oil	2.2	+0.2	NS	A	5	Ad	CVD	II
Grundt, 1999	28	Ethyl ester [i]	ED	3.4	28	Corn oil	2.9	-0.1	NS	B	2	Un	DysLip	II
Nordoy, 2000	21	Fish oil	ED	3.4	20	Corn oil	3.0	+0.1	NS	B	4	Un	DysLip	I
Deslypere, 1992	14	Fish oil	T	3.4	14	Olive oil	2.3	-0.1	NS	B	2	Un	GEN	III
	15	Fish oil	T	2.2			2.3	-0.3	NS					
	15	Fish oil	T	1.1			2.0	+0.1	NS					
Eritsland, 1995c	254	Fish oil	ED	3.3	249	No oil	2.6	-0.1	NS	B	2	Ad	CVD	II
Osterud, 1995	26	Cod liver oil	ED	3.1	28	No oil	2.6	0.0	NS	B	2	Un	GEN	I
	27	Seal\Cod oil	ED	2.8			2.5	+0.1	NS					
	27	Seal oil	ED	2.4			2.6	0.0	NS					
	26	Whale oil	ED	1.7			2.6	-0.1	NS					
Hendra, 1990	37	Fish oil	ED	3.0	37	Olive oil	3.2	+0.2	NS	B	4	Un	DM II	I
Gans, 1990	16	Fish oil	ED	3.0	16	Corn oil	3.3	+0.1	NS	A	3	Ad	CVD	II

Radack, 1989	10	Fish oil	ED	2.2	8	Olive oil	3.2	-0.6 [j]	<.05	B	3	Un	DysLip	II
	7	Fish oil	ED	1.1			2.9	0.0	NS					
Marckmann, 1997	23	Fish oil margarine	T	0.9	24	Sunflower margarine	2.4	-0.05	NS	B	3	Un	GEN	II
Nenseter, 2000	34	Fish powder	ED	0.2	36	Cellulose	3.0	-0.2	NS	B	3	Un	DysLip	I
Leng, 1998	37 [k]	Fish oil	ED	0.045 [L]	36 [m]	Sunflower oil	3.4	+0.04	NS	C	4	Ad	CVD	II
		Plant Oils												
Allman-Farinelli, 1999	15	Flaxseed oil diet	A	10% [n]	14	Safflower oil	2.1	+0.1	NS	B	2	Un	GEN	II
Junker, 2001	18	Rapeseed oil	T	2.5% [o]	40	Olive or Sunflower oil	2.3	+0.1 [p]	NS	C	1	Un	GEN	I
		Fish and Mediterranean Diets												
Muller, 1989	40	Mackerel paste	ED	4.7	42	Meat paste	2.7	-0.02	NS	B	1	Un	GEN	II
Dunstan, 1999	14	Fatty fish [q]	T	3.6	23	No fish	2.9	+0.2 [r]	NS	B	2	Un	DysLip NIDDM	I
	12	Fatty fish [s]					3.3	+0.1 [r]	NS					
Mezzano, 2001	21	Mediterranean	T	1.6	21	Red meat	2.3	-0.3	.03	C	1	In	GEN	III
		Combinations												
Freese, 1997b	24	Fish oil	ED	5.2	--	--	3.1	-0.06 [t]	nd [u]	C	3	Un	GEN	II
	22	Linseed oil	A	5.9			3.1	+0.05 [t]	nd [u]					
Cobiac, 1991	13	Fish oil	ED	4.6	6	Olive, Palm, Safflower oil	2.35	+0.4	NS	B	2	Un	GEN	II
	12	Fatty fish diet	ED	4.5			2.65	-0.15	<.05					
Agren, 1997	14	Fish oil	ED	2.3	14	No oil	3.6	+0.3	NS	B	3	Un	GEN	III
	14	Algae DHA oil	D	1.7			3.4	+0.1	NS					
	13	Fatty fish diet	ED	1.1			3.4	+0.3	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Triglycerides.

g *P*=.09 between treatments.

h Ethyl esters.

i No data on source.

j *P*<.05 compared to 1.1 g/day.

k Baseline data based on N=52.

L Plus 280 mg gamma linolenic acid (omega-6 fatty acid).

m Baseline data based on N=50.

n ALA = 10% of daily fatty acid intake.

o Kcal.

p Difference compared to average change in 2 control groups.

q Moderate exercise.

r Estimate from graph. Not clear which control group compared to (or combined). Possibly adjusted for age and sex.

s Light exercise.

t Pre-post difference (not compared to control).

u NS between treatments.

showed the largest benefit from omega-3 fatty acids and was the only study to show a dose effect (see below), was the only study performed in the United States [151].

Covariates

Eritsland et al., Haines et al. and Toft et al. found no association of effect of omega-3 fatty acids on fibrinogen with various factors including sex, baseline and change in weight, baseline blood pressure, change in lipids or insulin, or cardiovascular, lipid or antithrombotic drug use among patients with cardiovascular disease [115,142,152]. Mezzano et al. found no interaction of wine consumption with a Mediterranean diet in a multiphase trial [138]. No differences were found among studies with run-in phases of either high- or low-fat diets. No study quantified baseline fish consumption. Radack et al. reported that the relative effect of higher dose fish oil supplements was greater with higher baseline fibrinogen values ($r = -0.59$, $P < .01$) [151].

Dose and Source Effect

Two studies compared different doses of the same omega-3 fatty acid supplements. Radack et al. found that subjects with dyslipidemia who took 6 g of fish oil supplements (2.2 g EPA+DHA) for 20 weeks had a relatively large, statistically significant net reduction in fibrinogen [151]. This effect was significantly greater than in the subjects who took 3 g of fish oil (1.1 g EPA+DHA), who had no effect. Deslypere et al., however, found no difference in effect across 3 doses of fish oil supplements (3.4 g, 2.2 g, and 1.1 g EPA+DHA) in monks who took fish oils for 1 year. Across all studies the effect is not related to omega-3 fatty acid dosage.

Hansen et al. (1993a) reported a possible trend toward greater effect of fish oil ethyl esters than fish oil triglycerides [147]. Osterud et al. found no difference among different marine oils [74]. Two studies evaluated ALA oils. Both found no effect with dietary flaxseed oil or rapeseed oil supplements [46,56].

Three studies compared fish oil supplements with other sources of omega-3 fatty acids [100,140,143]. Cobiac et al. found a small significant reduction in fibrinogen only among the subjects consuming dietary fish; however the significance of the difference between the 2 treatments was not reported [100]. Overall, there were no clear differences in effect of different sources of omega-3 fatty acids.

Exposure Duration

Across studies, there was no apparent effect on fibrinogen of duration of consumption of omega-3 fatty acids in studies that reported data from 2 weeks to 2 years. Seven studies reported fibrinogen levels at various time points [56,69,85,115,138,149,151]. Although mean fibrinogen levels varied with time in most studies, no study found a difference in effect related to time.

Sustainment of Effect

Two studies, which both found no effect of omega-3 fatty acids on fibrinogen levels, reported no further change after stopping treatment. Deslypere et al. reported no difference in fibrinogen levels up to 6 months after 1 year of treatment [85]. Freese et al. likewise found no difference 4 weeks after finishing 4 weeks of treatment [143].

Factor VII, Factor VIII, and von Willebrand Factor

(Tables 3.17, 3.18, and 3.19)

Omega-3 fatty acids affect the clotting system in a number of ways in animal and *in vitro* models. Factors VII and VIII and von Willebrand factor (vWF) are factors in the extrinsic coagulation system that have been suggested to play a crucial role in the initiation of blood coagulation in atherosclerotic disease, particularly in diabetes [153]. Although the mechanism is not well-established, high vWF levels help to predict cardiovascular events, although the vWF level is not powerfully predictive in the individual at risk [154]. However, different laboratories use different methods to measure coagulation factors including antigen or activity level, percent compared to a standard or concentration, and other variations. This makes comparisons across studies difficult.

We found 44 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on factor VII, factor VIII, and/or vWF (40, 13, and 20 studies, respectively; See Table 3.1). Of these, we analyzed the 23 randomized trials that met additional criteria. For factor VII, we analyzed studies that had data on at least 15 subjects in parallel trials or 10 subjects in crossover trials who consumed omega-3 fatty acids (19 studies). For factor VIII and vWF, we analyzed all randomized trials (5 and 9 studies, respectively).

Overall Effect

Factor VII (Table 3.17) [46,56,74,89,90,115,116,138,140-143,145-147,149,150,152,155]**.** There is little consistency in effect across the 19 studies of factor VII activity. In general, the net change in factor VII in subjects consuming omega-3 fatty acids is small (7% change from baseline or less), although a nearly equal number of studies found net increases as found net decreases in levels.

Table 3.17 Effects of omega-3 fatty acids on factor VII activity (%) in randomized trials (4 weeks to 9 months)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]				Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal			
	DHA/EPA Oils														
Hansen, 1989	40 [e]	Cod liver oil	ED	5.8	40 [e]	No oil	90	+2	NS	C	1	Un		GEN	I
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	79	+5	NS	B	2	Ad		IDDM	II
Hansen, 1993a	11	Fish oil Tg [f]	ED	3.6	10	Corn oil	87	-1	NS	B	4	Un		GEN	II
	10	Fish oil EE [g]	ED	3.4			83	-2	NS						
Toft, 1997	38	Fish oil	ED	3.4	38	Corn oil	105	+1	NS	A	5	Ad		CVD	II
Grundt, 1999	28	Ethyl ester [h]	ED	3.4	28	Corn oil	119	-5	NS	B	2	Un		DysLip	II
Nordoy, 2000	21	Fish oil	ED	3.4	20	Corn oil	132	-2	NS	B	4	Un		DysLip	I
Eritsland, 1995c	90	Fish oil	ED	3.3	107	No oil	109	-6	NS	B	2	Ad		CVD	II
Osterud, 1995	26	Cod liver oil	ED	3.1	28	No oil	1.16 [i]	0	NS	B	2	Un		GEN	I
	27	Seal/Cod oil	ED	2.8			1.21 [i]	+0.03	NS						
	27	Seal oil	ED	2.4			1.23 [i]	-0.08	NS						
	26	Whale oil	ED	1.7			1.20 [i]	-0.01	NS						
Hendra, 1990	37	Fish oil	ED	3.0	37	Olive oil	94	+22	.02	B	4	Un		DM II	I
Berrettini, 1996	20	Fish oil	ED	2.6	19	Corn oil	116	0 [j]	NS	B	3	Un		CVD	II

Marckmann, 1997	23	Fish oil margarine	T	0.9	24	Sunflower margarine	104	0	NS	B	3	Un	GEN	II
Nenseter, 2000	34	Fish powder	ED	0.2	36	Cellulose	121	+1	NS	B	3	Un	DysLip	I
		Plant Oils												
Allman-Farinelli, 1999	15	Flaxseed oil diet	A	10% [k]	14	Safflower oil	83	+3 [j]	NS	B	2	Un	GEN	II
Junker, 2001	18	Rapeseed oil	T	2.5% [L]	40	Olive or Sunflower oil	101	+4 [m]	NS	C	1	Un	GEN	I
		Fish and Mediterranean Diets												
Muller, 1989	40	Mackerel paste	ED	4.7	42	Meat paste	99	-0.5	NS	B	1	Un	GEN	II
Dunstan, 1999	14	Fatty fish [n]	T	3.6	23	No fish	112	+1 [o]	NS	B	2	Un	DysLip NIDDM	I
	12	Fatty fish [p]					113	+5 [o]	<.05					
Mezzano, 2001	21	Mediterranean	T	1.6	21	Red meat	78	-4	.03	C	1	In	GEN	III
		Combinations												
Freese, 1997b	24	Fish oil	ED	5.2	--	--	89	+6 [q]	nd [r]	C	3	Un	GEN	II
	22	Linseed oil	A	5.9			90	+5 [q]	nd [r]					
Agren, 1997	14	Fish oil	ED	2.3	14	No oil	93	0	NS	B	3	Un	GEN	III
	14	Algae DHA oil	D	1.7			98	-6	NS					
	13	Fatty Fish diet	ED	1.1			94	-2	NS					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Triglycerides.

g Ethyl esters.

h No data on source.

i Factor VIIc activity in U/mL.

j Estimated from graph.

k ALA = 10% of daily fatty acid intake.

L Kcal.

m Difference compared to average change in 2 control groups.

n Moderate exercise.

o Estimate from graph. Not clear which control group compared to (or combined). Possibly adjusted for age and sex.

p Light exercise.

q Pre-post difference (not compared to control).

r NS between treatments.

Factor VIII (Table 3.18) [46,84,85,115,138]**.** Five studies reported data on factor VIII activity. (It is unclear whether Conquer et al. measured factor VIII activity or antigen [84].) There is no consistent effect across studies, with some finding a net increase and some a net decrease in factor VIII level.

Table 3.18 Effects of omega-3 fatty acids on factor VIII activity (%) in randomized trials (6 weeks to 1 year)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils													
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	123	+8	NS	B	2	Ad	IDDM	II
Deslypere, 1992	14	Fish oil	T	3.4	14	Olive oil	77	-1	NS	B	2	Un	GEN	III
	15	Fish oil	T	2.2			73	-2	NS					
	15	Fish oil	T	1.1			81	+4	NS					
Conquer, 1999	9	Seal oil	ED	3.0	10	Evening primrose	0.85 [e]	+0.12	NS	A	4	Un	GEN	II
	Plant Oils													
Allman-Farinelli, 1999	15	Flaxseed oil diet	A	10% [f]	14	Safflower oil	82	-5 [g]	NS	B	2	Un	GEN	II
	Fish and Mediterranean Diets													
Mezzano, 2001	21	Mediterranean	T	1.6	21	Red meat	68	-5	.006	C	1	In	GEN	III

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Factor VIII in U/mL (unclear whether activity or antigen).

f ALA = 10% of daily fatty acid intake.

g Estimated from graph.

von Willebrand Factor (Table 3.19) [46,69,84,85,89,147,149,150,156]. Nine studies reported data on various measurements of vWF using different measurement methods. Some studies were not explicit about the specific measurement used. Most studies found a net decrease in vWF level (of up to a 13% reduction from baseline), although in only 1 study was the difference with placebo reported to be statistically significant.

Table 3.19 Effects of omega-3 fatty acids on von Willebrand factor in randomized trials (4 weeks to 2 years)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]				Quality [c]			Applicability [d]	
	N	Source		g/d	N	Source	Base	Net Δ	Unit	*P*	Summary	Jadad	Allocation Conceal		
	DHA/EPA Oils														
Seljeflot, 1998	22	Fish oil	ED	4.8	19	Fatty acids	127	-17	% [e]	.03	B	4	Un	DysLip	II
Hansen, 1993a	11	Fish oil Tg [f]	ED	3.6	10	Corn oil	100	-13	% [g]	nd	B	4	Un	GEN	II
	10	Fish oil EE [h]	ED	3.4			121	-16		nd					
Nordoy, 2000	21	Fish oil	ED	3.4	20	Corn oil	101	-5	% [i]	NS	B	4	Un	DysLip	I
Deslypere,	14	Fish oil	T	3.4	14	Olive oil	133	-1		NS	B	2	Un	GEN	III

1992	15	Fish oil	T	2.2			141	-2	% [j]	NS					
	15	Fish oil	T	1.1			137	+7		NS					
Conquer, 1999	9	Seal oil	ED	3.0	10	Evening primrose	6.9	-0.5	µg/mL [k]	NS	A	4	Un	GEN	II
Marckmann, 1997	22	Fish oil margarine	T	0.9	24	Sunflower margarine	86	-6	% [e]	NS	B	3	Un	GEN	II
Leng, 1998	37 [L]	Fish oil	ED	0.045 [m]	36 [n]	Sunflower oil	118	+7	IU/dL [o]	NS	C	4	Ad	CVD	II
		Plant Oils													
Allman-Farinelli, 1999	15	Flaxseed oil diet	A	10% [p]	14	Safflower oil	96	-6 [q]	% [r]	NS	B	2	Un	GEN	II
		Fish and Mediterranean Diets													
Muller, 1989	40	Mackerel paste	ED	4.7	42	Meat paste	1.02	0	IU [e]	NS	B	1	Un	GEN	II

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e By enzyme-linked immunosorbent assay (ELISA).

f Triglycerides.

g Factor VIII-related antigen, by ELISA.

h Ethyl esters.

i Activity.

j Plasma content, by ELISA.

k By rocket immunoelectrophoretic procedure.

L Baseline data based on N=52.

m Plus 280 mg gamma linolenic acid (omega-6 fatty acid).

n Baseline data based on N=50.

o Concentration, by ELISA.

p ALA = 10% of daily fatty acid intake.

q Estimated from graph.

r Antigen, by ELISA.

Sub-populations

Factor VII. A small, inconsistent effect across studies was found among the 10 studies of a general population, the 3 studies of populations with CVD, and the 4 studies of people with dyslipidemia. The only statistically significant effects – both net increases in factor VII – were seen in 2 of the 3 studies of diabetic patients (one of which included only diabetics with dyslipidemia). The large increase in factor VII found by Hendra et al. in a 6 week study of fish oil versus olive oil supplements in non-insulin dependent diabetics was noted to be unexpected in light of a large decrease in Tg level [116].

Factor VIII. The single study of insulin dependent diabetics found a larger net increase of factor VIII than the studies of general populations, although the difference in this study was not significant. No study measured factor VIII in CVD or dyslipidemic populations.

von Willebrand Factor. With the exception of a low-dose arm in 1 study, the 6 studies of general populations found either net decreases or no effect in vWF, although none was statistically significant. The single study of a CVD population was the only study to find an

overall net increase in vWF level, although Leng et al. was also an anomaly in that the oil analyzed was primarily gamma-linolenic acid (GLA, 18:3 n-6), an omega-6 fatty acid, with a small amount of EPA [69].The only study to find a large, statistically significant decrease in vWF was 1 of the 2 studies of dyslipidemic patients. No study evaluated diabetic patients.

Covariates

Factor VII. Haines et al. found no association between change in factor VII with fish oil supplementation and either sex or Hgb A_{1c} in insulin dependent diabetics [115]. In contrast, in a study of non-insulin dependent diabetics, Dunstan et al. reported a significant positive association between the changes in factor VII and fasting blood sugar with a fatty fish diet; however, dietary fish significantly affected factor VII levels only in subjects who were not in a moderate exercise program [141]. Eritsland et al. reported no change in (lack of) effect of fish oil supplements in patients undergoing coronary bypass surgery after controlling for multiple factors including age, sex, weight, blood pressure, diabetes and CVD medications [142].

In possible contrast to the rest of the studies, only 1 of the 6 studies of male subjects, 3 of which were of younger men, found a net increase in factor VII; however all effects were small [46,89,138,140,147,149]. One study in which all subjects were on simvastatin [150] found a non-significant effect of fish oil supplements similar to other studies.

Factor VIII. Haines et al. found no relationship between effect of fish oil supplementation in insulin dependent diabetics who were taking aspirin on factor VIII and either sex or Hgb A_{1c} [115]. All other studies were in men, most of whom were under age 40 years. There were no other data relating to other covariates.

von Willebrand Factor. No study reported on correlations between effect on vWF and covariates. Notably, though, only 2 of the studies included women [69,150]. The effect of fish oil supplements in patients on simvastatin was similar to the effect of fish oil alone in other studies [150].

Dose and Source Effect

Factor VII. No study compared different doses of the same omega-3 fatty acid source. Across studies there does not appear to be a dose effect. Four studies compared different sources of omega-3 fatty acids. Hansen et al. (1993a) found no difference between fish oil triglycerides and fish oil ethyl esters [147]. Osterud et al. reported no difference in effect of different marine oils [74]. Freese et al. compared similar doses of fish oil and linseed oil supplements and found no difference between the 2 oils [143]. Agren et al. also did not report a difference in effect among fish oil supplementation, algae DHA oil supplementation, and fatty fish diet [140].

Factor VIII. Only Deslypere et al. compared different doses of fish oil supplements [85]. They reported no difference in effect of fish oil on factor VIII related to dose. None of the studies of fish oil supplements showed more than a marginal decrease in factor VIII level. In contrast, the single study of a flaxseed oil diet found a non-significant, approximately 6% net decrease in factor VIII activity and the single study of Mediterranean diet found a highly significant, approximately 7% net reduction in factor VIII activity. In the latter study, Mezzano et al. also found significant reductions in factor VII activity and fibrinogen levels, in contrast to most other studies [138]. They found no association between the effect on factor VIII and either ABO blood type (which is related to factor VIII level) or CRP, as a marker of inflammation.

von Willebrand Factor. Deslypere reported no difference in effect on vWF after 1 year in monks taking 3 different doses of fish oil supplements [85]. Hansen found similar effects among men taking either fish oil triglycerides or fish oil ethyl ester [147]. Across studies, though, the study by Seljeflot et al., which tested the largest dose of omega-3 fatty acid supplementation, found the largest, significant decrease in vWF. However, the study of mackerel paste diet, with a similar omega-3 fatty acid level, found no effect. The single study of plant oils found a non-significant decrease in vWF with an ALA-rich flaxseed oil diet that was similar to most marine oil studies.

Exposure Duration

Factor VII. Five studies measured factor VII levels at different time periods, ranging from 2 to 16 weeks [56,115,138,149,155]. No differences were seen in factor VII levels at any time point.

Factor VIII. Three studies measured factor VIII activity at different time periods. Haines et al. found no effect of fish oil supplements on factor VIII at either 3 or 6 weeks [115]. Deslypere et al. did find an occasional significant decrease of factor VIII from the second trial month on in multiple measurements done between 4 weeks and 12 months [85]. However, this effect was also seen in the olive oil group and no net differences were found. Mezzano et al. found similar responses to Mediterranean diet at both 1 and 3 months [138].

von Willebrand Factor. Three studies measured vWF at different time periods. Muller et al. found no change in vWF in either study arm at both 3 and 6 weeks [149]. Both Deslypere et al. and Leng et al. found that vWF levels fluctuated at different time points ranging from 3 weeks to 1 year, but that there were no differences among arms [69,85].

Sustainment of Effect

Factor VII. Only Freese et al. reported data on factor VII levels after stopping treatment [143]. There was no difference 4 weeks after finishing 4 weeks of treatment compared to either pre- or post-treatment levels.

Factor VIII and von Willebrand Factor. Only Deslypere et al. reported data on factor VIII activity and vWF after stopping treatment [85]. There was a large increase in factor VIII activity in all study arms, including the olive oil group, at both 1 and 2 months after stopping treatment. There were no differences between fish oil supplement and control groups. There was no difference in vWF after treatment.

Platelet Aggregation

(Table 3.20)

Platelet aggregation plays a central role in the pathogenesis of acute atherothrombosis and has been associated with cardiovascular disease in some, but not all, epidemiological studies. However, pharmacological agents that inhibit platelet aggregation, such as aspirin, clearly reduce the incidence of adverse clinical cardiovascular events. The most common method of measuring platelet aggregation involves *in vitro* tests of blood samples. Aggregating agents such as adenosine diphosphate (ADP) and collagen are added to the blood samples, or spontaneously occurring aggregation is measured. The resulting platelet aggregation is used as a measurement of the potential for platelets to aggregate in the human body. There is little agreement as to which

method is most meaningful and little standardization of dose of aggregating agent or test methodology. Omega-3 fatty acids may directly affect platelets, thus both reducing CVD but also possibly increasing bleeding risk.

We found 84 studies that met eligibility criteria and reported data on the effect of omega-3 fatty acids on platelet aggregation (See Table 3.1). Of these, we analyzed the 11 randomized trials with data on at least 15 subjects in parallel trials and 10 subjects in crossover trials who consumed omega-3 fatty acids and that also reported platelet aggregation in tabular or text format. Studies that presented platelet aggregation data graphically only were not analyzed. This additional criterion was used because of the particular difficulty in estimating data from graphs for this outcome and because of the large number of specific outcomes reported in each study.

Overall Effect [54,57,108,115,116,128,140,157-160]

Within the 11 studies, heterogeneous effects of omega-3 fatty acids were generally found depending on the aggregating agent, the dose of agent, and the measurement metric used. However, in most studies either no effect on platelet aggregation was found with omega-3 fatty acids or no difference in effect was seen between treatments and controls.

Sub-populations

Seven studies were performed in generally healthy individuals. Salonen et al., Junker et al., and Wensing et al. all found no effect of omega-3 fatty acid consumption and no difference with control groups in healthy men, non-obese individuals and elderly individuals, respectively [56,159,160]. Freese et al. (1994) found no significant effect from rapeseed oil supplements in male students; however, they did find an apparent comparative effect since Trisun sunflower oil, which was used as the comparison, significantly increased platelet aggregation [54]. Hansen et al., Freese et al. (1997a), and Agren et al. found mixed effects in younger individuals (Agren at al. in male students), with significantly decreased platelet aggregation in some study arms with some specific tests [128,140,157].

Two studies evaluated hypercholesterolemic subjects, both of which found no effect of omega-3 fatty acids on measures of platelet aggregation. An additional 2 studies included diabetic patients. Haines et al. reported no effect among insulin-dependent diabetics, while Hendra et al. reported small, but significant increases in spontaneous platelet aggregation among type 2 diabetics [115,116]. However, in the latter study it was also reported, without supporting evidence, that epinephrine-induced aggregation was unaffected by either treatment or control. No studies specifically included patients with known or suspected CVD.

Table 3.20 Effects of omega-3 fatty acids on platelet aggregation in randomized trials (4 to 15 weeks)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]				Quality [c]				
	N	Source		g/d	N	Source	Method, Unit	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal	Applicability [d]	
		DHA/EPA Oils													
Hansen, 1993b	14 [e] Women / 20 [e] Men	Cod liver oil	ED	5.3	14 [e] / 20 [e]	No oil	Collagen 0.5 µg/mL, %	47.0	+1.2	NS	C	1	Un	GEN	II
							Collagen 4 µg/mL, %	95.0	+1.4	NS					
							ADP 2.5 µmol/L, %	81.0	-4.3	NS					
							Collagen 0.5 µg/mL, %	56.0	-24.7	<.01					
							Collagen 4 µg/mL, %	95.0	-2.6	NS					
							ADP 2.5 µmol/L, %	76.0	-5.9	NS					
Haines, 1986	19	Fish oil	ED	4.6	22	Olive oil	Collagen 1 µg/mL, Unit	49.3	-3.1	NS	B	2	Ad	IDDM	II
							Collagen 10 µg/mL, Unit	59.1	+2.2	NS					
Sirtori, 1992	12 [e]	Fish oil	ED	4.5	12 [e]	No oil	Collagen AC_{50}, mg/L [f]	0.35	+0.05	NS	C	2	Un	DysLip	II
							Iloprost IC_{50}, nmol/L [g]	0.65	+0.07	NS					
Hendra, 1990	35	Fish oil	ED	3.0	32	Olive oil	Spontaneous 10 min, [h]	77.3	+3.2	.06	B	4	Un	DM II	I
							Spontaneous 20 min, [h]	70.3	+4.4	.02					
							Spontaneous 30 min, [h]	67.4	+4.7	.02					
							Spontaneous 60 min, [h]	62.9	+4.2	.02					
Salonen, 1987	20	Fish oil	ED	2.7	24	Olive oil	ADP 2.3-9.0 µmol/L Aggregation extent, mV	16.2	+3.3	NS	B	3	Un	GEN	II
							ADP 2.3-9.0 µmol/L Aggregation velocity, mV/sec	0.16	+0.05	NS					
		Plant Oils													
Kwon, 1991	16	Canola oil diet	T	8-9% [i]	14	Safflower oil diet	Collagen 1 mg/L Maximum aggregation, Ω	43.5	0	NS	C	1	Un	DysLip	II
							Collagen 2 mg/L Maximum aggregation, Ω	46.3	+1.5	NS					
Junker, 2001	18	Rapeseed oil diet	T	2.5% [j]	40	Olive or Sunflower oil diet	ADP 0.5 µmol/L, %	7.8	+19.7 [k]	NS	C	1	Un	GEN	I
							ADP 2 µmol/L, %	27.1	+31.4 [k]	NS					
							Adrenaline 1 µmol/L, %	82.3	+9.9 [k]	NS					
							Adrenaline 4 µmol/L, %	85.1	7.8 [k]	NS					
							Spontaneous	7.2	+1.3 [k]	NS					
Freese, 1994	20	Rapeseed oil diet	A	2.3% [j]	20	Trisun Sunflower oil diet [L]	ADP 1 µmol/L slope, %/min	19.9	-5.4 [m]	.004	C	1	Un	GEN	III
							ADP 2 µmol/L slope, %/min	43.4	-9.5 [m]	.002					
							ADP 3 µmol/L slope, %/min	56.4	-6.6 [m]	.001					
							Thrombin 0.12 NIH/mL slope, %/min [n]	20.7	-1.0	NS					
							Thrombin 0.15 NIH/mL slope, %/min [n]	33.5	-3.8	.03					
							Thrombin 0.18 NIH/mL slope, %/min [n]	36.7	-3.0 [m]	.02					

Continued

Table 3.20 Effects of omega-3 fatty acids on platelet aggregation in randomized trials (continued)

Author, Year	Omega-3 Fatty Acid Arm [a] N	Source	g/d	Control N	Source	Results [b] Method, Unit	Base	Net Δ	P	Quality [c] Summary	Jadad	Allocation Conceal	Applicability [d]
	Combinations												
Freese, 1997a	16	Fish oil	ED 5.2	--	--	ADP 1 µmol/L, %/min	34.4	+3.8 [o]	nd [p]	C	3	Un	GEN II
						ADP 2 µmol/L, %/min	60.0	+4.6 [o]	nd [p]				
						ADP 3 µmol/L, %/min	72.3	-0.7 [o]	nd [p]				
						Collagen 0.5 µg/mL, %/min	53.3	-22.2 [o]	nd [p]				
						Collagen 1 µg/mL, %/min	81.2	-2.2 [o]	nd [p]				
						Collagen 3 µg/mL, %/min	99.6	-3.4 [o]	nd [p]				
	14	Linseed oil	A 5.9			ADP 1 µmol/L, %/min	34.8	-0.7 [o]	nd [p]				
						ADP 2 µmol/L, %/min	56.3	-1.6 [o]	nd [p]				
						ADP 3 µmol/L, %/min	68.8	-5.0 [o]	nd [p]				
						Collagen 0.5 µg/mL, %/min	44.8	-9.6 [o]	nd [p]				
						Collagen 1 µg/mL, %/min	78.6	-1.8 [o]	nd [p]				
						Collagen 3 µg/mL, %/min	94.3	+4.1 [o]	nd [p]				
Agren, 1997	14	Fish oil	ED 2.3	14	No oil	ADP 2 µmol/L, %T [n]	49.9	-5.8	NS	B	3	Un	GEN III
						ADP 5 µmol/L, %T [n]	74.2	-9.3	NS				
						Collagen 50 µg/mL, %T [n]	51.3	-31.2	<.05				
	14	Algae DHA oil	D 1.7			ADP 2 µmol/L, %T [n]	37.2	+7.5	NS				
						ADP 5 µmol/L, %T [n]	64.5	-0.1	NS				
						Collagen 50 µg/mL, %T [n]	39.3	+13.7	NS				
	13	Fatty Fish diet	ED 1.1			ADP 2 µmol/L, %T [n]	35.1	+4.6	NS				
						ADP 5 µmol/L, %T [n]	70.0	-2.9	NS				
						Collagen 50 µg/mL, %T [n]	66.1	-20.7	<.05				
Wensing, 1999	14	Fish oil shortening	ED 1.6	11	Sunflower oil	ADP 1.5 µmol/L V_a, % [q]	48.2	+6.7	NS	B	2	Un	GEN II
						ADP 1.5 µmol/L I_{max}, % [r]	69.6	+2.2	NS				
						Collagen 1.0 µg/mL V_a, % [q]	46.5	-6.2	NS				
						Collagen 1.0 µg/mL I_{max}, % [r]	65.7	+2.8	NS				
	13	Linseed oil shortening	A 6.5			ADP 1.5 µmol/L V_a, % [q]	52.9	-1.9	NS				
						ADP 1.5 µmol/L I_{max}, % [r]	73.3	-15.6	NS				
						Collagen 1.0 µg/mL V_a, % [q]	40.2	-3.8	NS				
						Collagen 1.0 µg/mL I_{max}, % [r]	50.2	+10.4	NS				

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e Cross-over study.

f Concentration of collagen giving a 50% decrease in optical density.

g Concentration of Iloprost resulting in 50% inhibition of platelet aggregation.

h Percent platelets remaining after aggregation.

i Percent of total methyl esters in diet.

j Kcal.

k Difference compared to average change in 2 control groups.

L High linoleic acid (18:2 n-6) oil.

m No significant effect compared to baseline. Significant increase compared to Trisun oil, which increased platelet aggregation rate.

n No definition of unit provided.

o Pre-post difference (not compared to control).

p Not significant between treatments.

q Aggregation velocity.

r Maximal velocity.

Covariates

Hansen et al., recognizing that male and female sex hormones have different effects on platelet function, made an *a priori* evaluation of the potentially different effect of cod liver oil supplementation on platelet aggregation in men and women [157]. Healthy, young, normolipemic men and women were included in the study. A large, significant decrease in platelet aggregation with low dose collagen was seen in men on cod liver oil supplements, but not in women ($P < .01$ men vs. women). Otherwise the effect of fish oil was generally mixed and not different between the sexes. No explanation was offered for why the effect would have been seen only with low-dose collagen aggregation. In contrast, Haines et al. made the blanket statement that the baseline variables smoking, alcohol consumption, and sex were not related to the response to fish oil supplementation [115]. Four other studies included only men [54,57,140,159]. No clear difference was seen between these studies and studies that included both men and women. No other covariate was specifically analyzed in any study.

Dose and Source Effect

No study compared different doses of the same type of oil. Among the studies of fish oil supplements or diets, there was no clear association across studies between dose and change in platelet aggregation.

No significant effect was seen in any of the studies of plant oil supplements or diets, regardless of dose. Two studies compared fish oil (EPA+DHA) to linseed oil (ALA). Freese et al (1997a) was inconclusive regarding a difference between fish oil and linseed oil supplements [128]. However, Wensing et al. reported that platelet aggregation was prolonged by greater amounts in subject who consumed fish oil shortening compared to those who consumed linseed oil shortening [160]. Agren et al. compared 3 sources of EPA and/or DHA [140]. Collagen aggregation

was reduced in subjects on both fish oil supplementation and fish diet, but not in those consuming pure DHA oil. From this, they concluded that while omega-3 fatty acids impair platelet aggregation, DHA is less potent than fish oil or dietary fish at moderate doses.

Exposure Duration

Three studies measured platelet aggregation at different time points. Haines et al. and Junker et al. reported data at 3 and 6 weeks, and 2 and 4 weeks, respectively, but did not comment on a potential time effect [56,115]. However, no apparent difference in effect was seen between the earlier and later times. Kwon et al. noted that with 2 mg/L collagen aggregation a significant decrease in platelet aggregation was found at 3 weeks on canola oil diet, which reverted to baseline by 8 weeks [57].

Sustainment of Effect

Freese et al. (1997a) reported that the decrease in collagen-induced aggregation in the fish oil supplement arm did not return to baseline during a 12 week follow-up period, although, the other tests did [128].

Coronary Artery Restenosis

(Table 3.21, Figure 3.3)

The benefit of treatments given after percutaneous transluminal coronary angioplasty (PTCA) is often measured, in research studies, by performing a subsequent angiography and measuring the change in the luminal diameter at the sites of dilatation performed in the original angioplasty. The most common metric is restenosis rate, although there is no single standard definition of restenosis. Most researchers use minor variations of a 50% narrowing of the dilated vessel from the immediately post-dilation diameter. In theory, this level of restenosis corresponds with recurrence of angina, although clearly some patients develop symptoms with lesser levels of stenosis and some patients stay asymptomatic with greater levels of stenosis. If omega-3 fatty acids are effective at reducing clinical coronary artery disease, including angina and myocardial infarction, then the effect should be manifested in the diagnostic testing by angiography.

We found 17 studies that met eligibility criteria and reported data on coronary arteriography in patients taking omega-3 fatty acids (See Table 3.1). Of these, we analyzed the 12 randomized trials with data on restenosis rate after PTCA. Most studies re-evaluated patients at 6 months after PTCA. Maresta et al. started patients on omega-3 fatty acids 1 month prior to the initial PTCA [81]. In general, other studies started omega-3 fatty acid treatment up to a week prior to PTCA.

Overall Effect [63,64,81,161-169]

All studies compared a single dosage of fish oil supplementation to control. Definitions of restenosis, however, were not uniform as noted in the footnotes of the summary table. In particular, 3 studies included abnormal exercise tolerance tests (ETT) as a potential definition of

restenosis [166,167,169]. The results of random effects model meta-analysis are presented in both the Table 3.21 and Figure 3.3. Overall, although there is heterogeneity among the studies, there is a trend toward a net reduction of coronary artery restenosis with fish oil supplementation. The meta-analysis estimate is a lowering of risk of 14% (95% confidence interval –29%, +3%).

Table 3.21 Effects of omega-3 fatty acids on restenosis in randomized trials (approximately 3 months to 1 year)

Author, Year	Omega-3 Fatty Acid Arm [a]				Control		Results [b]			Quality [c]			Applicability [d]
	N	Source		g/d	N	Source	CR (%)	RR [e]	(95% CI)	Summary	Jadad	Allocation Conceal	
	DHA/EPA Oils												
Reis, 1989 [f]	124	Fish oil	T	6.0	63	Olive oil	22	1.60	(0.95, 2.68)	B	2	Un	CVD I
Cairns, 1996	312	Fish oil	ED	5.4	313	Corn oil	45	1.04	(0.88, 1.23)	B	3	Un	CVD II
Dehmer, 1988	43	Fish oil	ED	5.4	39	No oil	46	0.40	(0.20, 0.82)	B	3	Un	CVD II
Johansen, 1999	196	Fish oil	ED	5.0	192	Corn oil	45	1.03	(0.82, 1.28)	A	3	Ad	CVD I
Milner, 1989 [g]	84	Fish oil	ED	4.5	99	No oil	35	0.54	(0.32, 0.90)	B	3	Un	CVD I
Bairati, 1992a	59	Fish oil	ED	4.5	60	Olive oil	48	0.63	(0.40, 1.01)	B	5	Un	CVD I
Nye, 1990	35	Fish oil	ED	3.6	34	Olive oil	30	0.38 [h]	(0.17, 0.84)	C	4	Un	CVD I
Franzen, 1993	92	Fish oil	ED	3.1	83	Olive oil	35	0.93	(0.62, 1.41)	B	5	Ad	CVD II
Grigg, 1989	52	Fish oil	ED	3.0	56	Olive/corn	31	1.09 [i]	(0.65, 1.84)	C	3	Ad	CVD I
Bellamy, 1992	60	Fish oil	ED	3.0	53	No oil	40	0.80 [j]	(0.49, 1.32)	C	3	Un	CVD I
Kaul, 1992 [k]	58	Fish oil	ED	3.0	49	No oil	27	1.23	(0.68, 2.24)	B	2	Un	CVD II
Maresta, 2002	125	Fish oil	ED	2.6 [L]	132	Olive oil	41	0.76	(0.55, 1.06)	B	3	Un	CVD I
REM MA [m]	1,240				1,173			0.86	(0.71, 1.03)				

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.
b CR = control rate (the rate of restenosis in the control arm); RR = relative risk; 95% CI = 95% confidence interval.
c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
d Applicability based on generalizability to patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for coronary stenosis. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
e Relative risk calculated based on reported data.
f Three patients refused angiography and underwent exercise tolerance test instead. Angiographic restenosis defined as >70% narrowing.
g In asymptomatic patients, restenosis defined by abnormal exercise tolerance test. In patients with symptoms, restenosis defined by either exercise tolerance tests, angiography, or both.
h Based on lesions, not subjects
i Numbers in various sections of text and graph are not consistent. Data here derived from graph. Apparently, these numbers are based on numbers of lesions, but this is unclear.
j Only percentage of patients with restenosis reported. Percentage does not exactly match number of patients reported to have had follow-up restenosis.
k In asymptomatic patients, lack of restenosis defined by normal exercise tolerance test. Patients with symptoms or abnormal exercise tolerance tests underwent angiography.
L 5.1 g for 1 month before and 1 month after PTCA, then reduced to 2.6 g for an additional 5 months.
m Random effects model meta-analysis. See Methods.

Sub-populations and Covariates

Most studies included all patients who were undergoing first PTCA, therefore with known or suspected coronary artery disease. No study restricted eligibility to patients with either diabetes or dyslipidemia. A number of studies performed multivariate analysis including diabetic, lipid, and cardiovascular variables, generally finding no association between these covariates and

restenosis in the randomized trials. Only Bairati et al. commented about the effect of multivariate analysis on the relative risk of restenosis from fish oil supplement treatment [161]. The authors reported that after controlling for history of hypertension, myocardial infarction, and diabetes, and for smoking, body mass index, angina class, degree of stenosis, location and number of stenoses, and ejection fraction, the inverse association between fish oil supplementation and restenosis was stronger and of higher statistical significance (because of a higher risk profile in the fish oil group).

Reis et al. and Kaul et al. both compared relative risk of restenosis in men and women; neither found a significant difference in effect, although both found a higher (worse) relative risk in women than in men [166,169]. In men, the relative risks of restenosis were 1.33 and 1.29, respectively, compared to 2.20 and 1.78 in women. Notably, though, these 2 studies had the lowest control rates (the rate of restenosis in the control arm, a commonly used metric to estimate the underlying severity of disease) and were the only 2 studies with relative risks substantially greater than 1.0. Interestingly, the 1 study which was restricted to men, Dehmer et al., had about the lowest relative risk of restenosis among the studies.

Dose and Source Effect

No study compared doses of fish oils and all evaluated only fish oil. Across studies, no effect is apparent based on dose of fish oil supplement.

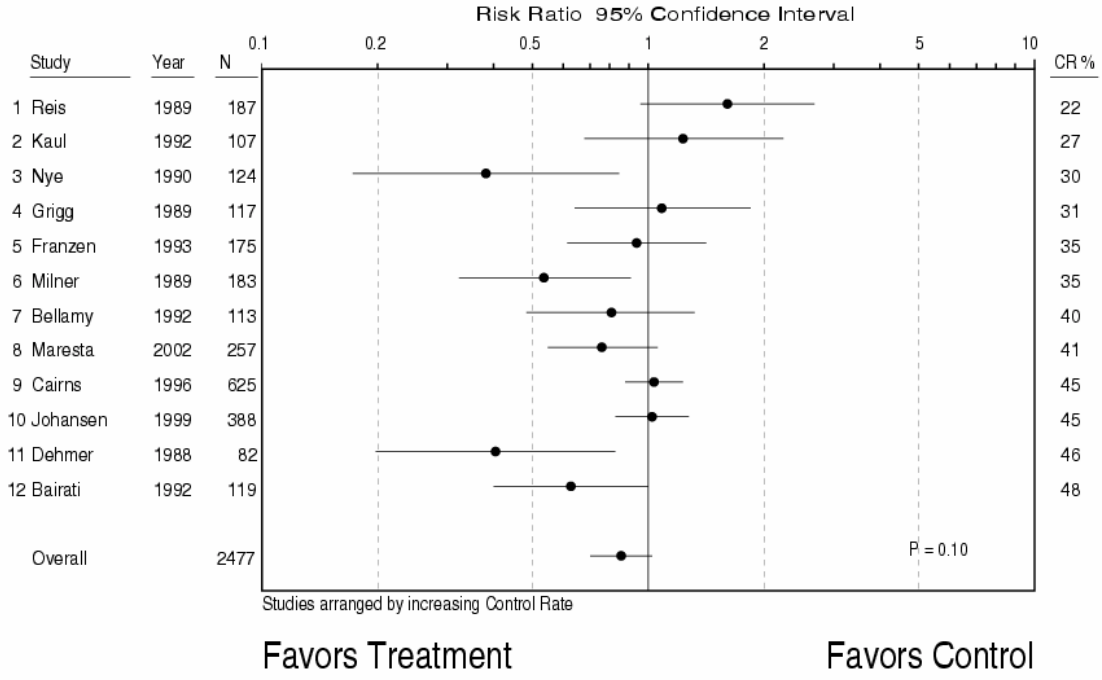
Exposure Duration

Each study evaluated restenosis at one time point only. Across studies, the duration of treatment does not appear to correlate with the relative risk of restenosis. In fact, both the longest study [168] (12 months) and the shortest study [163] (approximately 3-4 months) had similarly, low and statistically significant relative risks of restenosis.

Sustainment of Effect

No study re-evaluated for restenosis after stopping treatment.

Figure 3.3 Random effects model of effect of fish oil on coronary artery restenosis following percutaneous transluminal coronary angioplasty.



N = number of patients, except for 2 studies that reported number of lesions: Nye [168] had 35 patients on fish oil, 34 on control; Grigg [164] had 52 patients on fish oil, 56 on control. CR% = control rate, the restenosis rate in the control arm.

Carotid Intima-Media Thickness

(Table 3.22)

Ultrasound measurement of the thickness of the carotid arterial wall, termed carotid intima media thickness (IMT), has emerged as a practical technique that carries significant prognostic information in terms of future cardiovascular outcomes [170,171]. There are numerous methods of measuring carotid IMT, including using different sites and averaging different numbers of measurements. The more commonly reported methods include measurements of the common carotid artery and an average of multiple sites in the common and internal carotid arteries and the carotid bifurcation.

Four studies met eligibility criteria and reported data on the effect of omega-3 fatty acids on carotid IMT. Only one was a randomized trial of fish oil supplements. A second study reported IMT measurements only from the intervention arm of a randomized trial of ALA margarine. Two cross-sectional studies compared residents of a Japanese fishing village to a farming village and quartiles of white Americans based on ALA intake.

Table 3.22 Effects of omega-3 fatty acids on carotid intima-media thickness (mm) in studies (2 yr or cross-sectional)

Author, Year	Omega-3 Fatty Acid Arm [a] / Control Arm: N	Source		g/d	Arteries [e]	Base	Net Δ	P	Quality [c]: Summary	Jadad	Allocation Conceal	Applicability [d]
RCT												
	DHA/EPA Oils											
Angerer, 2002	87	Fish oil	ED	1.7	Overall; mean maximum	1.26	+0.02	NS	B	4	Ad	CVD II
					CCA; mean maximum	0.86	+0.02	NS				
	84	Fatty acid			CB; mean maximum	1.54	+0.03	NS				
					ICA; mean maximum	1.11	+0.02	NS				
Longitudinal Cohort (No Control)					**Pre-Post Δ**							
	Plant Oils											
Bemelmans, 2002	95	ALA margarine	A	1.7	Overall; mean	0.83	+0.05 [f]	<.01 [g]	--	--	--	CVD I
Cross-Sectional					**Cohort Δ**							
	Plant Oils											
Djousse, 2003 [h]	175	Mean total linolenic acid intake [i]	A	1.2	CCA; mean [j]	0.64	-0.06	.01 Trend	--	--	--	GEN I
	176		A	0.8		0.60	-0.10					
	174		A	0.6		0.63	-0.07					
	173		A	0.4		0.70	--					
	175	Mean total linolenic acid intake [i]	A	1.2	CB; mean [j]	0.94	-0.05	.0008 Trend				
	176		A	0.8		0.86	-0.13					
	174		A	0.6		0.91	-0.08					
	173		A	0.4		0.99	--					
	175	Mean total linolenic acid intake [i]	A	1.2	ICA; mean [j]	0.71	-0.01	NS Trend				
	176		A	0.8		0.70	-0.02					
	174		A	0.6		0.70	-0.02					
	173		A	0.4		0.72	--					
	Fish and Mediterranean Diets											
Yamada, 1997	248	Fishing village	F	146	CCA; mean	0.70	-0.03	<.05	--	--	--	GEN II
	197	Farming village	F	84		0.73	--					

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; F = Fish; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Pre-Post Δ = change in omega-3 fatty acid arm (no control); Cohort Δ = difference in IMT between cohort and reference cohort (cross-sectional); *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

e CB, Carotid bifurcation; CCA, Common carotid artery; ICA, Internal carotid artery.

f Change from baseline.

g Compared to baseline.

h The N's represent the number of subjects with baseline data. The numbers of subjects with each measurement of arteries' IMTs were not recorded. The range of number of arteries measured is 181-348 across arteries.

i By staff-administered semi-quantitative food-frequency questionnaire.

j Mean values adjusted for sex, age, energy, waist-to-hip ratio, field center, and smoking status.

Overall Effect [51,79,172,173]

The only placebo-controlled randomized trial found small, non-significant net thickening of carotid IMT, using 4 different measurements at 24 months, with fish oil supplementation. The uncontrolled cohort of subjects consuming ALA margarine had a significant thickening in IMT at 2 years. However, the absolute change in IMT in this cohort of subjects was similar to the absolute change in IMT in the fish oil supplementation arm in the randomized trial (an absolute increase of between 0.05 mm and 0.11 mm in the study by Angerer et al.) [79,172]. The cross-sectional studies both found that people with greater dietary intake of omega-3 fatty acids, either as total linolenic acid or as fish, had significantly thinner IMTs than those with less intake.

Sub-populations and Covariates

Other than study design, the primary difference between the studies that found no effect and the studies that found a beneficial effect of omega-3 fatty acids is that the former were both trials in patients with cardiovascular disease and the latter were both studies of generally healthy individuals. There is insufficient data, however, to conclude that the differences were due to study populations. There is no evidence among people with diabetes or hyperlipidemia. Bemelmans et al. performed a regression analysis of predictors of change in IMT among subjects taking ALA margarine [172]. Age, sex, blood pressure, LDL, and weight were not predictive of change in IMT. In addition, change in intake of polyunsaturated fatty acids, cholesterol and alcohol were not predictive of change in IMT. Change in intake of saturated fatty acids (SFA) was positively associated, and change in intake of fruit was negatively associated, with change in IMT in univariate analysis but not in multivariate analysis (although it is not clear what factors were included in multivariate analysis since none was significant).

In the cross-sectional study, IMT was greater in older than younger subjects in both the fishing and farming villages. Among younger villagers, IMT was non-significantly lower in the fishing village than the farming village; however, in subjects in their seventh and eighth decades IMT was marginally greater in the fishing village.

Dose and Source Effect, Exposure Duration, Sustainment of Effect

There are insufficient data to draw conclusions regarding dose effect, oil type, duration of intervention or exposure, or sustainment of effect after stopping omega-3 fatty acids.

Exercise Tolerance Test

(Table 3.23)

The exercise tolerance test (ETT), or stress test, measures the heart's aerobic exercise capacity and is a common test to determine clinical severity of coronary artery disease. The standard method of performing ETT is with the modified Bruce protocol on a treadmill. Some studies instead used a bicycle ergometer. A wide range of different metrics are used to measure patients' performance.

All eligible studies that reported data on the effect of omega-3 fatty acids on ETT were included; 6 studies qualified. Three were randomized trials and 3 were longitudinal cohort studies without control arms of subjects with known coronary artery disease who were treated with fish oil supplements.

Table 3.23 Effects of omega-3 fatty acids on treadmill and bicycle exercise tolerance tests in studies (6 weeks-6 months)

Author, Year	Omega-3 Fatty Acid Arm [a] / Control Arm: Source	g/d	N	Results [b]: Test	Base	Net Δ	P	Quality [c]: Summary	Jadad	Allocation Conceal	Applicability [d]
	DHA/EPA Oils										
RCTs											
Solomon, 1990	Fish oil	ED 4.6	5	Work load producing angina, kwatt-sec	18.87	-1.47	NS	B	4	Un	CVD II
	Olive oil		5								
Franzen, 1993	Fish oil	ED 3.1	92	Exercise capacity, kwatt-sec	29	+5.2	NS	B	5	Ad	CVD II
	Olive oil		83	Sum ST depression, mV	2.0	-0.2	nd				
Salachas, 1994	Fish oil	ED 3.0	20	Exercise duration, min	8.2	+1.7	<.05	B	4	Un	CVD II
	Olive oil		19	Maximum double product [e]	16.5	+6.2	<.05				
Longitudinal Cohorts (No Control)					**Pre-Post Δ**						
Warren, 1988	Cod liver oil	E 3.1	7	Peak exercise RPP [f]	18,800	+300	NS	--	--	--	CVD II
			7	Ratio resting/exercise RPP [f]	0.45	-0.08	<.05				
			6	Time to ischemia, min	7.6	+0.9	NS				
Verheugt, 1986	Fish oil	ED 3.0	5	Exercise duration, min	6.8	-0.2	NS	--	--	--	CVD I
				Max ST depression, mm	2.6	+0.2	NS				
Toth, 1995	Fish oil	T 1.7	10	Peak exercise TPR [g]	730 [h]	-40 [h]	<.01	--	--	--	CVD DysLip II
				Peak exercise Cardiac Index [i]	6.3 [h]	+1.0 [h]	<.05				
				Relative aerobic capacity, %	70 [h]	+10 [h]	<.01				
				ST score	1.2 [h]	-0.4 [h]	<.05				

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; F = Fish; T = Total omega-3 fatty acids.

b Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Pre-Post Δ = change in omega-3 fatty acid arm (no control); *P* = *P* value of difference; NS = not statistically significant.
c A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
d CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
e Maximum heart rate x maximum systolic pressure; likely divided by 1000
f Rate-pressure product; equivalent to work load.
g Total peripheral resistance during exercise, measured using impedance-cardiography.
h Estimated from graph.
i Cardiac index during exercise, measured using impedance-cardiography.

Overall Effect [64,174-178]

The 3 randomized trials each found a small relative improvement in exercise capacity in subjects with coronary artery disease who took fish oil supplements compared to those who took olive oil supplements. However, with a single exception, exercise capacity measurements improved in all study arms, regardless of whether subjects consumed fish oil or olive oil supplements. The maximum double product (heart rate multiplied by blood pressure) fell by a non-significant amount in the olive oil arm in Salachas et al. [174].

Warren et al. evaluated 7 patients with stable angina who took cod liver oil supplements for 6 weeks [178]. Exercise workload and time to ischemia improved, although the changes were not significant. The ratio of resting to exercise workload fell significantly. Verheugt et al. studied 5 men with moderate to severe exercise-induced angina [177]. They were given fish oil for 6 months. The patients' angina was sufficiently severe that all ETTs both before and after treatment were discontinued because of angina symptoms. Essentially no change was found in either exercise duration or maximal ST depression. Toth et al. enrolled 10 men with coronary artery disease and hyperlipidemia [176]. They fish oil supplements for 2 months. A variety of measures of cardiac function significantly improved.

Overall, given the small number of studies and subjects, the different metrics used across studies, and the lack of placebo control in half the studies, only limited conclusions can be drawn about the effect of omega-3 fatty acids in improving cardiac function in patients with coronary artery disease. The studies suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small.

Sub-populations, Dose Effect, Duration, Sustainment of Effect

There is no evidence regarding different doses, duration of fish oil consumption, other omega-3 fatty acids, the effect in various sub-populations, or sustainment of effect.

Heart Rate Variability

(Table 3.24)

Heart rate variability is measured on 24-hour ambulatory electrocardiography recordings. A number of different measurements can be used to estimate heart rate variability. The studies of omega-3 fatty acids primarily measured the mean standard deviation (SD) of the RR interval (the time between heart beats). Abnormal QRS complexes were excluded. The larger the SD of the RR interval (SDNN), the greater the variability of the time between heart beats. An increase in SDNN is protective against ventricular arrhythmias and, in post-myocardial infarction patients, is protective against mortality [179,180]. Notably, both beta blockers and angiotensin converting enzyme inhibitors both increase heart rate variability [179].

Only one set of investigators, in Denmark, have reported data on the effect of omega-3 fatty acids on heart rate variability in studies that met eligibility criteria. They analyzed 2 sets of subjects in randomized trials and also analyzed the cross-sectional data of one of the sets of subjects.

Table 3.24 Effects of omega-3 fatty acids on heart rate variability – SD of RR (msec) – in studies (12 weeks or cross-sectional) [a]

Author, Year	Omega-3 Fatty Acid Arm [b]				Control		Results [c]			Quality [d]				Applicability [e]
	N	Source	g/d		N	Source	Base	Net Δ	*P*	Summary	Jadad	Allocation Conceal		
RCTs														
	DHA/EPA Oils													
Christensen, 1999	20	Fish oil	ED	5.9	20	Olive oil	136	+13	NS	B	4	Un	GEN	II
	20	Fish oil	ED	1.7			164	+3	NS					
Christensen, 1996	26	Fish oil	ED	4.3	23	Olive oil	115	+18	<.05	B	4	Ad	CVD	III
Cross-sectional			**Frequency**				**Cohort Δ**							
	Fish and Mediterranean Diets													
Christensen, 1997 [f]	18	Fish diet	≥2x/wk		9	No fish	119	+16 [g]	NS	--	--	--	CVD	III
	25	Fish diet	1x/wk				122	+19 [g]	NS					

a Standard deviation of RR intervals on 24 hour ambulatory electrocardiography recordings.

b A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = Total omega-3 fatty acids.

c Base = baseline level in treatment arm; Net Δ = net difference in change in omega-3 fatty acids arm compared with the change in control arm, see Methods; Cohort Δ = difference in IMT between cohort and reference cohort (cross-sectional); *P* = *P* value of difference between treatment and control arms; NS = not statistically significant.

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Cross-sectional evaluation of baseline data from Christensen, 1996.

g Difference between fish cohort and no-fish cohort.

Overall Effect [181-183]

One randomized controlled trial was performed in 60 healthy volunteers who took either low or high dose fish oil supplements, or olive oil capsules for 12 weeks [183]. No significant effect was

found either within study arms or compared to olive oil. The authors concluded that among all subjects, fish oil supplementation had no effect on heart rate variability.

In a randomized trial of 49 patients who had had a recent myocardial infarction and had a ventricular ejection fraction below 0.40 those who consumed fish oil supplements (for 12 weeks) had a significant increase in SDNN compared to controls [181]. The authors concluded that omega-3 fatty acids may increase heart rate variability in survivors of myocardial infarction which may be protective against ventricular arrhythmias and mortality.

The same patients with recent myocardial infarction were divided at baseline into 3 groups based on their regular level of fish consumption [182]. Both groups who consumed at least 1 fish meal per week had greater SDNN than those who did not consume fish, though the difference was not statistically significant. This finding may suggest that dietary fish consumption increases SDNN and thus is protective against ventricular arrhythmia.

Sub-populations and Covariates

Neither study directly compared healthy subjects with those with CVD. Neither examined subjects with either diabetes or dyslipidemia. While the effect of fish oil supplementation appeared greater in the study of subjects with recent myocardial infarction, there is insufficient evidence to compare the effect in subjects with or without heart disease.

In the study of healthy subjects, sub-group analyses based on sex and baseline SDNN suggested that the effect of fish oil supplementation was greatest in the 18 men with below median (<150 msec) baseline SDNN. However, data were not reported for the other 3 subgroups (women and those with above median SDNN).

Dose and Source Effect and Exposure Duration

The study among healthy subjects compared low and high dose fish oil supplementation. While it appears that there may be a trend toward increasing SDNN with higher dose fish oil, it is noteworthy that the subjects on high dose fish oil had no change in their SDNN while those on olive oil had a decrease in SDNN. Both trials lasted 12 weeks. There is no evidence regarding the effect of duration of intervention or exposure.

Sustainment of Effect

Neither study re-examined subjects after stopping fish oil supplementation.

Tissue Levels of Dietary Omega-3 Fatty Acids

(Tables 3.25-3.31, Figures 3.4-3.6 [Figures at end of Tissue Levels section])

As noted in Chapter 1, in theory, the most immediate outcome related to omega-3 fatty acid intake is a change in tissue levels of the fatty acids. In this section, we review studies that examined the correlation between omega-3 fatty acid intake and tissue levels. Among studies analyzed for other outcomes, we found 60 studies that reported data on the association between omega-3 fatty acid consumption and changes in omega-3 fatty acid composition in various tissues. Of these, we analyzed the 33 largest randomized trials that reported percent phospholipid

levels in either plasma or serum or in 1 of 4 blood cell membranes (Table 3.25). For plasma and serum phospholipid composition and for platelet phospholipid composition we analyzed randomized trials with data on at least 25 subjects and crossover trials with at least 20 subjects in omega-3 treatment arms. Because few studies reported erythrocyte, granulocyte, or monocyte membrane phospholipid compositions, we analyzed all eligible randomized trials.

Summary (Table 3.26)

Meta-regression revealed direct relationships between dose of consumed EPA+DHA and changes in measured levels of EPA and DHA, either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membranes. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA is associated with, approximately, a 1% increase in EPA+DHA level. Granulocyte and monocyte membrane phospholipid levels also increased by roughly similar amounts after omega-3 fatty acid supplementation in individual studies. In these studies, ALA level did not change significantly after supplementation in any blood marker. In most studies, there was a decrease in arachidonic acid (AA, 20:4 n-6) level, which corresponded to the increase in EPA+DHA level.

Among eligible studies, only 3 included ALA supplementation arms [53,143,160]. The dose of ALA in these 3 studies ranged from 4.5 to 9.5 g/d. The studies consistently found an increase in both ALA and EPA levels in the blood markers, at these doses of ALA. In contrast, there was no significant change in DHA level when lower dose of ALA was used (up to 6.8 g/d) but in the study arm that received 9.5 g/d ALA a significant increase in DHA level was also found.

Table 3.25. Studies reporting plasma/serum, platelet, erythrocyte, and other phospholipid changes

Study	Study Design	N [a]	Plasma or Serum PL	Platelet PL	RBC PL	Granulocyte PL	Monocyte PL
Agren, 1988	RCT	29		√	√		
Agren, 1991	RCT	49		√	√		
Agren, 1996	RCT	41	√				
Angerer, 2002	RCT	87			√		
Bonaa, 1992	RCT	72	√				
Brox, 2001	RCT	80	√				
Cobiac, 1991	RCT	25	√				
Dehmer, 1988	RCT	43		√			
Dunstan, 1997	RCT	26		√ [b]			
Dunstan, 1999	RCT	26			√ [b]		
Finnegan, 2003	RCT	116	√ [c]				
Freese, 1997b	RCT	29		√ [c]			
Green, 1990	Crossover	27	√	√	√		
Grimsgaard, 1997	RCT	147	√				
Grundt, 1995	RCT	28	√				
Haines, 1986	RCT	19			√		
Hansen, 1989	Crossover	40	√				√
Hansen, 1993b	Crossover	34	√				
Hendra, 1990	RCT	37		√			
Leigh-Firbank, 2002	Crossover	55		√			
Luo, 1998	Crossover	10			√		
Madsen, 2003	RCT	40		√		√	
McVeigh, 1993	Crossover	23		√			
Mori, 1994	RCT	85		√			
Mori, 1999	RCT	27	√ [b]				
Mori, 2000	RCT	36	√	√			

Nenseter, 2000	RCT	34	√		
Osterud, 1995	RCT	106	√		
Rivellese, 1996	RCT	8			√
Sacks, 1994	RCT	60	√		
Solomon, 1990	RCT	5			√
Wensing, 1999	RCT	27			√ [c]
Woodman, 2002	RCT	35	√		

PL = phospholipids; RBC = red blood cell (erythrocyte); RCT = randomized controlled trial.

a Subjects consuming omega-3 fatty acids.

b Study reported total omega-3 fatty acids only. Not in the meta-regression analyses.

c Study included an ALA treatment arm.

Table 3.26. Association of EPA+DHA consumption and tissue levels. Meta-Regression Results

Markers	Studies	Arms [a]	Slope	SE [b] of Slope	Intercept	r^2	*P* value
Plasma or serum phospholipids	15	28	0.93	0.20	1.41	0.45	<.001
Excluding studies with incomplete data [c]	12	24	1.24	0.20	0.89	0.63	<.001
Platelet phospholipids	12	20	0.74	0.16	1.16	0.52	<.001
Excluding studies with incomplete data [d]	10	18	0.80	0.12	1.25	0.72	<.001
Erythrocyte membrane	10	13	0.63	0.40	3.22	0.11	.14
Excluding studies with incomplete data [e]	9	12	1.05	0.37	2.69	0.39	.02
Granulocyte membrane	1	2	--				
Monocyte membrane	1	1	--				

a Number of separate study arms of subjects who consumed omega-3 fatty acids.

b Standard error. Use number of treatment arms to back-calculate standard deviation.

c Hansen, 1989 [146]; Hansen, 1993b [157]; Green, 1990 [101]; Sacks, 1994 [75] were excluded because only change of EPA in the marker's phospholipid profile was reported.

d Green, 1990 [101]; Hendra, 1990 [116] were excluded because only change of EPA in the marker's phospholipid profile was reported.

e Green, 1990 [101] was excluded because only the change of EPA in the marker's phospholipid profile was reported.

Plasma or Serum Phospholipid Composition [48,53,62,66,74,90,97,100,101,120,129,131,132,146,157,184] (Table 3.27, Figure 3.4)

EPA/DHA. For plasma and serum phospholipid composition, 16 randomized trials with 30 omega-3 fatty acid arms were initially included; however, we excluded 1 study that reported only total omega-3 fatty acid dose and levels [131]. Among the 15 trials of EPA and/or DHA supplementation (which had 28 treatment arms), the dose of EPA+DHA ranged from 0.2 to 5.8 g/day. Study populations include general healthy population, and people with diabetes, dyslipidemia or cardiovascular diseases. Meta-regression shows a significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA+DHA compositions in plasma or serum phospholipids across studies. Across studies, the effect was similar regardless of source of EPA or DHA. Three studies compared purified EPA to purified DHA [66,120,132]. All found that purified EPA increased EPA and decreased DHA in plasma phospholipid and that purified DHA increased DHA by about 4 to 7 times as much as EPA in plasma phospholipid; however, combined EPA+DHA was increased by about the same amount by both fatty acids.

Meta-regression equation ($r^2 = 0.45$, $P < .001$):

Change in Plasma/Serum EPA+DHA Level (%) = 0.93 x [EPA+DHA Intake (g/day)] + 1.41

Because 4 studies reported only EPA levels, we re-analyzed the data with only the 12 studies with a complete EPA and DHA profile of plasma/serum phospholipids. As expected, since no study excluded DHA levels, the revised meta-regression equation indicates that the EPA+DHA level increases by a greater amount for each unit of omega-3 fatty acid supplementation and the r^2 was greater than in the meta-regression that included all studies.

Meta-regression equation ($r^2 = 0.63$, $P < .001$):

Change in Plasma/Serum EPA+DHA Level (%) = 1.24 x [EPA+DHA Intake (g/day)] + 0.89

ALA. One study also evaluated 2 linseed/rapeseed oil supplementation doses, which included primarily ALA with minimal EPA and DHA [53]. Finnegan et al. found that with higher dose ALA (9.5 g/d), EPA, DHA and ALA levels all significantly increased. With lower dose ALA (4.5 g/d), EPA and ALA levels rose by a degree consistent with the lower dose of omega-fatty acids; although DHA levels did not change. In the remaining study arms of fish oils and sunflower oils, small amounts of ALA (<= 1.5 g/d) did not affect ALA levels. In this study, a daily dose of 9.5 g or 4.5 g ALA (with 0.3 g EPA+DHA) had similar effects on plasma EPA levels as a daily dose of 1.7 g or 0.8 g EPA+DHA (with 1.4 g ALA), respectively. The plasma level of AA did not decrease in either ALA arm.

Table 3.27 Effect of omega-3 fatty acid supplementation on fatty acid profile of serum/plasma phospholipids in randomized trials (6 weeks to 14 months)

Study, Year	Omega-3 Fatty Acid Arms [a]				Base ED (%) [b]	Results (Δ%) [c]				Quality [d]				
	Control Arm													
	N	Source		g/d		AA [f]	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	Applicability [e]	
		EPA/DHA Oils												
Bonaa, 1992	72	Fish oil	ED	5.1	11.8	-1.00	0.00	+5.10	+1.70	B	4	Un	DysLip	I
	74	Corn oil	ED	0	11.5	+0.60	+0.10	-0.20	-0.20					
Green, 1990	27 [g]	Fish oil	ED	4.3	nd	0.00		+2.60		B	4	Un	DysLip	II
		Corn/Olive oil	ED	0	nd	nd		nd						
Grimsgaard, 1997	75	EPA ester	E	4.0	6.0	-0.98	-0.05	+4.65	-0.55	A	5	Un	GEN	I
	72	DHA ester	D	4.0	6.0	-0.82	-0.02	+0.47	+3.30					
	77	Corn oil	ED	0	6.2	+0.11	+0.01	-0.06	-0.10					
Mori, 2000	19	Purified EPA	E	4.0	nd	-3.00		+8.25	-0.25	B	4	Un	DysLip	II
	17	Purified DHA	D	4.0	nd	-2.25		+1.00	+7.25					
	20	Olive oil	ED	0	nd	+0.10		-0.10	+0.50					
Woodman, 2002	17	Purified EPA	E	4.0	5.9			+8.64	-1.29	B	3	Un	DM II	II
	18	Purified DHA	D	4.0	6.0			+1.09	+6.71					
	16	Olive oil	ED	0	6.8			nd	nd					
Grundt, 1995	28	Fish oil	ED	3.4	nd	-0.60		+3.80	+1.50	B	2	Un	DysLip	II
	28	Corn oil	ED	0	nd	-0.30		-0.50	-0.40					
Brox, 2001	40	Cod liver oil	ED	3.3	5.2	-0.34	-0.39	+1.27	+1.49	C	1	Un	DysLip	I
	40	Seal oil	ED	2.6	4.8	+0.14	-0.35	+2.61	+1.81					
	36	No oil	ED	0	5.1	+0.26	+0.91	+0.04	+0.81					
Osterud, 1995 [h]	26	Cod liver oil	ED A	3.1 0.2	nd	-0.25	-0.09	+2.36	+1.51	C	2	Un	GEN	I
	27	Seal/Cod liver oil	ED A	2.8 0.2	nd	-0.30	-0.04	+2.66	+1.85					
	27	Seal oil	ED A	2.4 0.2	nd	-0.20	-0.07	+2.01	+1.29					

Study, Year	Omega-3 Fatty Acid Arms [a] Control Arm N	Source	g/d	Base ED (%) [b]	Results (Δ%) [c] AA [f]	ALA	EPA	DHA	Quality [d] Summary	Jadad	Allocation Conceal	Applicability [e]	
	26	Whale oil	ED 1.7 A 0.2	nd	-0.15	-0.06	+1.14	+0.74					
	28	No oil	ED 0	nd	nd	nd	nd	nd					
Hansen, 1989	40 [g]	Cod liver oil	ED 5.8	nd	-0.70		+4.10		C	1	Un	GEN	I
		No oil	ED 0	nd	+0.10		0.00						
Hansen, 1993b	34 [g]	Cod liver oil	ED 5.3	nd			+5.44		B	1	Un	GEN	II
		No oil	ED 0	nd			nd						
Sacks, 1994	60	Fish oil	ED 2.4	nd			+2.95		C	3	Un	CVD	I
	60	Olive oil	ED 0	nd			+0.10						
Nenseter, 2000	34	Fish powder	ED 0.2	5.4	+0.20	-0.10	+0.20	+0.20	B	3	Un	GEN	II
	36	Cellulose	ED 0	6.1	+0.30	+0.10	-0.30	0.00					
	Fish Diets												
Mori, 1999	13	Fish & WMD [i]	T 3.7	nd	Total n-3 fatty acids: +6.0				B	2	Un	GEN	II
	16	WMD [i]	T nd	nd	Total n-3 fatty acids: -1.5								
	14	Fish & ERD [j]	T 3.7	nd	Total n-3 fatty acids: +5.0								
	16	ERD [j]	T nd	nd	Total n-3 fatty acids: -1.0								
	Combinations												
Cobiac, 1991	13	Fish oil	ED 4.6	2.5	-0.10	0.00	+5.80	+3.10	B	2	Un	GEN	II
	12	Fish [k]	ED 4.5	2.5	-0.70	+0.20	+3.10	+3.50					
	6	No oil	ED 0	2.4	+0.60	+0.10	-0.20	-0.20					
Agren, 1996	14	Fish oil	ED 2.3	nd			+4.00	+2.20	B	3	Un	GEN	III
	14	Algae DHA oil	D 1.7	nd			+0.50	+3.10					
	13	Fish [k]	ED 1.1	nd			+1.50	+1.50					
	14	No oil	ED 0	nd			-0.10	0.00					
Finnegan, 2003	28	Fish oil margarine and Fish oil	ED 1.7 A 1.4	5.02	-0.56	-0.07	+1.13	+2.71	A	4	Un	DysLip	I
	30	Fish oil margarine	ED 0.8 A 1.3	4.41	+0.44	-0.08	+0.80	+1.61					
	29	Rapeseed/Linseed margarine	ED 0.3 A 9.5	4.38	+0.53	+0.46	+1.22	+0.21					
	29	Rapeseed/Linseed margarine	ED 0.3 A 4.5	5.34	+0.74	+0.15	+0.95	-0.13					
	30	Sunflower seed oil margarine	ED 0.5 A 1.5	5.47	+0.64	-0.05	+0.28	-0.08					

nd = no data; n-3 = omega-3;

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.

b Baseline EPA + DHA profile (% of total fatty acids) of plasma/serum phospholipids.

c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Arachidonic acid (20:4 n-6)

g Cross-over study.

h Differences are from the control after 10-week treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.

i Weight-maintaining diet.

j Energy-restricted diet.

k Chemically analyzed.

Platelet Phospholipid Composition [68,71,95,96,101,116,122,123,132,137,143,163]

(Table 3.28, Figure 3.5)

EPA/DHA. For platelet phospholipid composition, we analyzed 12 randomized trials with 21 omega-3 fatty acid arms. All of these studies evaluated EPA and/or DHA supplementation. One treatment arm was ALA; therefore, there were 20 EPA and/or DHA treatment arms. The dose of EPA+DHA ranged from 0.8 to 5.9 g/day. Study populations include general healthy population and people with diabetes, dyslipidemia, or cardiovascular diseases. Meta-regression results show a significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA+DHA compositions in platelet phospholipids across studies. Studies that used fish or fish combined with fish oil supplement treatments generally had greater increases in platelet phospholipid EPA+DHA amounts than studies of fish oil supplements. This effect was seen in Mori, et al. (1994), which compared fish, fish oil supplements, and combination fish and fish oil [71]. They reported that the largest increase in DHA occurred in the groups consuming fish. In contrast to the finding in plasma phospholipids, Mori et al. (2000) reported that platelet EPA+DHA levels rose more in subjects taking DHA than in subjects taking EPA, although it is not reported whether this difference is statistically significant [132].

Meta-regression equation ($r^2 = 0.52$, $P < .001$):

Change in Platelet EPA+DHA Level (%) = 0.74 x [EPA+DHA Intake (g/day)] + 1.16

As was the case for plasma/serum phospholipid levels, the re-analysis of the platelet phospholipid data that excluded the 2 studies without a complete EPA and DHA profile indicates a larger increase in EPA+DHA level and a larger r^2 than in the complete meta-regression.

Meta-regression equation ($r^2 = 0.72$, $P < .001$):

Change in Platelet EPA+DHA Level (%) = 0.80 x [EPA+DHA Intake (g/day)] + 1.25

ALA. One study also evaluated linseed oil supplementation, which included only ALA without EPA or DHA [143]. Freese et al. found that a 5.9 g/d ALA supplementation significantly increased EPA and ALA platelet phospholipid levels. However, the effect on EPA levels was small in comparison to the effect of a similar dose of fish oil (+0.41% vs. +3.32% for 5.2 g/d EPA+DHA). In addition, DHA levels were unaffected. The AA level decreased in the ALA arm.

Table 3.28 Effect of omega-3 fatty acid supplementation on fatty acid profile of platelet phospholipids in randomized trials (6 weeks to 4 months)

Study, Year	Omega-3 Fatty Acid Arms [a]				Base ED (%) [b]	Results (Δ%) [c]				Quality [d]			Applicability [e]	
	Control Arm													
	N	Source		g/d		AA [f]	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal		
		EPA/DHA Oils												
Madsen, 2003	20	Fish oil	ED	5.9	3.6	-4.49	-0.03	+3.82	+0.92	B	3	Un	GEN	I
	20	Fish oil	ED	1.7	3.2	-1.97	+0.01	+1.27	+0.36					
	20	Olive oil	ED	0	3.2	+0.19	+0.01	+0.01	-0.06					
Dehmer, 1988	43	Fish oil	ED	5.4	0.6	-2.50		+3.66	+2.30	B	3	Un	CVD	III
	39	No oil	ED	0	nd	nd		nd	nd					
Green, 1990	27 [g]	Fish oil	ED	4.3	nd	-0.50		+1.90		B	4	Un	DysLip	II
		Corn/Olive oil	ED	0	nd	nd		nd						
Mori, 2000	19	Purified EPA	E	4.0	nd	-4.80		+3.80	-0.60	B	4	Un	DysLip	II
	17	Purified DHA	D	4.0	nd	-2.40		+0.60	+4.20					
	20	Olive oil	ED	0	nd	-0.60		+0.05	+0.10					
Leigh-Firbank, 2002	55 [g]	Fish oil	ED	3.0	3.3	+2.90		+2.60	+1.11	B	3	Un	DysLip	I
		Olive oil	ED	0	3.3	+0.60		+0.20	+0.10					
McVeigh, 1993	23 [g]	Fish oil	ED	3.0	2.5	-3.00		+1.70	+2.70	A	4	Un	DM II	II
		Olive oil	ED	0	2.5	-0.40		-0.10	+0.30					
Hendra, 1990	37	Fish oil	ED	3.0	nd			+1.75		B	4	Un	DM II	I
	37	Olive oil	ED	0	nd			-0.02						
		Fish Diets												
Dunstan, 1997	26	Fish and exercise	T	3.6	nd	Total n-6: -5.80		EPA+DPA+DHA: +4.80		B	2	Un	NIDDM DysLip	I
	23	No fish and exercise	T	nd	nd	nd		nd						
Agren, 1988	14	Fish	ED	0.8	4.5	-2.1	+0.10	+1.20	+1.20	B	3	Un	GEN	III
	15	Fish and low SFA [h]	ED	0.8	4.4	-2.6	+0.10	+0.80	+1.30					
	19	Control diet	ED	0.05	nd	nd	nd	nd	nd					
Agren, 1991	22	Fish	ED	0.8	3.8	-1.30		+0.70	+0.70	B	2	Un	GEN	III
	23	Control diet	ED	0.1	3.7	-0.10		0.00	0.00					
	27	Fish and exercise	ED	0.8	3.6	-0.90		+0.70	+0.70					
	27	Control diet and exercise	ED	0.1	3.8	+0.10		0.00	0.00					
		Combinations												
Freese, 1997b	14	Fish oil	ED A	5.2 0.1	5.2 [i]	-3.35	-0.21	+3.32 [i]	+0.88	C	3	Un	GEN	II
	15	Linseed oil	ED A	0 5.9	4.7 [i]	-0.79	+0.39	+0.41 [i]	-0.14					
Mori, 1994	16	Fish [j] and Fish oil (40% [k])	ED	5.2	5.2	-5.00		+3.75	+2.50	B	2	Un	GEN	II
	17	Fish oil (40% [k])	ED	4.2	5.2	-4.75		+3.25	+1.50					
	17	Fish [j] (40% [k])	ED	3.0	5.2	-3.75		+2.50	+2.50					
	17	Fish oil (40% [k])	ED	2.1	5.2	-1.50		+1.60	+0.50					
	18	Control [L] oils (40% [k])	ED	nd	5.2	+0.75		-0.05	-0.40					
	18	Fish [j] (40% [k])	ED	3.0	5.2	-4.00		+2.30	+2.50					
	17	Control [L] oils (40% [k])	ED	nd	5.2	-0.40		-0.20	-0.50					

nd = no data; n-6 = omega-6

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.

b Baseline EPA + DHA profile (% of total fatty acids) of platelet phospholipids.

c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Arachidonic acid (20:4 n-6)

g Crossover study.

h Low saturated fatty acid diet.

i Plus some 22:0.

j Chemically analyzed.

k Percent of fat in diet

L Olive/Palm/ Safflower oils

Erythrocyte Membrane Phospholipid Composition [79,88,95,96,101,115,134,141,160,175] (Table 3.29, Figure 3.6)

EPA/DHA. For erythrocyte membrane phospholipid composition, 10 randomized trials with 15 omega-3 fatty acid arms were included. All of these studies evaluated EPA and/or DHA supplementation. One study included 2 ALA treatment arms; therefore, there were 13 EPA and/or DHA treatment arms. The dose of EPA+DHA ranged from 0.8 to 4.6 g/day. Study populations include general healthy population and people with diabetes, dyslipidemia or cardiovascular diseases. Meta-regression results show no significant dose-response relationship between the dietary EPA and DHA supplementations and the changes in EPA plus DHA compositions in platelet phospholipids. No clear difference is seen in effect based on source of omega-3 fatty acids. No study compared different sources of EPA+DHA oil.

Meta-regression equation ($r^2 = 0.11$, $P = .14$):

Change in Erythrocyte EPA+DHA Level (%) = 0.63 x [EPA+DHA Intake (g/day)] + 3.22

The re-analysis of the data, excluding 1 study by Green et al. who did not report the change in DHA levels, greatly affected slope and statistical significance of the meta-regression equation [101]. The large effect of this single study can be explained by outlier status of the study. The change in EPA level reported in this study is considerably lower than the change in EPA+DHA levels in studies with similar supplementation doses.

Meta-regression equation ($r^2 = 0.39$, $P < .02$):

Change in Erythrocyte EPA+DHA Level (%) = 1.05 x [EPA+DHA Intake (g/day)] + 2.69

ALA. One study also evaluated a diet enriched in ALA and that contained no EPA or DHA among both young (16-33 years old) and old (60-78 years old) subjects [160]. Wensing et al. found that a 6.8 g/d ALA supplementation significantly increased both EPA and ALA levels but not DHA level. The effects on the changes in EPA and ALA compositions were larger among older subjects than among younger subjects. The higher dose ALA (6.8 g/d) had a smaller effect on EPA levels (+0.20% and +0.40%, for younger and older subjects, respectively) than a lower dose

of EPA+DHA (1.6 g/d, +1.30%). The AA level decreased among old subjects while it increased among young subjects.

Table 3.29 Effect of omega-3 fatty acid supplementation on fatty acid profile of red blood cell (erythrocyte) membrane/ghosts in randomized trials (6 weeks to 2 years)

Study, Year	Omega-3 Fatty Acid Arms [a]				Base ED (%) [b]	Results (Δ%) [c]				Quality [d]			Applicability [e]
	Control Arm												
	N	Source		g/d		AA [f]	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	
		EPA/DHA Oils											
Haines, 1986	19	Fish oil	ED	4.6	6.1	-2.20		+3.77	+2.23	B	2	Ad	IDDM II
	22	Olive oil	ED	0	6.1	0.00		-0.05	-0.22				
Solomon, 1990	5	Fish oil	ED	4.6	6.7	-3.44		+5.92	+2.19	B	4	Un	CVD II
	5	Olive oil	ED	0	6.4	+0.23		-0.07	-0.31				
Green, 1990	27 [g]	Fish oil	ED	4.3	nd	-2.00		+2.70		B	4	Un	DysLip II
		Corn/Olive oil	ED	0	3.6	nd		nd					
Rivellese, 1996	8	Fish oil	ED	1.97	5.8	-2.30		+1.50	+1.60	A	3	Un	DysLip NIDDM II
	8	Olive oil	ED	0.0	5.7	0.10		-0.10	-0.30				
Luo, 1998	10 [g]	Fish oil	ED	1.8	6.3			+1.44 [h]	+1.33 [h]	C	3	Un	DM II II
		Sunflower oil	ED	0	6.3			nd	nd				
Angerer, 2002	87	Fish oil	ED	1.65	nd			+2.60	+4.20	B	4	Ad	CVD II
	84	Fatty acid	ED	nd	nd			+0.10	+0.10				
		Fish Diets											
Dunstan, 1999	14	Fish and moderate exercise	T	3.6	nd	Total n-6: -4.50		EPA+DPA+DHA: +6.60		B	2	Un	NIDDM DysLip I
	11	No fish and moderate exercise	T	nd	nd	Total n-6: +0.60		EPA+DPA+DHA: 0.00					
	12	Fish and light exercise	T	3.6	nd	Total n-6: -6.7		EPA+DPA+DHA: +8.40					
	12	No fish and light exercise	T	nd	nd	nd		nd					
Agren, 1988	14	Fish	ED	0.8	8.8	-2.70	0.00	+1.30	+3.20	B	3	Un	GEN III
	15	Fish and low SFA [i]	ED	0.8	9.3	-2.40	0.00	+0.90	+2.70				
	19	Control diet	ED	0.05	nd	nd	nd	nd	nd				
Agren, 1991	22	Fish	ED	0.8	9.2	-1.30		+0.70	+1.80	B	2	Un	GEN III
	23	Control diet	ED	0.1	8.7	+0.10		0.00	-0.10				
	27	Fish and exercise	ED	0.8	8.7	-1.20		+0.80	+2.00				
	27	Control diet and exercise	ED	0.1	8.6	+0.40		0.00	-0.10				
Wensing, 1999	14	EPA+DHA	ED	1.6	4.5	-0.80	0.00	+1.30	+0.80	B	2	Un	GEN II
	13	ALA (old)	ED A	0.0 6.8	4.1	-0.70	+0.40	+0.40	-0.30				
	12	ALA (young)	ED A	0.0 6.8	4.0	+0.90	+0.20	+0.20	-0.10				
	11	Oleic acid	ED	0.0	3.8	-0.20	0.00	+0.00	+0.10				

nd = no data; n-6 = omega-6

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
b Baseline EPA + DHA profile (% of total fatty acids) of erythrocyte phospholipids.
c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).
d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
f Arachidonic acid (20:4 n-6)
g Crossover study.
h Difference from the control after 2-month treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.
i Low saturated fatty acid diet.

Granulocyte Membrane Phospholipid Composition [137] (Table 3.30)

One randomized controlled trial examined the changes of EPA+DHA composition in granulocyte membrane phospholipids after fish oil supplementation. Madsen et al. found that EPA and DHA compositions in granulocyte phospholipids significantly increased after 12 weeks of fish oil supplement treatment, while no significant changes were found in the placebo group [137]. In addition, the change in DHA profile was significantly larger in the higher-dose fish oil supplementation group than in the lower-dose fish oil group.

Table 3.30 Effect of omega-3 fatty acid supplementation on fatty acid profile of granulocyte membrane in randomized trials (12 weeks)

Study, Year	Omega-3 Fatty Acid Arms [a]			Control Arm		Base ED (%) [b]	Results (Δ%) [c]				Quality [d]				
	N	Source		g/d			AA [f]	ALA	EPA	DHA	Summary	Jadad	Allocation Conceal	Applicability [e]	
		EPA/DHA Oils													
Madsen, 2003	20	Fish oil	ED	5.9		2.2	-2.71	-0.03	+3.50	+0.57	B	3	Un	GEN	I
	20	Fish oil	ED	1.7		2.1	-1.21	0.00	+1.25	+0.29					
	20	Olive oil	ED	0		2.0	+0.03	+0.01	+0.04	-0.02					

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.
b Baseline EPA + DHA profile (% of total fatty acids) of granulocyte phospholipids.
c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).
d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.
e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.
f Arachidonic acid (20:4 n-6).

Monocyte Membrane Phospholipid Composition [146] (Table 3.31)

One crossover study examined the changes of EPA+DHA composition in monocyte phospholipids after cod-liver oil supplementation. Hansen, et al. showed the EPA profile in monocyte phospholipids significantly increased, while the arachidonic acid profile significantly decreased after 8 weeks of cod liver oil supplement treatment compared to the no treatment controls [146].

Table 3.31 Effect of omega-3 fatty acid supplementation on fatty acid profile of monocyte phospholipids in randomized trials (8 weeks)

Study, Year	Omega-3 Fatty Acid Arms [a] Control Arm N	Source	g/d	Base ED (%) [b]	Results (Δ%) [c] AA [f]	ALA	EPA	DHA	Quality [d] Summary	Jadad	Allocation Conceal	Applicability [e]
	EPA/DHA Oils											
Hansen, 1989	40 [g]	Cod liver oil	ED 5.8	nd	-4.00 [h]		+3.00 [h]		C	1	Un	GEN I
		No oil	ED 0	nd	nd		nd					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.

b Baseline EPA + DHA profile (% of total fatty acids) of monocyte phospholipids.

c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Arachidonic acid (20:4 n-6)

g Cross-over study.

h Difference from the control after 8-week treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.

Figure 3.4 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in plasma or serum phospholipids (PL)

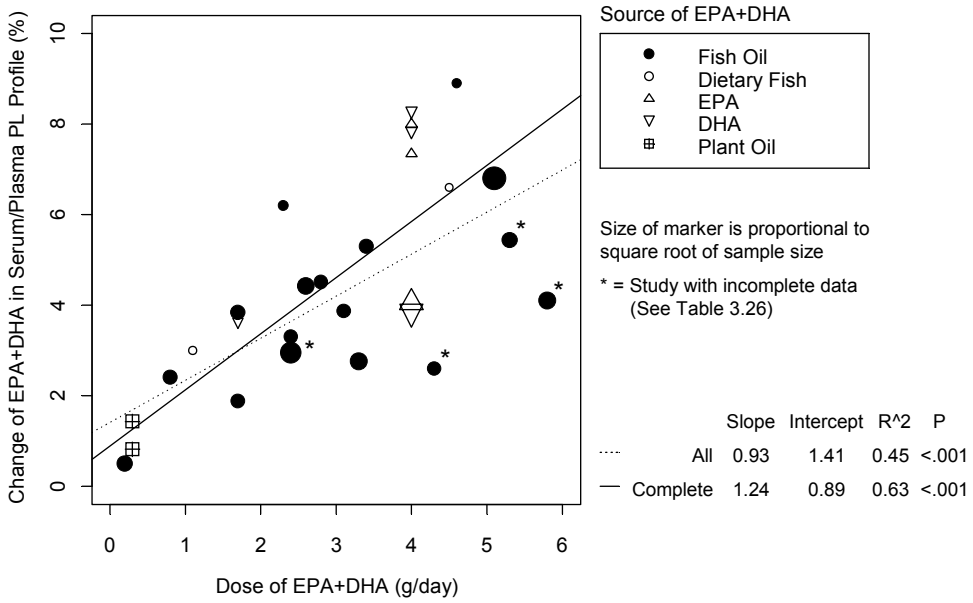


Figure 3.5 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in platelet phospholipids (PL)

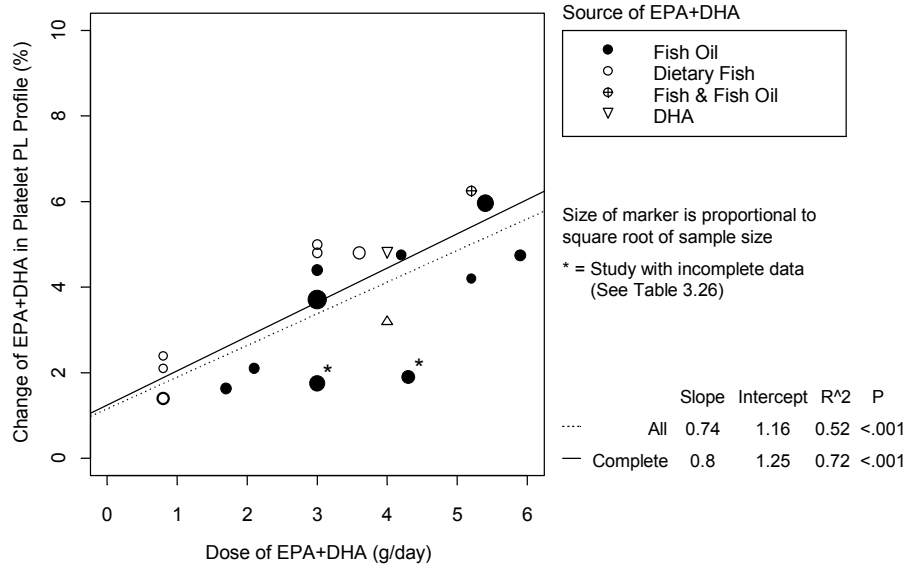
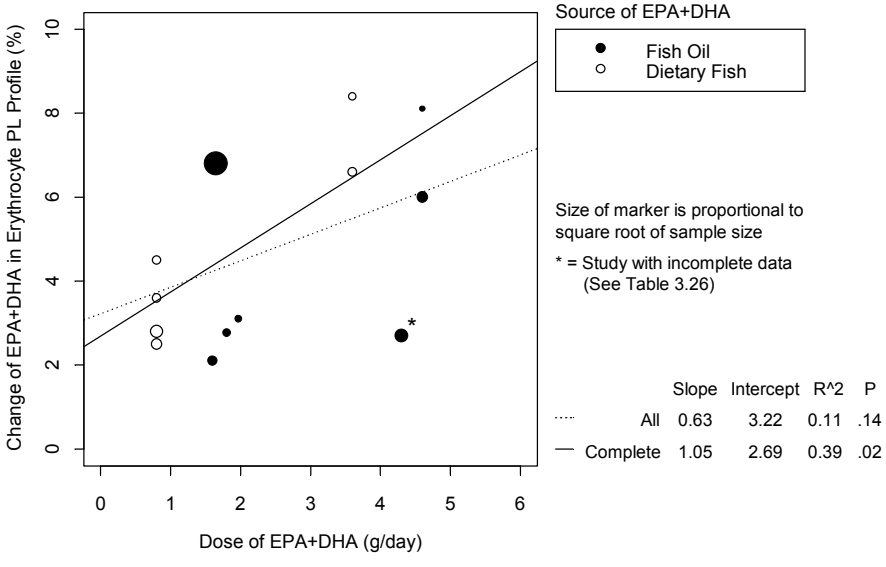


Figure 3.6 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in red blood cell (RBC, erythrocyte) membrane phospholipids (PL)



Chapter 4. Discussion

In this chapter, we summarize findings from our review of studies examining the effect of omega-3 fatty acids on cardiovascular disease (CVD) risk factors and intermediate markers of CVD, discuss limitations of our review, and offer recommendations for future research.

Overview

Through a structured literature review process, we screened over 7,464 abstracts and retrieved and screened 807 full text articles that addressed omega-3 fatty acids and CVD risk factors and intermediate markers of CVD. After narrowing the list of outcomes of interest and applying specific eligibility criteria, we analyzed 123 articles that examined the effects of eicosapentaenoic acid (EPA, 20:5 n-3), docosahexaenoic acid (DHA, 22:6 n-3), and alpha linolenic acid (ALA, 18:3 n-3) on one of the following risk factors or intermediate markers:

- Lipids (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides [Tg], lipoprotein (a), apolipoproteins [apo] A-I, B, B-100, and LDL apo B
- Blood pressure
- Measures of glucose tolerance (hemoglobin A_{1c} [Hgb A_{1c}], fasting blood sugar [FBS], and fasting insulin)
- C-reactive protein (CRP)
- Measures of hemostasis (fibrinogen, factors VII and VIII, von Willebrand factor [vWF], and platelet aggregation),
- Non-serum diagnostic tests (coronary artery restenosis – following angioplasty, carotid intima-media thickness [IMT], exercise tolerance testing [ETT], heart rate variability)
- Tissue levels of fatty acids including plasma or serum phospholipids, platelet phospholipids, erythrocyte membrane phospholipids, granulocyte membrane phospholipids, and monocyte membrane phospholipids.

For most outcomes, we analyzed only the approximately 20 to 30 largest randomized trials. The main findings from our review and analysis are summarized in the next section. While doing the review, we found that several of the key questions and sub-questions posed at the beginning of this report were not addressed by the available studies. For example, most studies that we analyzed evaluated fish or other marine oils and only a few evaluated plant oils. Furthermore, few studies compared doses of similar omega-3 fatty acids, compared different omega-3 fatty acids, reported on potential covariates such as age and sex, analyzed effects based on duration of intake, or repeated measurements after subjects had stopped omega-3 fatty acid supplementation. No study incorporated an analysis of how varying dietary omega-6 to omega-3 ratio may alter

the effect of omega-3 fatty acid consumption on outcomes. These and other limitations are addressed in more detail in the Limitations section of this chapter.

Main Findings

Overall, we found evidence that fish oils have a strong beneficial effect on Tg that is dose-dependent and similar in various populations. There is also evidence of a very small beneficial effect of fish oils on blood pressure, and possible beneficial effects on coronary artery restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and, possibly, heart rate variability, particularly in patients with recent myocardial infarctions. No consistent beneficial effect is apparent for the other CVD risk factors or intermediate markers of CVD we analyzed. In addition, there is also no consistent evidence of a detrimental effect of omega-3 fatty acids on glucose tolerance. Details on these and other key findings are summarized below.

As discussed in the accompanying report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, consumption of omega-3 fatty acids from dietary sources or from marine oil or ALA supplements reduces all cause mortality and various CVD outcomes. The cardiovascular benefits of omega-3 fatty acid consumption, though, are not well explained by the fatty acids' effects on the cardiovascular risk factors that we examined. However, the overall cardiovascular benefit may be due to the constellation of effects on lipids, blood pressure, coronary atherosclerosis, and heart rate variability. Reviewing the studies evaluated in this and the accompanying report on cardiovascular outcomes, we found no article that analyzed potential associations between omega-3 fatty acid's effect on cardiovascular risk factors and cardiovascular outcomes.

Effect on Triglycerides and Other Serum Lipids

The strongest, most consistent effect of omega-3 fatty acids was among the 19 studies of Tg. Most of these studies reported a net decrease in Tg of about 10% to 33%. The effect was dose-dependent and generally consistent among healthy subjects and patients with CVD, dyslipidemia, or at elevated risk of CVD. The effect was also greater in studies with higher mean baseline Tg. However, 1 of 2 studies of plant oils (ALA) found a net increase in Tg. Limited data suggest that the effect is not related to sex, age, weight, background diet, or lipid treatment. The effect of duration of intervention is unclear and there were no data regarding sustainment of effect. In addition, no study of diabetic patients had sufficient number of subjects to be analyzed.

The effect of omega-3 fatty acids on other serum lipids was weaker. The 23 studies of total cholesterol and the 19 studies of HDL we analyzed were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in levels of both lipids. The 15 analyzed trials of LDL were fairly uniform in finding small net increases in LDL. The effect of plant oils (ALA) on these lipoproteins was possibly weaker but similar to the effect of marine oils. No differences in effect were seen among different populations, including the diabetic subjects who were evaluated in a sub-analysis. One study found a larger net increase in total cholesterol among subjects on a higher fat diet compared to those on a lower fat diet, but this effect was not seen for other lipids. A single study of fish oil reported a steady increase in HDL levels over time beginning at 6 weeks and ending at 12 months. No other studies found an effect of time on lipids and no other covariates were reported to interact with fish oil effects on lipids.

One study compared the effect of purified EPA to purified DHA on these 4 lipids. The results were mixed. EPA lowered total cholesterol significantly (and substantially) more than DHA, DHA increased HDL by a small but significant amount more than EPA, and the effects of the 2 oils were similar in their lack of effect on LDL and their ability to lower Tg.

Effect on Blood Pressure

A recent meta-regression of the effect of fish oils on blood pressure found a small but significant reduction in both systolic and diastolic blood pressure of about 2 mm Hg. The effect was stronger in older and hypertensive populations. Because the meta-regression excluded diabetic populations, we evaluated the 6 randomized studies of diabetics and found similar results. One study reported that neither sex nor Hgb A_{1c} levels were related to the fish oil effect on blood pressure. No study analyzed plant oils. One study reported no significant difference in blood pressure effect of purified EPA compared to purified DHA.

Effect on Restenosis after Coronary Angioplasty

We performed a meta-analysis of the 12 randomized trials that reported restenosis rates after coronary angioplasty. All evaluated fish oils. We found heterogeneity of results across studies but an overall trend toward a net reduction of relative risk of 14% with fish oil intake. Two studies reported no significant difference in effect between men and women.

Effect on Exercise Capacity and Heart Rate Variability

The 6 available studies examining exercise tolerance testing suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small. Three analyses of heart rate variability in 2 study populations concluded that fish oil supplementation among patients with recent myocardial infarction, and dietary fish consumption in healthy people, improves heart rate variability, which may, in turn, reduce the incidence of ventricular arrhythmias. However, fish oil supplementation did not improve heart rate variability in the same healthy population.

Effect on Other Cardiovascular Risk Factors and Intermediate Markers

The effects of omega-3 fatty acids on the other outcomes that we evaluated were either small or inconsistent across studies.

Apolipoproteins. No consistent effect was found across 14 studies of Lp(a), although one study reported a small but significant net decrease in subjects with elevated baseline Lp(a) levels compared to those with lower baseline levels. There were insufficient studies to compare different omega-3 fatty acids. The 27 studies of apo A-I that we analyzed generally found no effect or either a small increase or decrease in level with omega-3 fatty acid consumption. Limited evidence suggested that purified EPA may decrease apo A-I levels while DHA has no effect, and that there is no difference in effect between fish oils and ALA. There was little consistency of effect in the 25 studies of total apo B. The 4 available studies of apo B-100 found

a range of effects from a 5% decrease to a 15% increase in level. Most of the 6 studies of LDL apo B found large, significant net increases in LDL apo B with omega-3 fatty acid consumption.

C-reactive protein. The 5 available studies of CRP found no effect with fish oil supplementation or dietary fish.

Measures of hemostasis. No consistent effect was found among the 24 analyzed studies of fibrinogen, the 19 analyzed studies of factor VII, or the 5 available randomized trials of factor VIII. The 9 randomized trials of vWF mostly found a small, non-significant decrease in level with omega-3 fatty acid consumption. The results among the 11 analyzed studies of platelet aggregation were heterogeneous depending on aggregating agent, dose of agent, and measurement metric used, however, generally no effect was found with omega-3 fatty acid intake. The few studies that compared types of omega-3 fatty acids found no difference in effect on these measures of hemostasis, with the exception that 2 studies came to opposite conclusions regarding whether fish oil prolonged platelet aggregation by a greater degree than ALA, and 1 study concluded that DHA may be less potent at prolonging platelet aggregation than EPA.

Carotid intima-media thickness. The 4 available studies of carotid IMT were heterogeneous. The randomized trial found no effect of fish oil but 2 cross-sectional studies found that dietary omega-3 fatty acid was correlated with thinner IMT; the cohort study of plant oil margarine was inconclusive.

Glucose tolerance. Overall, the studies of markers of glucose tolerance found no consistent effect of omega-3 fatty acids. There was a wide range of net effects of omega-3 fatty acids on fasting blood sugar across the 17 analyzed studies. Heterogeneity was present regardless of the make-up of the study population, although the range of effect was widest among diabetic patients. Within studies there were no apparent differences in effect of different omega-3 fatty acids on fasting blood sugar. Among the 18 analyzed studies of Hgb A_{1c} there was no substantial significant effect of omega-3 fatty acid consumption, regardless of study population. A single study found no difference in effect of purified EPA and purified DHA on Hgb A_{1c}. The 15 randomized trials of fasting insulin levels were very heterogeneous. Similar heterogeneity existed among the 9 studies of generally euglycemic populations as among the studies of diabetics and obese subjects. Within studies there were no apparent differences in effect of different omega-3 fatty acids on fasting insulin levels.

Tissue Levels of Fatty Acids

Meta-regression of 30 studies revealed direct relationships between dose of omega-3 fatty acids consumed and changes in measured levels of eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), either as plasma or serum phospholipids, platelet phospholipids, or erythrocyte membranes. The correlation between dose and change in level appears to be fairly uniform, where 1 g supplementation of EPA and/or DHA corresponds to approximately a 1% increase in EPA+DHA level. Granulocyte and monocyte membrane phospholipid levels also increased after omega-3 fatty acid supplementation in individual studies.

Limitations

We identified about 60 potential CVD risk factors and intermediate markers of CVD and evaluated 23 of these in this evidence report. While some of these outcomes have been demonstrated to be important risk factors for CVD or markers of CVD, it is unclear whether this is true for all. The measurement techniques for a number of the outcomes we evaluated also have not been standardized, which complicated our interpretation of individual study findings and limited our ability to compare studies. Thus, the effects of omega-3 fatty acids on various putative risk factors and intermediate markers, and the implications for risk of CVD events, are uncertain.

While we endeavored to do a complete, systematic review of the literature on the effect of omega-3 fatty acids on CVD risk factors and intermediate markers of CVD, we were unable to critically evaluate all 350 potentially eligible studies due to time and resource limitations. Nevertheless, our findings regarding the main effects of omega-3 fatty acids on the outcomes we evaluated should be valid since we analyzed the largest randomized trials. Thus, studies not included were either non-randomized studies, which would provide more biased effect estimates, or smaller trials, which, by definition, are generally less powered than the larger studies. However, excluding non-randomized studies and small trials may have affected the availability of evidence regarding many of the secondary questions related to the effect of covariates, dosage, duration, and the like. In particular, few of the studies we analyzed evaluated plant oils. However, since few of the excluded studies evaluated plant oils, broadening our inclusion criteria may not have been helpful to this area of inquiry. In addition, for several outcomes, we analyzed a minority of the potentially available studies of diabetic patients. This was particularly the case for studies of lipid outcomes.

Although several studies performed multivariate analyses to adjust for potential confounders, few studies explicitly evaluated the effects of omega-3 fatty acids on specific subgroups as identified in the key questions. Thus, conclusions regarding these questions are all weak and based on limited data. With the exceptions of studies confined to men or to specific populations of interest (e.g., diabetics), studies generally did not base eligibility criteria on factors of particular interest here. Furthermore, only one study evaluated only women, limiting conclusions that could be made across studies based on sex.

Most conclusions that we were able to draw, particularly for different populations, were based on across-study comparisons, which cannot account for confounders.

Many studies evaluated multiple risk factors. Thus, many of the outcomes we analyzed were secondary outcomes that were often inadequately powered and reported. Many studies simply reported that the results were not significant without quantifying their results; these studies were not included in our analyses. Non-significant results would still be useful in a systematic review and meta-analysis.

Finally, the ratio of omega-6 to omega-3 fatty acids was so rarely reported that no analyses could be performed on this metric.

Future research

We offer the following recommendations for future research on omega-3 fatty acids and their effect on CVD risk factors and intermediate markers of CVD:

- Future studies on CVD risk factors and intermediate markers of CVD should address the question of possible differences in the effect of omega-3 fatty acids in different sub-populations and as related to different covariates, including dose and duration of intake.

- The potential effect of alpha linolenic acid (ALA, 18:3 n-3) is unknown. More multi-center trials are needed to assess the effect of ALA, separate from the effect of EPA+DHA, on CVD risk factors.

- Additional research is needed to clarify the effect of omega-3 fatty acids on markers of glucose tolerance. Specifically, sufficiently large trials are needed that perform appropriate sub-analyses to determine the cause of heterogeneity in effect across studies.

- The total dietary omega-6 to omega-3 fatty acid ratio should be estimated, reported, and analyzed in terms of its effect on outcomes and its association with any effect of omega-3 fatty acid treatment.

- Future research should attempt to determine the effect of higher fish intake on the consumption of other foods in the diet, specifically sources of saturated fat such as meat and cheese.

- Future prospective cohort studies and diet trials on fish consumption should place special emphasis to collecting data regarding the quantity and type of fish consumed and the method of preparation.

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List of Acronyms/Abbreviations

Abbreviation	Definition
I	Broadly applicable study
II	Study applicable to sub-group of population
III	Narrowly applicable study
Δ%	Difference of the marker's profile (post-treatment minus pre-treatment)
A	Alpha linolenic acid or "good" quality study (see Summary Table footnotes)
AA	Arachidonic acid (20:4 n-6)
AC_{50}	Concentration of collagen giving a 50% decrease in optical density
Ad	Adequate allocation concealment
ADP	Adenosine diphosphate
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
ALA	Alpha linolenic acid (18:3 n-3)
Allocation Conceal	Allocation concealment
apo	Apolipoprotein
apo A-I	Apolipoprotein A-I
apo B-100	Apolipoprotein B-100
apo B-48	Apolipoprotein B-48
apo C-III	Apolipoprotein C-III
B	Fair quality study
Base	Baseline level in treatment arm
BMI	Body mass index
C	Poor quality study
CAB	Commonwealth Agricultural Bureau
CB	Carotid bifurcation
CCA	Common carotid artery
CI	Confidence interval
Cohort Δ	Difference between cohort and reference cohort (cross-sectional)
CR	Control rate
CRP	C-reactive protein
CSFII	Continuing Food Survey of Intakes by Individuals
CVD	Cardiovascular disease
D	Docosahexaenoic acid
DHA	Docosahexaenoic acid (22:6 n-3)
DM	Diabetes mellitus
DM I	Diabetes mellitus, type 1
DM II	Diabetes mellitus, type 2
DPA	Docosapentaenoic acid (DPA, 22:5 n-3)
DysLip	DysLipidemia
E	Eicosapentaenoic acid
ECG	Electrocardiogram
ED	EPA+DHA
EE	Ethyl ester
ELISA	Enzyme-linked immunosorbent assay
EPA	Eicosapentaenoic acid (20:5 n-3)
EPC	Evidence-based practice center
ERD	Energy-restricted diet
ETT	Exercise tolerance test
FA	Fatty acid
FBS	Fasting blood sugar
GEN	General, healthy population
GLA	Gamma-linolenic acid (18:3 n-6)
HDL	High density lipoprotein
Hgb A_{1c}	Hemoglobin A_{1c}
I_{max}	Maximal velocity
IC_{50}	Concentration of Iloprost resulting in 50% inhibition of platelet aggregation
ICA	Internal carotid artery

Abbreviation	Definition
IDDM	Insulin dependent diabetes mellitus
IDL	Intermediate density lipoprotein
IL	Interleukin
IMT	Intima-media thickness
In	Inadequate allocation concealment
Jadad	Jadad score (see Methods)
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LA	Linoleic acid (18:2 n-6)
LDL	Low density lipoprotein
LDL apo B	LDL apolipoprotein B
LT	Leukotriene
N	Number of subjects analyzed in study arm
n-3	Omega-3 (fatty acid)
n-6	Omega-6 (fatty acid)
NCEP	National Cholesterol Education Program
NCEP I	National Cholesterol Education Program step I prudent diet
nd	No data
Net % Δ	Net percent difference in change in omega-3 fatty acids arm compared with the change in control arm
Net Δ	Net difference in change in omega-3 fatty acids arm compared with the change in control arm
NHANES III	The third National Health and Nutrition Examination
NIDDM	Non-insulin dependent diabetes mellitus
NIH	National Institutes of Health
NS	Non-significant
P	P value
PAI	Plasminogen activator inhibitor
PG	Prostaglandin
PL	Phospholipids
Pre Post Δ	Change in omega-3 fatty acid arm (no control)
PTCA	Percutaneous transluminal coronary angioplasty
RBC	Red blood cell
RCT	Randomized controlled trial
REM MA	Random effects model meta-analysis
RPP	Rate-pressure product
RR	Relative risk
SD	Standard deviation
SDNN	Standard deviation of the RR interval
SEM	Standard error of the mean
SFA	Saturated fatty acid
Sp.	Species
Summary	Summary quality score (see Methods)
T	Total omega-3 fatty acids
TEP	Technical Expert Panel
Tg	Triglycerides
TNF-α	Tumor necrosis factor α
TPA	Tissue plasminogen activator
TPR	Total peripheral resistance
Tufts-NEMC	Tufts-New England Medical Center
TX	Thromboxane
Un	Unclear allocation concealment
UO	University of Ottawa
USDA	United States Department of Agriculture
V_a	Aggregation velocity
VCAM-1	Vascular cell adhesion molecule 1
VLDL	Very low density lipoprotein
vWF	von Willebrand factor
WBC	White blood cell

Abbreviation	Definition
WMD	Weight-maintaining diet
Xover	Cross-over study

Listing of Excluded Studies

Excluded studies were categorized by the following sets of reasons for exclusion. Only the primary reason for exclusion is listed here, along with the number of articles in each category.

- Studies not analyzed because of non-randomized design or small size (N=221)
- Articles rejected because in English (N=1)
- Articles rejected because not Human study (N=4)
- Articles rejected because not primary study (N=7)
- Articles rejected because not omega-3 fatty acid (n-3) intake study, insufficient data regararding omega-3 fatty acid trial, or no data on omega-3 fatty acid intake amount (N=95)
- Articles rejected because inappropriate human population (N=15)
- Articles rejected because pediatric population (N=5)
- Articles rejected because no outcome of interest or insufficient data to extract outcomes (N=110)
- Articles rejected because sample size too small (N=45)
- Articles rejected because omega-3 fatty acid dose > 6 g (N=46)
- Articles rejected because duration < 4 weeks (N=80)
- Articles rejected because cross-over study with < 4 week washout (N=32)
- Articles rejected because duplicate publications (N=14)
- Articles rejected for other listed reasons (N=9)

Adler AI, Boyko EJ, Schraer CD, Murphy NJ. Lower prevalence of impaired glucose tolerance and diabetes associated with daily seal oil or salmon consumption among Alaska Natives. Diabetes Care 1994; 17(12):1498-1501.
(Not n-3 study, Insufficient data on n-3)

Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. American Journal of Clinical Nutrition 1997; 65(2):445-450.
(Non -randomized or Small size)

Agren JJ, Hanninen O, Hanninen A, Seppanen K. Dose responses in platelet fatty acid composition, aggregation and prostanoid metabolism during moderate freshwater fish diet. Thrombosis Research 1990; 57(4):565-575.
(No outcome of interest or Insufficent data)

Ahmed AA, Holub BJ. Alteration and recovery of bleeding times, platelet aggregation and fatty acid composition of individual phospholipids in platelets of human subjects receiving a supplement of cod-liver oil. Lipids 1984; 19(8):617-624.
(Duration < 4 weeks)

Akoh CC, Hearnsberger JO. Effect of catfish and salmon diet on platelet phospholipid and blood clotting in healthy men. Journal of Nutritional Biochemistry 1991; 2(6):329-333.
(Duration < 4 weeks)

Allard JP, Kurian R, Aghdassi E, Muggli R, Royall D. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. Lipids 1997; 32(5):535-541.
(No outcome of interest or Insufficent data)

Allard JP, Royall D, Kurian R, Muggli R, Jeejeebhoy KN. Effect of omega 3 fatty acids and vitamin E supplements on lipid peroxidation measured by breath ethane and pentane output: a randomized controlled trial. World Review of Nutrition & Dietetics 1994; 75:162-165.
(No outcome of interest or Insufficent data)

Allman MA, Pena MM, Pang D. Supplementation with flaxseed oil versus sunflowerseed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. European Journal of Clinical Nutrition 1995; 49(3):169-178.
(Duration < 4 weeks)

Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. American Journal of Clinical Nutrition 2001; 74(1):72-79.
(Non -randomized or Small size)

Almdahl SM, Nilsen DW, Osterud B. Thromboplastin activities and monocytes in the coronary circulation of

reperfused human myocardium. No effect of preoperative treatment with n-3 fatty acids. Scandinavian Journal of Thoracic & Cardiovascular Surgery 1993; 27(2):81-86.
(No outcome of interest or Insufficent data)

Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. Journal of Lipid Research 1995; 36(6):1370-1384.
(Duration < 4 weeks)

Almendingen K, Seljeflot I, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on hemostatic variables in men. Arteriosclerosis Thrombosis & Vascular Biology 1996; 16(3):375-380.
(Duration < 4 weeks)

Anderssen SA, Hjermann I, Urdal P, Torjesen PA, Holme I. Improved carbohydrate metabolism after physical training and dietary intervention in individuals with the "atherothrombogenic syndrome'. Oslo Diet and Exercise Study (ODES). A randomized trial. J Intern Med 1996; 240(4):203-209.
(Not n-3 study, Insufficient data on n-3)

Ando M, Sanaka T, Nihei H. Eicosapentanoic acid reduces plasma levels of remnant lipoproteins and prevents in vivo peroxidation of LDL in dialysis patients. Journal of the American Society of Nephrology 1999; 10(10):2177-2184.
(Inappropriate Human population)

Anttolainen M, Valsta LM, Alfthan G, Kleemola P, Salminen I, Tamminen M. Effect of extreme fish consumption on dietary and plasma antioxidant levels and fatty acid composition. European Journal of Clinical Nutrition 1996; 50(11):741-746.
(Non -randomized or Small size)

Archer SL, Green D, Chamberlain M, Dyer AR, Liu K. Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the coronary artery risk development in young adults (CARDIA)study. Arteriosclerosis Thrombosis & Vascular Biology 1998; 18(7):1119-1123.
(Non -randomized or Small size)

Arjmandi BH, Khan DA, Juma S, Drum ML, Venkatesh S, Sohn E et al. Whole flaxseed consumption lowers serum LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. Nutrition Research 1998; 18(7):1203-1214.
(n-3 dose > 6 g)

Armstrong RA, Chardigny JM, Beaufrere B, Bretillon L, Vermunt SH, Mensink RP et al. No effect of dietary trans isomers of alpha-linolenic acid on platelet aggregation and haemostatic factors in european healthy men. The TRANSLinE study. Thrombosis Research 2000; 100(3):133-141.
(Not n-3 study, Insufficient data on n-3)

Atkinson PM, Wheeler MC, Mendelsohn D, Pienaar N, Chetty N. Effects of a 4-week freshwater fish (trout) diet on platelet aggregation, platelet fatty acids, serum lipids, and coagulation factors. American Journal of Hematology 1987; 24(2):143-149.
(Non -randomized or Small size)

Avellone G, Garbo Vd, Cordova R, Scaffidi L, Bompiani GD, di G, V. Effects of Mediterranean diet on lipid, coagulative and fibrinolytic parameters in two randomly selected population samples in Western Sicily. Nutrition Metabolism and Cardiovascular Diseases 1998; 8(5):287-296.
(Not n-3 study, Insufficient data on n-3)

Axelrod L, Camuso J, Williams E, Kleinman K, Briones E, Schoenfeld D. 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; 17(1):37-44.
(Non -randomized or Small size)

Bach R, Schmidt U, Jung F, Kiesewetter H, Hennen B, Wenzel E et al. Effects of fish oil capsules in two dosages on blood pressure, platelet functions, haemorheological and clinical chemistry parameters in apparently healthy subjects. Annals of Nutrition & Metabolism 1989; 33(6):359-367.
(Non -randomized or Small size)

Bagdade JD, Buchanan WE, Levy RA, Subbaiah PV, Ritter MC. Effects of omega-3 fish oils on plasma lipids, lipoprotein composition, and postheparin lipoprotein lipase in women with IDDM. Diabetes 1990; 39(4):426-431.
(Sample size too small)

Bagdade JD, Ritter M, Subbaiah PV. Marine lipids normalize cholesteryl ester transfer in IDDM. Diabetologia 1996; 39(4):487-491.
(Non -randomized or Small size)

Baggio B, Budakovic A, Nassuato MA, Vezzoli G, Manzato E, Luisetto G et al. Plasma phospholipid arachidonic acid content and calcium metabolism in idiopathic calcium nephrolithiasis. Kidney International 2000; 58(3):1278-1284.
(Inappropriate Human population)

Baggio B, Gambaro G, Zambon S, Marchini F, Bassi A, Bordin L et al. Anomalous phospholipid n-6 poly unsaturated fatty acid composition in idiopathic calcium nephrolithiasis. Journal of the American Society of Nephrology 1996; 7(4):613-620.
(Inappropriate Human population)

Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. Hypertension 1998; 32(4):710-717.
(Non -randomized or Small size)

Barcelli U, Glas-Greenwalt P, Pollak VE. Enhancing effect of dietary supplementation with omega-3 fatty acids on plasma fibrinolysis in normal subjects. Thrombosis Research 1985; 39(3):307-312.
(Duration < 4 weeks)

Barstad RM, Roald HE, Petersen LB, Stokke KT, Kierulf P, Sakariassen KS. Dietary supplement of omega-3 fatty acids has no effect on acute collagen-induced thrombus

formation in flowing native blood. Blood Coagulation & Fibrinolysis 1995; 6(5):374-381.
(No outcome of interest or Insufficent data)

Basu A, De JK, Datta S. Studies on the lipid profile and atherogenic factors in adult males. Indian Journal of Nutrition and Dietetics 2001; 38(12):441-454.
(Not n-3 study, Insufficient data on n-3)

Bates C, van Dam C, Horrobin DF. Plasma essential fatty acids in pure and mixed race American Indians on and off a diet exceptionally rich in salmon. Prostaglandins Leukotrienes and Medicine 1985; 17(1):77-84.
(No outcome of interest or Insufficent data)

Baumann KH, Hessel F, Larass I, Muller T, Angerer P, Kiefl R 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 randomized volunteer study. Arteriosclerosis Thrombosis & Vascular Biology 1999; 19(1):59-66.
(No outcome of interest or Insufficent data)

Baumstark MW, Frey I, Berg A, Keul J. Influence of n-3 fatty acids from fish oils on concentration of high- and low-density lipoprotein subfractions and their lipid and apolipoprotein composition. Clinical Biochemistry 1992; 25(5):338-340.
(Non -randomized or Small size)

Beil FU, Terres W, Orgass M, Greten H. Dietary fish oil lowers lipoprotein(a) in primary hypertriglyceridemia.Atherosclerosis 1991; 90(1):95-97.
(Letter)

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Appendix A.

A.1 Primary Search Strategy

1. exp cardiovascular diseases/
2. Adhesion molecule expression.mp.
3. Angiographic progression.mp.
4. Angioplast$.mp.
5. (atherogen$ or antiartherogen$).mp.
6. (arrhythmi$ or Antiarrhythmi$).mp.
7. Antithrombo$.mp.
8. endotheli$.mp.
9. exp endothelium, vascular/
10. Beta-thromboglobulin.mp.
11. Cardi$.mp.
12. CHD.mp.
13. Coronary.mp.
14. Hypotens$.mp.
15. Hypotriglyceridem$.mp.
16. heart disease$.mp.
17. Myocardial infarct$.mp.
18. Platelet adhesi$.mp.
19. (postprandial adj (lipemia or lipoprotein$)).mp.
20. Pulmonary Embol$.mp.
21. Heart failure$.mp.
22. Arteriosclerosi$.mp.
23. cardioprotect$.mp.
24. Homocystine/
25. exp Homocysteine/
26. homocyst$.mp.
27. Cystine/
28. cystine.mp.
29. exp Acute-Phase Proteins/
30. acute phase protein$.mp.
31. Acute-Phase Reaction/
32. acute phase react$.mp.
33. exp Blood Coagulation Factor Inhibitors/
34. exp Blood Coagulation Factors/
35. blood coagulation factors$.mp.
36. exp Cell Adhesion Molecules/
37. cell adhesion molecule$.mp.
38. exp Interleukins/
39. interleukin$.mp.
40. Lipid Peroxidation/
41. lipid peroxidat$.mp.

42. exp Hemostasis/
43. hemosta$.mp.
44. haemosta$.mp.
45. exp Diagnostic Techniques, Cardiovascular/
46. or/1-45
47. exp fatty acids, omega-3/
48. fatty acids, essential/
49. Dietary Fats, Unsaturated/
50. linolenic acids/
51. exp fish oils/
52. (n 3 fatty acid$ or omega 3).tw.
53. docosahexa?noic.tw,hw,rw.
54. eicosapenta?noic.tw,hw,rw.
55. alpha linolenic.tw,hw,rw.
56. (linolenate or cervonic or timnodonic).tw,hw,rw.
57. menhaden oil$.tw,hw,rw.
58. (mediterranean adj diet$).tw.
59. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
60. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
61. (fish adj2 oil$).tw.
62. (cod liver oil$ or marine oil$ or marine fat$).tw.
63. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
64. (fish consumption or fish intake or (fish adj2 diet$)).tw.
65. diet$ fatty acid$.tw.
66. or/47-65
67. dietary fats/
68. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
69. random$.tw.
70. exp clinical trials/ or evaluation studies/
71. follow-up studies/ or prospective studies/
72. or/68-71
73. 67 and 72
74. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
75. (omega 3 or n 3).mp.
76. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
77. 75 and 76
78. 66 or 73 or 74 or 77
79. 46 and 78
80. limit 79 to (addresses or bibliography or biography or congresses or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or

letter or news or newspaper article or patient education handout or periodical index or review of reported cases)
81. 79 not 80
82. limit 81 to human
83. (guidelines or practice guideline or meta analysis or review or revewi, academic or review, tutorial or review literature).pt.
84. 82 and 83
85. limit 84 to english language
86. 84 not 85
87. (random$ or rct$).tw.
88. exp randomized controlled trials/
89. exp random allocation/
90. exp double-blind method/
91. exp single-blind method/
92. randomized controlled trial.pt.
93. clinical trial.pt.
94. (clin$ adj trial$).tw.
95. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
96. exp placebos/
97. placebo$.tw.
98. exp comparative study/
99. exp clinical trials/
100. follow-up studies/
101. (follow up or followup).tw.
102. exp case-control studies/
103. (case adj20 control).tw.
104. exp longitudinal studies/
105. longitudinal.tw.
106. exp cohort studies/
107. cohort.tw.
108. exp prospective studies/
109. exp evaluation studies/
110. or/87-109
111. (82 and 110) not 83
112. limit 111 to english language
113. 111 not 112
114. 82 not (111 or 83)
115. limit 114 to english language
116. 114 not 115

A.2 Diabetes Search Strategy

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. (mediterranean adj diet$).tw.
12. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
13. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
14. (fish adj2 oil$).tw.
15. (cod liver oil$ or marine oil$ or marine fat$).tw.
16. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
17. (fish consumption or fish intake or (fish adj2 diet$)).tw.
18. diet$ fatty acid$.tw.
19. menhaden oil$.tw,hw,rw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. or/20,27-28,31
33. limit 32 to (addresses or bibliography or biography or congresses or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or review of reported cases)
34. Case Report/
35. 32 not (33 or 34)
36. exp Diabetes Mellitus/
37. diabet$.af.
38. 35 and (36 or 37)
39. limit 38 to human

40. limit 39 to english language
41. limit 40 to (guideline or meta analysis or review or review, academic or review, multicase or review, tutorial or review literature)
42. 40 not 41

A.3 Nut Search Strategy

1. exp Nuts/	964
2. exp Cardiovascular Diseases/	1123117
3. (nut or nuts).tw.	1762
4. 1 or 3	2318
5. 4 and 2	145
6 limit 5 to (human and english language)	122

A.4 Risk Factor Update Search Strategy

1. exp fatty acids, omega-3/
2. exp fish oils/
3. (n 3 fatty acid$ or omega 3).tw.
4. docosahexa?noic.tw,hw,rw.
5. eicosapenta?noic.tw,hw,rw.
6. alpha linolenic.tw,hw,rw.
7. (linolenate or cervonic or timnodonic).tw,hw,rw.
8. (fish adj2 oil$).tw.
9. or/1-8
10. limit 9 to human
11. limit 10 to english language
12. exp "Lipoprotein(a)"/
13. c-reactive protein.mp.
14. insulin.mp.
15. exp Factor VIII/
16. exp von Willebrand Factor/
17. heart rate variab$.mp.
18. ankle brachial index.mp.
19. ankle-arm blood pressure index.mp.
20. exp Hemoglobin A, Glycosylated/
21. glycohemoglobin hgb a1c.mp.
22. hgb a1c.mp.
23. exp Apolipoproteins B/
24. apolipoprotein b-100.tw.
25. intima media thickness.mp.
26. carotid doppler.mp.
27. exp Heart Function Tests/
28. exp PLETHYSMOGRAPHY/
29. exp Ultrasonography, Doppler/
30. glycated hemoglobin.mp.
31. or/12-30
32. 11 and 31

Design

Submit This Section

Multiple vs Single Cohorts ☐ ND

- ○ Multiple study arms/cohorts (Comment:)
- ○ Single study arm/cohort (Comment:)

SCREENING QUESTION:

Randomized? ☐ ND

- ○ Randomized
- ○ Non-randomized
- ○ Unclear (Explain:)

SCREENING QUESTION:

Prospective vs Retrospective? ☐ ND

- ○ Prospective (Treatment based on predefined protocol)
- ○ Retrospective (Treatment NOT based on predefined protocol)
- ○ Unclear (Explain:)

Longitudinal vs Cross-sectional? ☐ ND

- ○ Longitudinal (start and end of trial separated in time, multiple measurements made)
- ○ Cross-sectional (single time point, single set of measurements made)
- ○ Unclear (Explain:)

Submit This Section

SCREENING QUESTION:

What is the specific study design? ☐ ND

- ○ Clinical Trial: Randomized Parallel
- ○ Clinical Trial: Randomized Cross-over (results reported from FIRST PHASE)
- ○ Clinical Trial: Randomized Cross-over (results reported from COMBINED PHASES)
- ○ Clinical Trial: Randomized Factorial Design
- ○ Clinical Trial: Non-Randomized Controlled trial
- ○ Clinical Trial: Non-Randomized Non-Controlled trial (single cohort given Tx)
- ○ Observational: Single Cohort (all subjects analyzed as single group)

- Observational: Multiple Cohorts (distinct groups)
- Observational: Case-Control (not as sub-analysis of other trial)
- Observational (quasi): Nested Case Control (as sub-analysis of other study)
- Miscellaneous: Other or Mixed (Describe:)

Comments about Study Design:

What is the name of this study? (e.g. DART, Physician's Health Study) ☐ ND

Was any aspect of this trial reported elsewhere? ☐ ND

- Yes - This is a secondary or sub-analysis of:
- Yes - Same or similar results reported in:
- Yes - Different outcomes also reported in:
- Yes - Other:
- No, this appears to be a unique publication of this trial

Submit This Section

Blinding

Were subjects explicitly reported to be blinded to intervention? ☐ ND

- Yes blinded
- Not blinded
- Unclear (Explain:)
- ND

Were caregivers (or researchers) explicitly reported to be blinded to intervention? ☐ N

- Yes blinded
- Not blinded
- Unclear (Explain:)
- ND

Were outcome assessors explicity reported to be blinded to intervention? ☐ ND

- Yes blinded
- Not blinded
- Unclear (Explain:)
- ND

If blinding was reported but it was not clearly reported who was blinded, was blinding reported as: ☐ ND

- "Single Blind"

- "Double Blind"
- Other:

Comments about Blinding

Submit This Section

Randomization

If "Randomized" Trial:

Did authors explicitly state that study was "randomized"? ND

- Yes
- No

What was method of randomization? ND

- Not reported (only stated "randomized")
- Reported (What was method?)

Submit This Section

Allocation Concealment

If Randomized trial:

Allocation Concealment = Method by which allocation (which cohort a subject was assigned to) is conceale from subject, caretaker, and all others involved in study. The purpose is to prevent subjects being allocated one or another cohort based on any subject or researcher characteristics or biases (such as peaking into envelope to give sicker patients active treatment because "they need it more.")

Examples (of both good and bad allocation concealment) = Central randomization site, Pharmacy-randomization, Opaque envelope, Alternating, List

What was method of Allocation Concealment? ND

- None reported
- Reported (What was method?)

Submit This Section

Overall Study Design Quality

Also consider reporting of drop-outs/withdrawals and actual drop-out rate.

Is overall quality of Study Design: ND

- Good
- Fair
- Poor

Why?

Do you find substantial biases related to Study Design: ☐ ND

- ○ Yes
- ○ No

What?

Submit This Section

Is this article REJECTED?

- ○ Yes
- ○ No

If YES, Why?

Submit This Section

Characteristics

Submit This Section

Check all responses that apply. Complete all sections fully. Check ND if data not reported

Country in which study conducted (where subjects live) ☐ ND

- ☐ US
- ☐ Canada
- ☐ Denmark
- ☐ Finland
- ☐ Germany
- ☐ Greece
- ☐ Italy
- ☐ Japan
- ☐ Netherlands
- ☐ Norway
- ☐ Sweden
- ☐ UK (England, Scotland, Wales, Northern Ireland; NOT Ireland)
- ☐ Other(s) [Separate countries with commas]:

☐ ND

Number of Sites (enter # or "multiple"): ☐ ND

Funding source: ☐ ND

- ☐ Government
- ☐ Industry (specify which):
- ☐ Private -- non-industry (specify which):
- ☐ Hospital
- ☐ Unclear (specify which):
- ☐ ND

SCREENING QUESTION:

Average Study duration/follow-up [REJECT if less than 4 weeks]:

Choose ☐ ND

Is "average duration" mean or median, or are all subjects followed for the same duratio

☐ ND

- ○ Mean
- ○ Median
- ○ All Subjects

Study Duration Range **to** ☐ ND

Does study report Outcome results after Prolonged Follow-up (AFTER Treatment has stopped)?

(Is the following question addressed? "Are treatment effects...sustained after interventi stops?") ☐ ND

- ○ Yes
- ○ No
- ○ Unclear (why?)

Submit This Section

Is overall quality of Study Characteristics: ☐ ND

- ○ Good
- ○ Fair
- ○ Poor

Why?

Do you find substantial biases related to Study Characteristics? ☐ ND

- ○ Yes
- ○ No

What?

Submit This Section

Eligibility

Submit This Section

Inclusion Criteria:

Exclusion Criteria:

Comment about Eligibility Criteria:

Was this a Primary or Secondary Prevention study? ☐ **ND**

- ○ **Primary Prevention (to prevent first CVD event, none had MI)**
- ○ **Secondary Prevention (to prevent new CVD event, all had MI)**
- ○ **Unclear / Neither / ND**

Submit This Section

At baseline, Were ALL subjects...? ☐ **ND**

- ☐ **Healthy and Without Known or Suspected CVD**
- ☐ **With Known or Suspected CVD**
- ☐ **With Known Lipid Abnormalities / Dyslipidemia**
- ☐ **Have Hypertension**
- ☐ **Have Diabetes**
- ☐ **Pre-Menopausal Women**
- ☐ **Post-Menopausal Women**

If necessary, for each condition, What was the reported definition?

History of CVD?

History of Lipid Abnormality/Dyslipidemia?

Abnormality/Dyslipidemia?

History of Hypertension?

History of Diabetes?

Pre-Menopause?

Post-Menopausal?

Comment about Definitions:

Submit This Section

Is overall quality of Eligibility: ☐ **ND**

- ○ **Good**
- ○ **Fair**
- ○ **Poor**

Why?

Do you find substantial biases related to Eligibility Criteria? ☐ **ND**

- ○ **Yes**
- ○ **No**

What?

Submit This Section

Population

Submit This Section

Subjects and Controls

(Provide largest #, if multiple analyses reported. If possible, number enrolled should be based on Intention-tc Treat principle: All subjects who were randomized or put into a treatment cohort)

SCREENING QUESTION (control and Tx descriptions and N):

Control (No intervention or Placebo OR Controls in Case-Control) -- Number enrolled: ☐ **ND**

IF THERE IS MORE THAN 1 NON-OMEGA-3 CONTROL ARM, CONSULT ETHAN, CHENCHEN, OR JOS BEFORE PROCEEDING

Treatment Arm 1 or Single Cohort or Cases -- Simple description: ☐ **ND**

Treatment Arm 1 or Single Cohort or Cases -- Number enrolled [REJECT if 5 or fewer]: ☐ **ND**

Treatment Arm 2 -- Simple description: ☐ **ND**

Treatment Arm 2 -- Number enrolled: ☐ **ND**

Treatment Arm 3 -- Simple description: ☐ **ND**

Treatment Arm 3 -- Number enrolled: ☐ **ND**

Treatment Arm 4 -- Simple description: ☐ **ND**

Treatment Arm 4 -- Number enrolled: ☐ **ND**

More Arms: Number each arm, Describe, and give Sample Size

The number of subjects enrolled is based on which of the following criteria? ☐ **ND**

- ○ **Intention-to-treat (everyone randomized or initially enrolled)**
- ○ **Those who received treatment at start of study**
- ○ **Only those with follow-up data (who completed study)**
- ○ **Not described**
- ○ **Other (Describe:)**

Explanation of how Number Enrolled defined (if necessary):

Were the number of enrolled subjects and drop-outs explicitly and clearly reported? ☐ **ND**

- ○ **Yes**
- ○ **No**

Were the reasons for drop-outs/withdrawals clearly stated? ☐ **ND**

- ○ **Yes**
- ○ **No**

Reason for dropouts, withdrawals, etc.

Comment about Number Enrolled etc.:

Submit This Section

Demographics etc.

(Choose one group of subjects to report on. Choose COMBINED over SINGLE Omega 3. If necessary, Choo LARGEST Omega 3 cohort.)

...

For each variable, answer whether there is a difference among treatment groups. If yes, describe in Comme box below.

...

Skip (and check NA) if Demographic info requested is also Outcome of interest (data recored in form's result section)

Which cohort/group of subjects are baseline data reported for? ☐ **ND**

- ○ **Combined**
- ○ **Omega 3 (only n3 cohort)**
- ○ **Largest (by N) Omega 3 cohort**
- ○ **Specific (Other) Omega 3 cohort (describe:)**

Are statistical analyses (eg, p-values) reported comparing cohorts?

- ○ **Yes**
- ○ **No**

AGE [REJECT if not adults]

Is there a Difference in Age among cohorts? ☐ **ND**

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Mean/Median Age: Choose 1 ☐ **ND**

+/- SD/SE: Choose 1 ☐ **ND**

Age Range: **to** ☐ **ND**

SEX

Is there a Difference in Sex Ratio among cohorts? ☐ **ND**

- ○ **Yes (describe below)**
- ○ **No**

- ND / NA / Unclear

Sex: Male (%): ☐ ND

RACE

Is there a Difference in Race among cohorts? ☐ ND

- Yes (describe below)
- No
- ND / NA / Unclear

Race (%, Put Whole Number only in text box): ☐ ND

- ☐ White/European
- ☐ Black/African-American/etc.
- ☐ Asian
- ☐ Hispanic
- ☐ Inuit/Eskimo
- ☐ Other 1 (% here, describe below)
- ☐ Other 2 (% here, describe below)
- ☐ Other 3 (% here, describe below)
- ☐ ND

Describe Races (as necessary, Remember to check boxes) ☐ ND

- ☐ Asian
- ☐ Hispanic
- ☐ Inuit/Eskimo
- ☐ Other 1
- ☐ Other 2
- ☐ Other 3

BLOOD PRESSURE

Do Not Extract Baseline BP Data Here If BP is an Outcome Being Analyzed

Is there a Difference in BP among cohorts? ☐ ND

- Yes (describe below)
- No
- ND / NA / Unclear

Mean Systolic Blood Pressure (SBP) ☐ ND

+/- SD/SE Choose 1 ☐ ND

SBP Range: to ☐ ND

Mean Diastolic Blood Pressure (DBP) ☐ ND

+/- SD/SE Choose 1 ☐ **ND**

DBP Range: **to** ☐ **ND**

Mean of Mean Arterial Pressure (MAP: ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

MAP range **to** ☐ **ND**

LIPIDS

Do Not Extract Baseline Lipids Data Here if Lipids are an Outcome Being Analyzed

Is there a Difference in Lipids among cohorts? ☐ **ND**

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Mean Total Cholesterol: Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

Total Cholesterol Range: **to** ☐ **ND**

Mean LDL: Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

LDL Range: **to** ☐ **ND**

Mean HDL Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

HDL Range: **to** ☐ **ND**

Average Triglycerides Choose unit ☐ **ND**

Mean or Median? Choose 1 ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

Tg Interquartile Range (IQR) **to** ☐ **ND**

Tg Total Range **to** ☐ **ND**

BODY MASS INDEX / WEIGHT

Is there a Difference in Weight/BMI among cohorts? ☐ **ND**

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Mean BMI of Men: ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

BMI range (men): **to** ☐ **ND**

Mean BMI of Women: ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

BMI range (women) **to** ☐ **ND**

Mean BMI of all (if no sex-specfic data): ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

BMI range (combined sexes): **to** ☐ **ND**

Mean Weight of Men (if no BMI data): Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

Weight range (men): **to** ☐ **ND**

Mean Weight of Women (if no BMI data): Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

Weight range (women): **to** ☐ **ND**

Mean Weight of combined sexes (if no BMI data and no sex-specific data): Choose unit ☐ **ND**

+/- SD/SE Choose 1 ☐ **ND**

Weight range (combined sexes): **to** ☐ **ND**

DIABETES

Do Not Extract Baseline DM Data Here If DM is an Outcome Being Analyzed

Is there a Difference in Diabetes among cohorts? ☐ **ND**

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

Diabetes Measurement compared: ☐ **ND**

- ○ **Prevalence (%)**
- ○ **HgbA1c**
- ○ **Fasting Blood Sugar (FBS)**
- ○ **Other:**

Diabetes measure Unit ☐ **ND**

- ○ **%**
- ○ **mg/dL**

- mmol/L
- Other:

Mean/Median/Prevalence DM measure: Choose 1 ND

+/- SD/SE: Choose 1 ND

DM Range: to ND

FATTY ACIDS (SERUM, TISSUE, OR CELL MEMBRANE)

DO (Yes, do) Extract Baseline FA Data Here Even If FA is and Outcome of Study

Is there a Difference in Fatty Acids among cohorts? ND

- Yes (describe below)
- No
- ND / NA / Unclear

FATTY ACID: ALPHA LINOLENIC ACID (ALA)

Mean ALA (18:3 n3) level 1 ND

ALA unit 1 ND

+/- SD 1 Choose 1 ND

Definition of ALA measurement 1

Mean ALA (18:3 n3) level 2 ND

ALA unit 2 ND

+/- SD 2 Choose 1 ND

Definition of ALA measurement 2

FATTY ACID: EICOCAPENTAENOIC ACID (EPA)

Mean EPA (20:5 n3) level 1 ND

EPA unit 1 ND

+/- SD 1 Choose 1 ND

Definition of EPA measurement 1

Mean EPA (20:5 n3) level 2 ND

EPA unit 2 ND

+/- SD 2 Choose 1 ND

Definition of EPA measurement 2

FATTY ACID: DOCOSAPENTAENOIC ACID (DPA)

Mean DPA (22:5 n3) level 1 ☐ **ND**

DPA unit 1 ☐ **ND**

+/- SD 1 Choose 1 ☐ **ND**

Definition of DPA measurement 1

Mean DPA (22:5 n3) level 2 ☐ **ND**

DPA unit 2 ☐ **ND**

+/- SD 2 Choose 1 ☐ **ND**

Definition of DPA measurement 2

FATTY ACID: DOCOSAHEXAENOIC ACID (DHA)

Mean DHA (22:6 n3) level 1 ☐ **ND**

DHA unit 1 ☐ **ND**

+/- SD 1 Choose 1 ☐ **ND**

Definition of DHA measurement 1

Mean DHA (22:6 n3) level 2 ☐ **ND**

DHA unit 2 ☐ **ND**

+/- SD 2 Choose 1 ☐ **ND**

Definition of DHA measurement 2

FATTY ACIDS: COMBINED EPA + DHA

Mean EPA+DHA level 1 ☐ **ND**

EPA+DHA unit 1 ☐ **ND**

+/- SD 1 Choose 1 ☐ **ND**

Definition of EPA+DHA measurement 1

Mean EPA+DHA level 2 ☐ **ND**

EPADHA unit 2 ☐ **ND**

+/- SD 2 Choose 1 ☐ **ND**

Definition of EPA+DHA measurement 2

FATTY ACIDS: n6 LINOLEIC ACID (LA)

Mean Linoleic Acid (18:2 n6) level 1 ☐ **ND**

LA unit 1 ☐ **ND**

+/- SD 1 Choose 1 ☐ **ND**

Definition of LA measurement 1

Mean Linoleic Acid (18:2 n6) level 2 ☐ **ND**

LA unit 2 ☐ **ND**

+/- SD 2 Choose 1 ☐ **ND**

Definition of LA measurement 2

FATTY ACIDS: n6 ARACHADONIC ACID (AA)

Mean Arachadonic Acid (18:4 n6) level 1 ☐ **ND**

AA unit 1 ☐ **ND**

+/- SD 1 Choose 1 ☐ **ND**

Definition of AA measurement 1

Mean Arachadonic Acid (18:4 n6) level 2 ☐ **ND**

AA unit 2 ☐ **ND**

+/- SD 2 Choose 1 ☐ **ND**

Definition of AA measurement 2

COMMENTS

Comments about Demographics etc.:

Submit This Section

Is overall quality of Population data/reporting: ☐ **ND**

- ○ **Good**
- ○ **Fair**
- ○ **Poor**

Why?

Do you find substantial biases related to Population: ☐ **ND**

- ○ **Yes**
- ○ **No**

What?

Submit This Section

Confounders

Submit This Section

Other Confounders etc.

CONCOMITANT MEDICATIONS

Is there a Difference in Medication Use among cohorts?

- ○ **Yes (describe below)**
- ○ **No**
- ○ **ND / NA / Unclear**

.....Type in All, None, Some or ND ☐ **ND**

- ☐ **Beta Blocker**
- ☐ **Calcium Channel Blocker**
- ☐ **ACE Inhibitor**
- ☐ **Diuretic**
- ☐ **Other CVD treatment (which?)**
- ☐ **Aspirin**
- ☐ **Warfarin (coumadin)**
- ☐ **Other "blood thinner" (which?)**
- ☐ **Statin**
- ☐ **Fibrate**
- ☐ **Niacin**
- ☐ **Other lipid lowering agent (which?)**
- ☐ **Insulin**
- ☐ **Oral hypoglycemic agent (which?)**
- ☐ **Hormone replacement therapy**
- ☐ **Other Dietary Supplements (Which?)**

- ☐ Vitamins (Which?)
- ☐ Other 1 (Which?)
- ☐ Other 2 (Which?)
- ☐ Others >2 (Which?)

BASELINE DIET FACTORS

Difference in Baseline Diet among cohorts? ☐ ND

- ○ Yes (describe below)
- ○ No
- ○ ND / NA / Unclear

.....Type in All, Some, None, ND ☐ ND

- ☐ High fish diet
- ☐ Pisco-vegetarian diet (non-meat except fish)
- ☐ Other low fish diet
- ☐ Low fat diet
- ☐ High fat diet
- ☐ "Mediterranean diet"
- ☐ Other1
- ☐ Other2
- ☐ Other3

Definitions of Diets:

Comments about Other Confounders:

Submit This Section

For each condition below, Were Sub-Group analyses reported?

Ie, Either:

1. Subjects were divided into groups based on condition (eg, diabetics vs non-diabetics) and study questior analyzed based on condition.

2. Regression analysis was done based on condition (eg, mean blood pressure) and association of conditio study question was estimated.

Check all factors for which sub-group analyses are reported (put relevant definitions of factors under Eligibility Criteria tab) (If unclear, state why in text box) ☐ ND

- ☐ None
- ☐ Age

- ☐ Sex
- ☐ Race
- ☐ Blood Pressure or Hypertension
- ☐ Dyslipidemia or Lipid Level
- ☐ BMI / Weight
- ☐ History of CVD
- ☐ History of Diabetes or Marker of Diabetes (eg, Hgb A1c)
- ☐ Menopausal Status
- ☐ Concomitant medication (which?)
- ☐ Baseline diet factors (which?)

Comments about Sub-Group Analyses:

Submit This Section

Regression Covariates

If regression performed, what variables were controlled for? ☐ ND

- ☐ Age
- ☐ Sex
- ☐ Race
- ☐ Blood Pressure or Hypertension
- ☐ Lipid levels (Total, HDL, LDL, or Tg)
- ☐ BMI / Weight
- ☐ History of CVD
- ☐ Diabetes / Hgb A1c etc.
- ☐ Menopausal status
- ☐ Medications
- ☐ Diet
- ☐ Smoking
- ☐ Others (separate with commas)

Comments about Regression Covariates:

Submit This Section

Is overall quality of Confounder data/reporting: ☐ ND

- Good
- Fair
- Poor

Why?

Do you find substantial biases related to Confounders? ND

- Yes
- No

What?

Submit This Section

Applicability

Submit This Section

Sample representative of...

- "Typical" healthy people (similar to Americans)
- "Typical" people with CVD (similar to Americans)
- "Typical" people with Diabetes or Abnormal Lipids (similar to Americans)
- Healthy people who are not typical because of diet, demographics, etc.
- People with CVD who are not typical because of diet, demographics, etc.
- People with DM or Dyslipidemia who are not typical because of diet, demographics, etc.
- Narrow, Atypical group of people, including highly controlled diet
- Cannot categorize because of incomplete demographic or other data

If sample not fully generalizable, what are the limiting factors?

Other Comments about Applicability:

Submit This Section

Control Arm

Submit This Section

INTERVENTION vs OBSERVATIONAL

Study type? ☐ **ND**

- ○ **Interventional study (fill in section immediately below)**
- ○ **Observational study (jump to 2nd section)**

Complete "Interventional Study" OR "Observational Study" Sections below
THEN ALSO Complete "Amounts of FA" Section (regardless of study design)

Submit This Section

INTERVENTIONAL STUDY

What was the authors' description of Control or Placebo

What was used as Control / "Placebo" ☐ **ND**

- ○ **Olive oil**
- ○ **Safflower oil**
- ○ **Other oil, which?**
- ○ **Other, What?**

How much per day? ☐ **ND**

Comments on Control/Placebo source:

Submit This Section

OBSERVATIONAL STUDY

What was the author's description of the Omega 3-poor diet?

Submit This Section

AMOUNTS OF FATTY ACIDS IN DIET (observational) OR TREATMENT (interventional)

The frequency of Fatty Acid intake amounts was: Choose 1 ☐ **ND**

Report estimates of grams, % energy (Kcal), and % fat for each fatty acid

ALA (18:3)

ALA grams (mean): ☐ **ND**

ALA grams SD/SE Choose 1 ☐ **ND**

ALA grams range **to** Choose 1 ☐ **ND**

ALA % Kcal (mean): ☐ **ND**

ALA % Kcal SD/SE Choose 1 ☐ **ND**

ALA % Kcal Range **to** Choose 1 ☐ **ND**

ALA % fat intake (mean): ☐ **ND**

ALA % fat SD/SE Choose 1 ☐ **ND**

ALA % fat Range **to** Choose 1 ☐ **ND**

EPA (20:5)

EPA grams (mean): ☐ **ND**

EPA grams SD/SE Choose 1 ☐ **ND**

EPA grams range **to** Choose 1 ☐ **ND**

EPA % Kcal (mean): ☐ **ND**

EPA % Kcal SD/SE Choose 1 ☐ **ND**

EPA % Kcal Range **to** Choose 1 ☐ **ND**

EPA % fat intake (mean): ☐ **ND**

EPA % fat SD/SE Choose 1 ☐ **ND**

EPA % fat Range **to** Choose 1 ☐ **ND**

DPA (22:5)

DPA grams (mean): ☐ **ND**

DPA grams SD/SE Choose 1 ☐ **ND**

DPA grams range **to** Choose 1 ☐ **ND**

DPA % Kcal (mean): ☐ **ND**

DPA % Kcal SD/SE Choose 1 ☐ **ND**

DPA % Kcal Range **to** Choose 1 ☐ **ND**

DPA % fat intake (mean): ☐ **ND**

DPA % fat SD/SE [ ] Choose 1 ☐ **ND**

DPA % fat Range [ ] **to** [ ] Choose 1 ☐ **ND**

DHA (22:6)

DHA grams (mean): [ ] ☐ **ND**

DHA grams SD/SE [ ] Choose 1 ☐ **ND**

DHA grams range [ ] **to** [ ] Choose 1 ☐ **ND**

DHA % Kcal (mean): [ ] ☐ **ND**

DHA % Kcal SD/SE [ ] Choose 1 ☐ **ND**

DHA % Kcal Range [ ] **to** [ ] Choose 1 ☐ **ND**

DHA % fat intake (mean): [ ] ☐ **ND**

DHA % fat SD/SE [ ] Choose 1 ☐ **ND**

DHA % fat Range [ ] **to** [ ] Choose 1 ☐ **ND**

COMBINED EPA+DHA

EPA+DHA grams (mean): [ ] ☐ **ND**

EPA+DHA grams SD/SE [ ] Choose 1 ☐ **ND**

EPA+DHA grams range [ ] **to** [ ] Choose 1 ☐ **ND**

EPA+DHA % Kcal (mean): [ ] ☐ **ND**

EPA+DHA % Kcal SD/SE [ ] Choose 1 ☐ **ND**

EPA+DHA % Kcal Range [ ] **to** [ ] Choose 1 ☐ **ND**

EPA+DHA % fat intake (mean): [ ] ☐ **ND**

EPA+DHA % fat SD/SE [ ] Choose 1 ☐ **ND**

EPA+DHA % fat Range [ ] **to** [ ] Choose 1 ☐ **ND**

Omega 6 (total, add together if necessary)

Omega 6 grams (mean): [ ] ☐ **ND**

Omega 6 grams SD/SE [ ] Choose 1 ☐ **ND**

Omega 6 grams range [ ] **to** [ ] Choose 1 ☐ **ND**

Omega 6 % Kcal (mean): [ ] ☐ **ND**

Omega 6 % Kcal SD/SE [ ] Choose 1 ☐ **ND**

Omega 6 % Kcal Range [ ] **to** [ ] Choose 1 ☐ **ND**

Omega 6 % fat intake (mean): ☐ ND

Omega 6 % fat SD/SE Choose 1 ☐ ND

Omega 6 % fat Range to Choose 1 ☐ ND

Comments about Fatty Acid values

Submit This Section

Is overall quality of Control data/reporting: ☐ ND

- ○ Good
- ○ Fair
- ○ Poor

Why?

Do you find substantial biases related to Control/Placebo? ☐ ND

- ○ Yes
- ○ No

What?

Submit This Section

Tx Arm No.

Submit This Section

[REJECT if Omega-3 intake in more than 5 g per day]

DUPLICATE THIS SECTION FOR EACH TREATMENT ARM
Do Not Use The Template (titled Tx Arm No.) to Enter Data.
Name each new section by an appropriate Brief Description (eg, Fish Oil, O3 Diet)
Number each new section's Section ID Tx Arm number from the POPULATION section

Treatment Arm No.

Submit This Section

INTERVENTION vs OBSERVATIONAL

SCREENING QUESTION (for screening, do not duplicate, combine all Tx arms):

Study type? ND

- Interventional study (fill in section immediately below)
- Observational study (jump to 2nd section)

Complete "Interventional Study" OR "Observational Study" Sections below
THEN ALSO Complete "Amounts of FA" Section (regardless of study design)

Submit This Section

INTERVENTIONAL STUDY

What was the authors' description of Omega 3 intervention?

SCREENING QUESTION:

Was Intervention a branded supplement? ND

- Yes
- No

If Yes, which? and How many capsules per day? ND

- Almarin
- Coromega
- Efamed
- Epagis
- MaxEPA
- Omacor
- Ropufa
- Other, which? (give dose below)

Other, How many capsules per day? ND

SCREENING QUESTION (for screening, just check boxes):

If not brand name supplement, what was/were the source(s) of the Omega 3 FA? and hc much (WITH UNITS)? ND

- Fish/Marine oil, general
- Cod liver oil
- Other fish oil, which?

- ☐ Other fish oil, how much?
- ☐ Flax seed / Linseed
- ☐ Rape seed / Canola
- ☐ Mustard seed
- ☐ Walnut oil
- ☐ Whole fish, which?
- ☐ Whole fish, how much?
- ☐ Other source, which?
- ☐ Other source, how much?
- ☐ No Data

Comments on Omega-3 source:

Submit This Section

OBSERVATIONAL STUDY

What was the author's description of the Omega 3-rich diet?

SCREENING QUESTION:

Mediterranean diet? ☐ ND

- ○ Yes (Author definition):
- ○ No

SCREENING QUESTION (for screening, just check box):

Source of Omega 3-rich intake: ☐ ND

- ☐ Dietary fish (which?)
- ☐ Dietary oils (which?)
- ☐ Dietary nuts (which?)
- ☐ Other (describe)

How was dietary intake of Omega 3 estimated [These questions appear only under Intervention #1]? ☐ ND

- ○ Nutritionist-administered food survey, performed once
- ○ Nutritionist-administered food survey, performed multiple times (how many?)
- ○ Self-administered food survey, performed once
- ○ Self-administered food survey, performed multiple times (how many?)

- Food survey, ND on how administered, performed once
- Food survey, ND on how performed, performed multiple times (how many?)
- Direct Measurement of food intake (describe below)
- No Data (explain below)

What were the details of how Omega 3 intake was measured?

Comments about Omega 3 intake measurement

Submit This Section

AMOUNTS OF FATTY ACIDS IN DIET (observational) OR TREATMENT (interventional)

The frequency of Fatty Acid intake amounts was: Choose 1 ND

SCREENING QUESTION:

Are the specific amounts of FAs in diet or intervention reported?

- Yes (If yes, compete sections below)
- No

If necessary (and if possible) calculate total daily amounts (eg, 120 mg x 3 times/day = 0.36 g/d) Or simply data as reported (eg, 120 mg x 3)

Report estimates of grams, % energy (Kcal), and % fat for each fatty acid

Omega 3 (total)

Omega 3 grams (mean): ND

Omega 3 grams SD/SE Choose 1 ND

Omega 3 grams range to Choose 1 ND

Omega 3 Kcal (mean): ND

Omega 3 Kcal SD/SE Choose 1 ND

Omega 3 % Kcal Range to Choose 1 ND

Omega 3 % fat intake (mean): ND

Omega 3 % fat SD/SE Choose 1 ND

Omega 3 % fat Range to Choose 1 ND

ALA (18:3)

ALA grams (mean): ☐ **ND**
ALA grams SD/SE Choose 1 ☐ **ND**
ALA grams range **to** Choose 1 ☐ **ND**

ALA % Kcal (mean): ☐ **ND**
ALA % Kcal SD/SE Choose 1 ☐ **ND**
ALA % Kcal Range **to** Choose 1 ☐ **ND**

ALA % fat intake (mean): ☐ **ND**
ALA % fat SD/SE Choose 1 ☐ **ND**
ALA % fat Range **to** Choose 1 ☐ **ND**

EPA (20:5)

EPA grams (mean): ☐ **ND**
EPA grams SD/SE Choose 1 ☐ **ND**
EPA grams range **to** Choose 1 ☐ **ND**

EPA % Kcal (mean): ☐ **ND**
EPA % Kcal SD/SE Choose 1 ☐ **ND**
EPA % Kcal Range **to** Choose 1 ☐ **ND**

EPA % fat intake (mean): ☐ **ND**
EPA % fat SD/SE Choose 1 ☐ **ND**
EPA % fat Range **to** Choose 1 ☐ **ND**

DPA (22:5)

DPA grams (mean): ☐ **ND**
DPA grams SD/SE Choose 1 ☐ **ND**
DPA grams range **to** Choose 1 ☐ **ND**

DPA % Kcal (mean): ☐ **ND**
DPA % Kcal SD/SE Choose 1 ☐ **ND**
DPA % Kcal Range **to** Choose 1 ☐ **ND**

DPA % fat intake (mean): ☐ **ND**
DPA % fat SD/SE Choose 1 ☐ **ND**
DPA % fat Range **to** Choose 1 ☐ **ND**

DHA (22:6)

DHA grams (mean): ☐ ND

DHA grams SD/SE Choose 1 ☐ ND

DHA grams range to Choose 1 ☐ ND

DHA % Kcal (mean): ☐ ND

DHA % Kcal SD/SE Choose 1 ☐ ND

DHA % Kcal Range to Choose 1 ☐ ND

DHA % fat intake (mean): ☐ ND

DHA % fat SD/SE Choose 1 ☐ ND

DHA % fat Range to Choose 1 ☐ ND

COMBINED EPA+DHA

EPA+DHA grams (mean): ☐ ND

EPA+DHA grams SD/SE Choose 1 ☐ ND

EPA+DHA grams range to Choose 1 ☐ ND

EPA+DHA % Kcal (mean): ☐ ND

EPA+DHA % Kcal SD/SE Choose 1 ☐ ND

EPA+DHA % Kcal Range to Choose 1 ☐ ND

EPA+DHA % fat intake (mean): ☐ ND

EPA+DHA % fat SD/SE Choose 1 ☐ ND

EPA+DHA % fat Range to Choose 1 ☐ ND

Omega 6 (total, add together if necessary)

Omega 6 grams (mean): ☐ ND

Omega 6 grams SD/SE Choose 1 ☐ ND

Omega 6 grams range to Choose 1 ☐ ND

Omega 6 % Kcal (mean): ☐ ND

Omega 6 % Kcal SD/SE Choose 1 ☐ ND

Omega 6 % Kcal Range to Choose 1 ☐ ND

Omega 6 % fat intake (mean): ☐ ND

Omega 6 % fat SD/SE Choose 1 ☐ **ND**

Omega 6 % fat Range **to** Choose 1 ☐ **ND**

Comments about Fatty Acid values

Submit This Section

For all interventions/exposures,

Is overall quality of Intervention/Exposure data/reporting: ☐ **ND**

- ○ **Good**
- ○ **Fair**
- ○ **Poor**

Why?

Do you find substantial biases related to Treatments: ☐ **ND**

- ○ **Yes**
- ○ **No**

What?

Submit This Section

Outcomes

Submit This Section

SCREENING QUESTION (Complete WHOLE section, INCLUDING 4 Y/N questions at end):

Submit This Section

OUTCOME CATEGORY

What types of Outcomes are reported in study?

- ☐ **Clinical Outcome**
- ☐ **Intermediate Outcome (including CVD risk factors)**

Submit This Section

Clinical Outcomes

CLINICAL OUTCOMES

Describe, if necessary

Mortality/Death:

- ☐ **All Cause Mortality** **Description:**
- ☐ **CVD Mortality** **Description:**
- ☐ **Cardiac Mortality** **Description:**
- ☐ **Stroke Mortality** **Description:**
- ☐ **Other CVD Mortality (or combination) 1** **Description:**
- ☐ **Other CVD Mortality (or combination) 2** **Description:**
- ☐ **Other CVD Mortality (or combination) 3** **Description:**

Ischemic Heart Disease (Coronary Artery Disease):

- ☐ **All Myocardial Infarction (MI, AMI)** **Describe:**
- ☐ **Non-fatal Myocardial Infarction (MI, AMI)** **Describe:**
- ☐ **Unstable Angina (UA)** **Describe:**
- ☐ **Acute Cardiac Ischemia (ACI: combination MI and UA)** **Describe:**
- ☐ **New Onset (Stable) Angina** **Describe:**
- ☐ **Other Cardiac Ischemic Outcome (or combination) 1** **Describe:**
- ☐ **Other Cardiac Ischemic Outcome (or combination) 2** **Describe:**
- ☐ **Other Cardiac Ischemic Outcome (or combination) 3** **Describe:**

Arrhythmia:

- ☐ **Sudden Death** **Description:**
- ☐ **Ventricular Fibrillation** **Description:**
- ☐ **Ventricular Tachycardia** **Description:**
- ☐ **Atrial Fibrillation** **Description:**
- ☐ **Other Arrhythmia (or combination) 1** **Description:**
- ☐ **Other Arrhythmia (or combination) 2** **Description:**
- ☐ **Other Arrhythmia (or combination) 3** **Description:**

Other Non-Ischemic Heart Disease:

- ☐ **Congestive Heart Failure** **Description:**

- ☐ **Left Ventricular Hypertrophy (LVH, not by Echo), How measured?** **D**

Description:

☐ Valvular Disease, which? Description:

☐ Other Non-Ischemic Heart Disease (or combination) 1 Description:

☐ Other Non-Ischemic Heart Disease (or combination) 2 Description:

☐ Other Non-Ischemic Heart Disease (or combination) 3 Description:

Non-Fatal Cerebrovascular Disease

☐ All Stroke Description:

☐ Hemorrhagic Stroke Description:

☐ Thrombotic Stroke Description:

☐ Transient Ischemic Attacks (TIA) Description:

☐ Carotid Artery Disease (not measured by IMT or Doppler), how measured?
Description:

☐ Other Cerebrovascular Disease (or combination) 1 Description:

☐ Other Cerebrovascular Disease (or combination) 2 Description:

☐ Other Cerebrovascular Disease (or combination) 3 Description:

Peripheral Vascular Disease (PVD)

☐ Limb Thrombosis / Leg Ischemia Description:

☐ Claudication (pain walking) Description:

☐ Mesenteric Ischemia Description:

☐ Other Clinical PVD (or combination) 1 Description:

☐ Other Clinical PVD (or combination) 2 Description:

☐ Other Clinical PVD (or combination) 3 Description:

CVD Surgery

☐ Coronary Artery Revascularization (CABG, PTCA, Stent) Description:

☐ Valve Replacement Description:

☐ Carotid Revascularization (+/- stent) Description:

☐ Peripheral Revascularization (+/- stent) Description:

☐ Amputation Description:

☐ Other CVD Surgery, which? Description:

Other

☐ Other Clinical (or combination) 1 Description:

☐ Other Clinical (or combination) 2 Description:

☐ Other Clinical (or combination) 3 Description:

☐ Other Clinical (or combination) 4 Description:

☐ Other Clinical (or combination) 5 Description:

☐ Other Clinical (or combination) 6 Description:

Comment about Clinical Outcomes

Submit This Section

Definite Intermediate

INTERMEDIATE OUTCOMES

!! Complete WHOLE Data Extraction Form !!

Describe, if necessary

Lipids:

- ☐ **ND**
- ☐ **Total Cholesterol** **Description:**
- ☐ **LDL** **Description:**
- ☐ **HDL** **Description:**
- ☐ **Triglycerides** **Description:**
- ☐ **Lp(a)** **Description:**

.....Lipid units: Ignore this box | Choose 1

Blood Pressure:

- ☐ **ND**
- ☐ **Systolic (SBP)** **Description:**
- ☐ **Diastolic (DBP)** **Description:**
- ☐ **Hypertension (HTN) prevalence (DEFINE HTN):** **Description:**

Diabetes:

- ☐ **Hgb A1c (Glycohemoglobin)** **Description:**
- ☐ **Fasting Glucose/Blood Sugar (FBS)** **Description:**
- ☐ **Diabetes incidence (new cases)** **Description:**

.....Hgb A1c and FBS units: Ignore this box | Choose 1

ECG Measurements (24 hour, or longer, Holter):

- ☐ **Heart Rate Variability** **Describe:**

Other Serum Markers:

- ☐ **C-reactive Protein (CRP)** **Description:**
- ☐ **Fibrinogen** **Description:**

.....CRP units: Ignore this box | Choose 1

.....Hcy units: Ignore this box | Choose 1

.....Fibrinogen units: Ignore this box | Choose 1

Other Diagnostic Tests [Extract Results on Paper]:

☐ **Carotid Intima Media Thckness (IMT) aka Doppler** **Description:**

☐ **Coronary Arteriography** **Description:**

☐ **Endothelial-Dependent Vasorelaxation; aka angiography, stenosis, restenosis, minimum lume diameter, mean lumen diameter, MLD, ?PTCA** **Description:**

Submit This Section

Possible Intermediate

INTERMEDIATE OUTCOMES

!! Complete Only Selected SECTIONS of Data Extraction Form !!

Describe, if necessary

Lipids:

☐ **Apo A-1** **Description:**

☐ **Apo B-48** **Description:**

☐ **Apo B-100** **Description:**

☐ **Apo B (total, any)** **Description:**

☐ **Apo C-III** **Description:**

☐ **VLDL (only if Tg NOT reported)** **Description:**

☐ **Remnant-like Particles (RLP) or Total Atherogenic Particles or Intermediate Density Lipoprotei (IDL)** **Description:**

☐ **Free Fatty Acids (FFA) or Non-Esterified FA (NEFA) [SEE NOTE BELOW]** **Description:**

☐ **Lipoprotein or Apo C-III Genetic Polymorphisms [SEE NOTE BELOW]** **Description:**

.....FFA or NEFA = Concentration in circulation. Not composition.

Genetic Polymorphisms:

☐ **Genetic Polymorphism** **Description:**

Blood Pressure:

☐ **MAP (ONLY if no results for SBP or DBP)** **Description:**

Diabetes:

☐ **Insulin, Fasting** **Description:**

☐ **Microalbuminuria (albumin in urine)** **Description:**

☐ **Glycosuria (glucose/sugar in urine)** **Description:**

ECG Measurements (Regular ECG or Holter):

☐ **Heart Rate** **Describe:**

☐ **QTc** **Describe:**

☐ **ST elevation** **Describe:**

☐ **PR inteval** **Describe:**

- [ ] QRS duration Describe:
- [ ] Other ECG measurement Which?

Other Diagnostic Tests:

- [ ] Echocardiography Description:
- [ ] Exercise Tolerance Test (ETT, Treadmill) Description:
- [ ] Other Nuclear Cardiac Study, which? Description:
- [ ] Carotid Doppler (carotid ultrasonography) Description:
- [ ] Ankle-Arm Brachial Index (AABI) Description:
- [ ] Carotid Stenosis (by Doppler or MRA) Description:
- [ ] Extra-Carotid (Head/Neck) Stenosis (by MRA) Description:
- [ ] Brain MRI (White matter lesions) Description:
- [ ] Other Diagnostic Test, which? Description:

Other Serum Markers etc.:

- [ ] Bleeding Time Description:
- [ ] Homocysteine (Hcy) Description:
- [ ] Platelet Aggregability Description:
- [ ] Creatine Kinase Description:
- [ ] Factor VII Description:
- [ ] Factor VIII Description:
- [ ] Factor XII Description:
- [ ] von Willebrand Factor (vWF) Description:
- [ ] Interleukin-6 (IL-6) Description:
- [ ] VCAM-1 Description:

Comment about Intermediate Outcomes

Submit This Section

Does study report on correlation between dose of Omega 3 and treatment effect? ☐ N

- ○ Yes
- ○ No

Submit This Section

Does study report association/correlation between intake levels of DHA, EPA, DPA, ALA with blood, tissue or cell membrane levels ☐ ND

- ○ Yes

○ No

Submit This Section

ADVERSE EVENTS/SIDE EFFECTS

SCREENING QUESTION:

Are Adverse Events, Side Effects, Complications DUE TO Omega-3 or Fish Oil SUPPLEMENT Reported? ☐ **ND**

○ **Yes**

○ **No**

If YES, What was reported?

Submit This Section

INTERACTIONS WITH OTHER MEDICATIONS

Are Interactions between Omega 3 SUPPLEMENTS and Any Medications Reported ☐ I

○ **Yes**

○ **No**

If YES, What was reported?

Submit This Section

Results (continuous data)

Submit This Section

DUPLICATE THIS SECTION FOR EACH RESULT SECTION.
THERE SHOULD BE A NEW SECTION FOR EACH "STUDY ARM - OUTCOME" COMBINATION
(e.g., If supplement vs placebo with LDL, HDL, Tg outcomes, there should be 6 (2x3) Results sections.)
Do Not Use The Template (titled Result) to Enter Data.
Title each new Continuous Result section with "Outcome_Tx Arm No." or "Outcome_Control"
Also name Section ID the same
(eg, LDL_1, LDL_2, LDL_Control, HDL_1, HDL_2, HDL_Control)

Treatment Arm # or Placebo/Control ☐ **ND**

Treatment Arm Brief Description ☐ **ND**

Number evaluated for this outcome ☐ **ND**

Submit This Section

Answer the following question Once only for each outcome

Was this outcome reported as a Primary or Secondary Outcome? ☐ **ND**

- ○ **Primary Outcome**
- ○ **Secondary Outcome**
- ○ **Unclear (Desribe why below)**

Why unclear?

Description of Outcome (if necessary):

Outcome Units (type in if not in menu. Use Dichotomous form if N or % subjects) mg/dL ☐ **ND**

Submit This Section

Reported Within-Treatment Difference:

Reported data re: difference in outcome level between final and baseline times.
NOT differences between interventions.
Reported value for final value minus baseline value.
Be Careful: Studies can report a decrease as either a positive or negative number (and vice versa).
Report Real change.

Reported difference Choose 1 ☐ **ND**

+/- SD / SE Choose 1 ☐ **ND**

Range **to** Choose 1 ☐ **ND**

Comment about Within-Treatment Difference

Submit This Section

Baseline Data:

Baseline level Choose 1 ☐ **ND**

+/- SD / SE Choose 1 ☐ **ND**

Range [ ] **to** [ ] Choose 1 ☐ **ND**

Comment about Baseline Data

[ ]

----- ----- ----- -----

Submit This Section

Follow-up / Final Data or Clinical Event Data:

Final level or Events [ ] Choose 1 ☐ **ND**

+/- SD / SE [ ] Choose 1 ☐ **ND**

Range [ ] **to** [ ] Choose 1 ☐ **ND**

Comment about Final Data

[ ]

----- ----- ----- -----

Submit This Section

Reported Treatment vs Control Difference:

Reported data re: difference between CHANGE in outcome leve between intervention and control.
NOT difference between final outcome levels.
[Tx(final) - Tx(baseline)] - [Control(Final) - Control(Baseline)]

Reported difference [ ] Choose 1 ☐ **ND**

+/- SD / SE [ ] Choose 1 ☐ **ND**

Range [ ] **to** [ ] Choose 1 ☐ **ND**

Comment about Between-Treatment Difference

[ ]

----- ----- ----- ----- ----- -----

Submit This Section

Statistical Significance

p-value of Within-Treatment Difference [ ] ☐ **ND**

p-value of Difference in Change Treatment vs Control [ ] ☐ **ND**

Comment about Statistical Significance

[ ]

----- ----- ----- ----- ----- -----

Submit This Section

Correlation (r or r^2)

Eg, Spearman correlation

r value between predictor ("intervention") and outcome ☐ **ND**

p-value (r) ☐ **ND**

OR

r^2 (r squared) value between predictor and outcome ☐ **ND**

p-value (r^2) ☐ **ND**

Comment about correlation

Submit This Section

Results (dichotomous data or OR/RR)

Submit This Section

DUPLICATE THIS SECTION FOR EACH RESULT SECTION.
This will include both treatment and control arm
THERE SHOULD BE ONE NEW SECTION FOR EACH "OUTCOME."
Title each new Dichotomous Result section with "Outcome"

Submit This Section

Answer the following question Once only for each outcome

Was this outcome reported as a Primary or Secondary Outcome? ☐ **ND**

- ○ **Primary Outcome**
- ○ **Secondary Outcome**
- ○ **Unclear (Desribe why below)**

Why unclear?

Description of Outcome (if necessary):

Submit This Section

2x2 Data

PREFERABLY ENTER NUMBER OF SUBJECTS. IF NOT REPORTED ENTER % OF SUBJECTS IN SECTION BELOW.

NUMBER

Enter NUMBER of Subjects That Belong in Each Cell

Enter EITHER (number with outcome AND number w/o outcome) OR (number with outcome AND total (denominator))

CONTROL: Number WITH Outcome

CONTROL: Number WITHOUT Outcome

CONTROL: Total (Denominator)

Tx Arm 1: Number WITH Outcome

Tx Arm 1: Number WITHOUT Outcome

Tx Arm 1: Total (Denominator)

Tx Arm 2: Number WITH Outcome

Tx Arm 2: Number WITHOUT Outcome

Tx Arm 2: Total (Denominator)

Tx Arm 3: Number WITH Outcome

Tx Arm 3: Number WITHOUT Outcome

Tx Arm 3: Total (Denominator)

Tx Arm 4: Number WITH Outcome

Tx Arm 4: Number WITHOUT Outcome

Tx Arm 4: Total (Denominator)

----- ----- ----- -----

Submit This Section

PERCENT

Enter PERCENT of Subjects With Outcome AND Denominator

Control: Percent WITH Outcome

Control: Total (Denominator)

Tx 1: Percent WITH Outcome

Tx 1: Total (Denominator)

Tx 2: Percent WITH Outcome

Tx 2: Total (Denominator)

Tx 3: Percent WITH Outcome

Tx 3: Total (Denominator)

Tx 4: Percent WITH Outcome

Tx 4: Total (Denominator)

--- --- --- ---

Submit This Section

Odds Ratio / Risk Ratio Data

If Results Presented in OR or RR format, Enter Here

There Are Separate Sections Below for UNADJUSTED and ADJUSTED OR/RR

UNADJUSTED OR/RR

Metric ☐ **ND**

- ○ **OR (odd ratio)**
- ○ **RR (Risk Ratio/Relative Risk)**
- ○ **Other** **Which?**

Tx 1 vs Control:

Tx 2 vs Control:

Tx 3 vs Control:

Tx 4 vs Control:

--- --- --- ---

ADJUSTED OR/RR

Variables Adjusted For:

Metric ☐ **ND**

- ○ **OR (odd ratio)**
- ○ **RR (Risk Ratio/Relative Risk)**
- ○ **Other** **Which?**

Tx 1 vs Control:

Tx 2 vs Control:

Tx 3 vs Control:

Tx 4 vs Control:

Submit This Section

Statistical Significance

For 2x2 data, OR, RR, etc.

p-value of UNADJUSTED Tx 1 vs Control ☐ **ND**

p-value of UNADJUSTED Tx 2 vs Control ☐ ND

p-value of UNADJUSTED Tx 3 vs Control ☐ ND

p-value of UNADJUSTED Tx 4 vs Control ☐ ND

p-value of ADJUSTED Tx vs Control ☐ ND

Comment about Statistical Significance

Submit This Section

Questions

Submit This Section

Instructions

After Extracting Data from the Article, Please Review the List of Questions.

Check off all questions that are potentially addressed by this paper.

Use a LOW THRESHOLD for checking a question.

Ie, If you think this paper might answer a question, check off the question.

It's better to incorrectly connect a paper to a question than to incorrectly not mark a paper as addressing a question.

However, a study should DIRECTLY address a problem. For example, to address the question about the ef of baseline diet on treatment effect, the paper should directly compare different cohorts who had different baseline diets.

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The Questions are Sorted by Chapter and Human Topic

Note that Questions Appropriate for Both Clinical and Intermediate Outcomes are Listed under BOTH Secti

Check off both if appropriate.

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Submit This Section

Chapter 1 Questions ☐ ND

☐ **What are the estimates of the average intakes of DHA, EPA, ALA, fish, fish oil, omega-6, omega 6/omega-3 ratio in the US population?**

☐ **What are the consumption levels of various subpopulations, based on geography (within the U ethnicity, socio-economic status, gender, age, urban vs rural?**

☐ **What are the estimates of the average intakes of DHA, EPA, ALA, fish, fish oil, omega 6, and omega 6/omega 3 ratio in individuals with and without CVD?**

Chapter 3 CLINICAL ☐ ND

☐ **What is the efficacy of omega-3 fatty acids (DHA, EPA, ALA, supplements, and fish consumpti in reducing CVD events (including all-cause mortality, CVD mortality, non-fatal CVD events, and r diagnosis of CVD)?**

☐ **What is the efficacy of omega 3 FAs in preventing incident CVD events in people without know**

CVD (primary prevention) and with known CVD (secondary prevention)?

☐ **How does the efficacy of omega 3 FAs to prevent incident CVD events differ in sub-population including men, pre-menopausal women, post-menopausal women, and different age groups?**

☐ **What is effect of potential confounders such as lipid levels, body mass index (BMI), blood pressure, diabetes, aspirin use, and hormone replacement therapy, cardiovascular drugs ? on associations from prospective cohort studies?**

☐ **What is the efficacy of different specific omega 3 FAs (DHA, EPA, ALA) and different ratios of omega 3 FA components in dietary supplements on CVD events?**

☐ **Does the ratio of omega 6 FA to omega 3 FA intake affect the efficacy of omega 3 FA intake on CVD events?**

☐ **How does the efficacy of omega 3 FAs on CVD events differ by source (e.g., dietary fish, dietar oils, dietary plants, fish oil supplement, flax seed supplement)?**

☐ **Is there a threshold or dose-response relationship between omega 3 FAs and CVD events?**

☐ **How does the duration of intervention or exposure affect the treatment effect of omega 3 on C events?**

☐ **Are treatment effects of omega 3 FAs on CVD events sustained after the intervention or expos stops?**

☐ **What is the effect of baseline dietary intake of omega 3 FAs on the efficacy of omega 3 FA supplements on CVD events?**

☐ **Does the use of CVD and CVD-risk-factor medications (including lipid lowering agents and diabetes medications) affect the efficacy of omega 3 FAs?**

☐ **What is the relative efficacy of omega 3 FAs on different CVD events? Can the CVD events be ordered by strength of treatment effect of omega 3 FAs?**

Chapter 3 INTERMEDIATE ☐ ND

☐ **What is the effect of omega-3 fatty acids (DHA, EPA, ALA, supplements, and fish consumption CVD markers**

☐ **What is the efficacy of omega-3 fatty acids (DHA, EPA, ALA, supplements, and fish consumpti in reducing CVD risk factors, specifically, new-onset Type II DM, new-onset insulin resistance/metabolic syndrome, progression of insulin resistance, new-onset HTN, BP among hypertensive patients, Abnormal lipoprotein levels?**

☐ **What is the efficacy of different specific omega 3 FAs (DHA, EPA, ALA) and different ratios of omega 3 FA components in dietary supplements on CVD markers?**

☐ **What is effect of potential confounders such as lipid levels, body mass index (BMI), blood pressure, diabetes, aspirin use, and hormone replacement therapy, cardiovascular drugs ? on associations from prospective cohort studies?**

☐ **Does the ratio of omega 6 FA to omega 3 FA intake affect the efficacy of omega 3 FA intake on CVD markers and risk factors?**

☐ **How does the efficacy of omega 3 FAs on CVD markers differ by source (e.g., dietary fish, dieta oils, dietary plants, fish oil supplement, flax seed supplement)?**

☐ **Is there a threshold or dose-response relationship between omega 3 FAs and CVD risk factors markers?**

☐ **How does the duration of intervention or exposure affect the treatment effect of omega 3 on C markers?**

☐ **Are treatment effects of omega 3 FAs on CVD markers sustained after the intervention or expo stops?**

- [ ] **What is the effect of baseline dietary intake of omega 3 FAs on the efficacy of omega 3 FA supplements on CVD markers?**
- [ ] **Does the use of CVD and CVD-risk-factor medications (including lipid lowering agents and diabetes medications) affect the efficacy of omega 3 FAs?**
- [ ] **What is the relative efficacy of omega 3 FAs on different CVD markers? Can the CVD markers b ordered by strength of treatment effect of omega 3 FAs?**

Adverse Events / Drug Interactions ☐ ND

- [ ] **What adverse events of omega 3 FA dietary supplements intake are reported in studies of CVD events and markers?**
- [ ] **What adverse events of omega 3 FA dietary supplements intake are reported specifically amor diabetics and people with CVD in studies of CVD events and markers?**
- [ ] **What interactions of omega 3 FA dietary supplements with medications are reported in studies CVD events and markers?**
- [ ] **What interactions of omega 3 FA dietary supplements with medications are reported specifical among diabetics and people with CVD in studies of CVD events and markers?**

Miscellaneous ☐ ND

- [ ] **What is the association of intake levels of DHA, EPA, ALA with blood, tissue, and cell membra levels?**
- [ ] **What are the metabolic pathways from dietary sources of omega 3 and omega 6 FAs to prostaglandins and other key metabolites?**
- [ ] **What is the efficiency of conversion from ALA to DHA/EPC, DHA/EPC to ALA, DHA to EPA and EPA to DHA?**

Possible Duplicate Questions that may be deleted ☐ ND

- [ ] **Do different dietary sources of omega 3 FAs and different ratios of DHA, EPA, and ALA have different physiologic actions on CVD, diabetes, and hypertension?**
- [ ] **What is the effect of baseline dietary intake of specific fats on associations from prospective cohort studies?**

Comments:

Submit This Section

Appendix C. Evidence Table (Part 1)

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Agren 1988	n3 Enrol: 43 Control enrol: 19 Age: 22±3 y SD % Male: 100 Country: Finland Sites: 1	Randomized controlled trial (parallel) 15 wk	Male students Exclusion: Fish allergy	SBP: 125 DBP: 78 TC: 4.49 mmol/L Tg: 0.97 mmol/L BMI Men: 22.3 kg/m^2	1. Fish diet: 180 g/d, Total n-3: 1.8 g 2. Fish diet and low saturated fat: 180 g/d. Advised diminishing fat intake Total n-3: 1.8 g	1. One fish meal (180 g) every 2 weeks. 2. Low saturated fat diet	Apo A1 Apo B Platelet PL RBC PL
Agren 1991	n3 Enrol: 49 Control enrol: 50 Age: 22±3 y SD % Male: 0 Country: Finland Sites: 1	Randomized controlled trial (parallel) 14 wk	Healthy female students Exclusion: Athletes	TC: 4.17 mmol/L LDL: 2.58 mmol/L HDL: 1.21 mmol/L Tg: 0.83 mmol/L BMI Women: 21.0 kg/m^2	1 One fish meal (150 g) Actual fish eaten (fish and fish+exercise) = 3.5/week, 39% rainbow trout, 20% vendace, 12% perch, 7% pike, 22% Baltic herring. Total n-3: 0.9 g, EPA: 0.25 g, DHA: 0.5 2. Same as above. Recommended increase of 30 min aerobic exercise 3x/w.	1. No change in diet or exercise, Average 0.4 fish meal (150 g) per week (both controls) 2. As above, with exercise	Apo A1 Apo B Platelet PL RBC PL
Agren 1996	n3 Enrol: 15 n3 Enrol: 15 n3 Enrol: 15 Control enrol: 15 Age: 23±2 y SD % Male: 100 Country: Finland Sites: 1	Randomized controlled trial (parallel) 15 wk	Healthy male students	TC: 291 mg/dL BMI Men: 23.7 kg/m^2	1. Fish meal qD, rainbow trout, Baltic herring, vendace (4.3 meals/week) 2. 4 g fish oil 3. 4 g algae DHA oil	No supplement, regular diet	Apo A1 Apo B Plasma PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Agren 1997	n3 Enrol: 15 n3 Enrol: 15 n3 Enrol: 15 Control enrol: 15 Age: 23±2 y SD % Male: 100 Country: Finland Sites: 1	Randomized controlled trial (parallel) 15 wk	Healthy male students	TC: 291 mg/dL BMI Men: 23.7 kg/m^2	1. Fish meal qD, rainbow trout, Baltic herring, vendace (4.3 meals/week) 2. 4 g fish oil 3. 4 g algae DHA oil	No supplement, regular diet	Factor VII Fibrinogen Plt Aggr
Alaswad 1999	n3 Enrol: 11 Control enrol: 12 Age: 55±11 y SD % Male: 89 combined Country: US Sites: 1	Randomized controlled trial (parallel) 3 mo	HDL ≤ 35 mg/dL and Tg ≤ 400 Exclusion: Fertile premenopausal women peptic ulcer gout organ transplant liver kidney or thyroid disease DM	TC: 194 mg/dL LDL: 124 mg/dL HDL: 33 mg/dL Tg: 183 mg/dL Wgt: 84 Kg Glucose: 84 mg/dL	Omacor 4 g/d	Calcium gluconate 1500 mg	Lp(a)
Allman-Farinelli 1999	n3 Enrol: 15 Control enrol: 15 Age: 18-35 % Male: 100 Country: Australia Sites: 1	Randomized controlled trial (parallel) 6 wk	Healthy men TC<6.8 mmol/L Tg<3.0 Exclusion: Chronic illness Rx use, excessive exercise erratic food habits smokers	No differences in BMI,TC, Tg	ALA-rich diet, flaxseed 18.3 mg per 100 g	LA-rich safflower oil	Factor VII Factor VIII Fibrinogen vWF
Angerer 2002 SCIMO subset	n3 Enrol: 112 Control enrol: 111 Age: 58.2 % Male: 82 Country: Germany Sites: 1	Randomized controlled trial (parallel) 2 y	Pts 18-75 y with diagnostic coronary angiography with >20% stenosis in >1 vessel. Exclusion: PCTA w/in 6 mo, cardiac transplant hemodynamic relevant left main stenosis or prox stenosis in 3 vessels, biplane LVEF <35%, diabetes	Prior MI 49 v 56% Prior TIA: 2.3 v 1% Prior stroke: 1 v 2.4% HTN: 52 v 44% 1 Aspirin=97%	6 caps/d EPA+DHA =3.3 g/d EPA+DHA Then 3 caps/d for 21 mo 1.7 g EPA+DHA		Tg LDL HDL IMT RBC PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Bairati 1992a	n3 Enrol: 59 Control enrol: 60 Age: 54 Male: 81 Country: Canada Sites: 1	Randomized controlled trial (parallel) 6 mo	Patients referred for first angioplasty	Hx HTN: 36 vs 35 % Hx DM: 7% Angina classes III and IV: 61 vs 63%	15 caps 1-g fish oil EPA: 2.7 g DHA 1.8 g	Olive oil 15 g	Restenosis
Bairati 1992b	n3 Enrol: 107 Control enrol: 98 Age: 54±9.8 y SD % Male: 80 Country: Canada Sites: 1	Randomized controlled trial (parallel) 6 mo	Referred for a first PTCA Exclusion: PTCA was not performed was tried unsuccessfully or led to severe complications.	SBP: 127.1 DBP: 77.1 TC: 6.24 mmol/L LDL: 4.08 mmol/L HDL: 1.04 mmol/L Tg: 2.31 mmol/L BMI: 26.7 kg/m^2 DM: 9% Prevalence	15 MaxEPA EPA: 2.7 g DHA: 1.8 g	Olive oil 15 g	TC Tg LDL HDL
Balestrieri 1996	n3 Enrol: 14 Control enrol: 14 Age: 45.2 % Male: 44 Country: Italy Sites: 1	Cross-over 4 wk	Heterozygous familial hyperlipidemia on simvastatin		6 g Esapent containing 85% n3 FA	Olive oil 6 g	Apo A1 Apo B
Bellamy 1992	N3 enrol: 60 Control enrol: 53 Age: 54 y % Male: 75 Race: ND Country: UK Number of Sites: 1	Randomized controlled trial (parallel) 6 mo	All patients undergoing coronary angioplasty	%diabetes: 3.3 vs 3.8 HTN 8.3 vs 15.1% Hyperlipidemic: 20% vs 17% Previous MI: 32 vs 36% Stable Angina: 70 vs 77% Unstable angina: 18 vs 13%	3 g of n-3 FA started 1-2 days prior to angioplasty EPA: 1.8 g DHA: 1.2 g	Standard treatment	Restenosis

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Bemelmans 2002 MARGARIN	n3 Enrol: 103 Control enrol: 0 Age: 55±10 y SD % Male: 36.9 Country: Netherlands Sites: 1	Non-Randomized non-controlled study 2 yr	30-70 y TC 6.0- 8.0 mmol/l at least 2 CVD risk factors: HTN (diastolic ≥ 95 mmHg and/or systolic ≥ 160 mm Hg) or HTN Rx BMI ≥ 27 kg/m^2 smoking hx of CVD or a family hx of onset of CVD before 60 y Exclusion: DM hypothyroidism use of aspirin anti-coagulants or lipid lowering drugs	SBP: 146 TC: 6.8 mmol/L LDL: 4.6 mmol/L HDL: 1.2 mmol/L Tg: 2.1 mmol/L BMI: 29.7 kg/m^2	Nutritional educaton + ALA margarine-enriched diet (46% LA + 15% ALA)= 6.3 g/d	No control arm	IMT
Berrettini 1996	n3 Enrol: 20 Control enrol: 20 Age: 58 y % Male: 77 Country: Italy Sites: ND	Randomized controlled trial (parallel) 16 wk	Chronic vascular atherosclerotic disease stable obstructive arterial disease of lower limbs; previous stroke (>12 mo) or TIA (> 3 mo) previous MI (> 12 mo) or stable exertional angina Exclusion: > 75 y IDDM severe HTN (DBP > 120 mmHg) chronic wasting disease (malignanacy acute or chronic liver disease) kidney insufficiency (blood creatinine > 2 mg/d) and active peptic diseases compliance to Rx extreme dietary habits	TC: 234 mg/dL LDL: 102 mg/dL HDL: 37 mg/dL Tg: 209 mg/dL BMI: 25 kg/m^2 %DM: 10 v 15	3 g/d Seacor EPA: 1.53 g DHA:1.05 g	Corn oil 3 g/d	Factor VII

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Bonaa 1992	n3 Enrol: 72 Control enrol: 74 Age: 49±7 y SD % Male: 61 Country: Norway Sites: ND	Randomized controlled trial (parallel) 10 wk	TC 5.2 - 10.0 DBP 85 -100 mmHg SBP < 180 mmHg Exclusion: CVD bleeding disorder DM disabling chronic disease psychiatric disease alcoholism BMI > 32 kg/m^2	SBP: 144.3 DBP: 94.9 BMI: 26.0 kg/m^2	6 g K85 per day EPA: 3.3 g DHA: 1.8 g	Corn oil 6 g	TC Tg LDL HDL Apo A1 Apo B Plasma PL
Bonnema 1995	n3 Enrol: 14 Control enrol: 14 Age: 47 ±16 y SD % Male: 57 Country: Denmark Sites: 1	Randomized controlled trial (parallel) 6 mo	Insulin-treated DM with incipient nephropathy (microalbuminuria 0.3 - 3.0 mmol/L Exclusion: Non-diabetic nephrological disorder lipid-lowering or vasoactive Rx other than diuretics	All on conventional diabetic diet SBP: 139 DBP: 78 TC: 5.8 mmol/L HDL: 1.63 mmol/L Tg: 1.22 mmol/L	6 Pikasol	Olive oil 6 g	Hbg A1c
Borchgrevink 1966	n3 Enrol: 100 Control enrol: 37 Age: 57.3 y % Male: 100 Country: Norway Sites: 1	Randomized controlled trial (parallel) Mean 8.5 mo	Male <70 y , discharged with dx of impending MI Exclusion: ND	%previous MI: 22 %previous angina: 49 %previous stroke: 3 % DM: 3 % on diuretics: 13 % anticoagulant: 11	10 ml/d linseed oil 50% ALA 17% LA 19% oleic acid 14% saturated FA	10 ml/d Corn oil	TC
Brox 2001	n3 Enrol: 37 n3 Enrol: 38 Control enrol: 37 Age: 55 y Country: Norway Sites: 1	Randomized controlled trial (parallel) 14 mo	Clinically healthy adult TC 7.0 - 9.5 mmol/L no lipid-lowering Rx		1. 14 mL/d seal oil EPA: 1.1 g DHA: 1.5 g 2. 15 mL/d cod liver oil EPA: 1.5 g DHA: 1.8 g	No oil	TC HDL Lp(a) Apo A1 Apo B-100 Plasma PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Cairns 1996 EMPAR Study	n3 Enrol: 325 Control enrol: 328 Age: 57 y % Male: 82 Country: Canada Sites: 4	Randomized controlled trial (parallel) ~18 wk	Scheduled for PTCA diagnostic coronary angiogram with at least 1 localized coronary artery stenosis ≥ 50% reduction of lumen diameter ≥ 18 y Exclusion: Certain CAD characteristics (culprit lesion in saphenous bypass graft at site of previously dilated Restenosis or involving left main coronary artery MI < 28 d UA necessitating PTCA < 48 hr variant angina	DM: 9% Prevalence	18 MaxEPA EPA 3.24 g DHA 2.16 g	18 corn oil	TC Tg LDL HDL Restenosis
Chan 2002	n3 Enrol: 12 n3 Enrol: 11 Control enrol: 12 Age: 54±9.5 y SD % Male: 100 Country: Australia Sites: 1	Randomized controlled trial (parallel) 6 wk	Obese men (BMI > 29 kg/m^2 waist circumference > 100 cm waist-to-hip ratio > 0.97) with dyslipidemia (TC >5.2 and Tg > 1.2 mmol/L) Exclusion: DM macroproteinuria Cr > 120 mcg/L hypothyroidism abnormal LFTs or muscle enzymes > 30 g alcohol/day.	SBP: 133 DBP: 78.5 TC: 5.95 mmol/L LDL: 3.89 mmol/L HDL: 1.04 mmol/L Tg: 1.90 mmol/L BMI Men: 33.6 kg/m^2	1. 4 Omacor g/d EPA: 1.8 g DHA: 1.56 g 2. Omacor 4 g and atorvastatin 40 mg EPA: 1.8 g DHA: 1.56 g	1. Corn oil 4 g 2. Corn oil 4 g and atorvastatin	CRP Apo A1 Apo B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Chan 2003	n3 Enrol: 12 Control enrol: 12 Age: 58±8 y SD % Male: 100 Country: Australia Sites: ND	Randomized controlled trial (parallel) 6 wk	Obese Males (> 100 cm waist circumference waist-hip ratio > 0.97 BMI > 29 kg/m^2) Exclusion: DM apolipoprotein E2/E2 genotype macroproteinuria creatinemia (> 120 mmol/L) hypothyroidism abnormal liver enzymes	SBP: 132 DBP: 74 TC: 5.93 mmol/L LDL: 3.92 mmol/L HDL: 0.99 mmol/L Tg: 2.00 mmol/L BMI Men: 35 kg/m^2	1. 4 Omacor g/d EPA: 1.8 g DHA: 1.56 g 2. Omacor 4 g and atorvastatin 40 mg EPA: 1.8 g DHA: 1.56 g	1. Corn oil 4 g 2. Corn oil 4 g and atorvastatin	Insulin
Christensen 1996	n3 Enrol: 28 Control enrol: 27 Age: ND % Male: ND Country: Denmark Sites: 1	Randomized controlled trial (parallel) 12 wk	Discharged hospital after MI and had EF<0.40 Exclusion: Age >75 y pacer permanent tachyarrhythmia serious non-cardiac disease		8 g Pikasol Total n-3: 5.2 g	Olive oil 8 g	HR var
Christensen 1997	n3 Enrol: 25 n3 Enrol: 18 Control enrol: 9 Age: 63±7 y SD % Male: ND Country: Denmark Sites: 1	Cross-sectional study	Discharged hospital after MI and had EF<0.40 Exclusion: Age >75 y pacer permanent tachyarrhythmia serious non-cardiac disease		1. Fish ~1x/wk 2. Fish at least 2x/wk	Never ate fish	HR var

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Christensen 1999	n3 Enrol: 20 n3 Enrol: 20 Control enrol: 20 Age: 38 y % Male: 58 Country: Denmark Sites: 2	Randomized controlled trial (parallel) 12 wk	Healthy subjects recruited from medical staff bank employees and students in Aalborg Denmark.	BMI Men: 25 kg/m^2 BMI Women: 23 kg/m^2	1. 3 Pikasol, 2.0 g n-3 PUFA, 7 capsules olive oil placebo capsules EPA: 0.9 g DHA: 0.8 g 2. 10 Pikasol 6.6 g n-3 PUFA, EPA: 3.0 g DHA: 2.9 g	10 olive oil	Granulocyte PL HR var Plt PL
Cobiac 1991	n3 Enrol: 12 n3 Enrol: 13 Control enrol: 6 Age: 30-60 y % Male: 100 Country: Australia Sites: 1	Randomized controlled trial (parallel) 5 wk	Men aged 30-60 y. mildly hyperlipidemic (TC>5.8 mmol/L) normotensive (BP<160/90) Exclusion: Heart disease bleeding disorder liver or kidney disorders gout DM recent CVA obesity steroids NSAIDs ASA beta-blocker allopurinol cardiac glycoside. EtOH > 40 g/d Cigarettes > 20/d	All on low fish diet SBP: 128 mm Hg DBP: 80 mm Hg TC: 6.7 mmol/L Tg: 1.9 mmol/L	1. Fish oil 4.6g/d EPA+DHA 2. Fatty fish diet: Atlantic salmon (1 kg /wk) and Norwegian sardines (150 g/wk) EPA+DHA 4.6 g/d	Palm oil, safflower oil and olive oil.	Apo A1 Apo B Fibrinogen Plasma PL
Conquer JA 1999	n3 Enrol: 10 Control enrol: 10 Age: 30±1.5 y SD % Male: 100 Country: Canada Sites: ND	Randomized controlled trial (parallel) 42 d	Healthy normolipidemic males	BMI Men: 26.4 kg/m^2	20 1-g seal oil capsules per day EPA: 1.3 g DHA: 1.7 g DPA: 0.8 g	Vegetable oil (evening primrose oil) supplement, 20 capsules per day	Lp(a) Factor VIII vWF

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
de Lorgeril 1994 Lyon Diet Heart Study	n3 Enrol: 302 Control enrol: 303 Age: 53.5±10 y SD % Male: 89.4 Country: France Sites: 6 clinics	Randomized controlled trial (parallel) 104 wk	Survived MI within 6 mo of enrolment Age < 70 y clinically stable Exclusion: Heart failure (NYHA III or IV); HTN (>180/110); Inability to complete exercise test due to recurrent angina ventricular arrhythmias or AV block; any other condition thought to limit survival or ability to participate in a long-term trial	BMI: 25.8 kg/m^2	Mediterranean diet with canola based margarine: More bread, more root and green vegetables, more fish, less meat (beef, lamb, and pork to be replaced with poultry), no day without fruit. Butter and cream replaced with margarine from canola.	Prudent diet	TC Tg LDL HDL Lp(a) Apo A1 Apo B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Deck 1989	Enrol n-3: 8 Enrol Cont: 8 Age: 51.3 +/- 8.94 y SD % Male: 75 Race: ND Country: US Sites: 2	Cross-over 8 wk	Adult, 21 - 65 y, hypertriglyceridemia including lipoprotein phenotypes IIB (Tg > 2.25 mmol/L, LDL > 4.15 mmol/L) or IV (Tg > 2.25 mmol/L, LDL < 4.15 mmol/L) Exclusion: Tg > 8.46 mmol/L, lipoprotein phenotyes I, IIA, & V, lipid-lowering Rx, addition of diuretics or B-blocker Tx, corticosteroids < 6 wks, NSAIDs < 2 wks, concomitant drug Tx with steroids, anticoagulants or antiplatelet Rx, hx of < 6 mo active CVD, cerebrovascular, hepatobiliary, pancreatic, kidney, endocrinologic, hematologic, or GI disorders including malabsorption states, any coagulopathies, significant abnormal blood chem levels exceeding 20% of upper limits of normal other than lipids abnormal platelets, pregnancy, DM, fasting glucose > 7.8 mmol/L, drug or alcohol abuse	TC: 5.77 mmol/L Tg: 4.13 mmol/L BMI: Men 26.6 Women: 31.5	9 Fish/marine oil 4.6 g/d	Corn oil	LDL Apo B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Dehmer 1988	n3 Enrol:149 Control enrol: 43 Age: 56 y % Male: 100% Country: US Sites: 1	Randomized controlled trial (parallel) 3-4 mo	Referrals to cardiac catheterization lab Exclusion**:** Age >80 y severe medical problems	%DM: 28 vs 21 %previous MI: 72 vs 60 %previous CABG: 23 vs 21% %unstable angina: 41 vs 32	18 MaxEpa: EPA 3.2 g DHA 2.2 g	No oil	Restenosis Plt PL
DeLany 1990	n3 Enrol: 5 Control enrol: 5 Age: 23 y % Male: 100% Country: US Sites: 1	Parallel controlled trial 5 wk	Healthy males Exclusion: metabolic disease, smoking or drug use		5 g fish oil substituted for margarine in prepared 2 day rotating menu	5 g margarine as part of prepared 2 day rotating menu	Apo B100
Deslypere 1992	n3 Enrol: 15 n3 Enrol: 15 n3 Enrol: 14 Control enrol: 14 Age: 56±16.5 y SD % Male: 100 Country: Belgium Sites: 4	Randomized controlled trial (parallel) 1 yr	Trappist or Benedictine monks in good health Exclusion: Rx which influence lipid metabolism/cyclo oxygenase enzyme; serious illness (diabetes cancer CHD); BMI > 30 kg/m^2; SBP > 160; DBP > 95; TC > 7 mmol/1 & Tg 3>mmol/1 < 21 or > 90 yr age		1. 3 fish oil plus 6 placebo Total n-3: 1.12 g 2. 6 fish oil plus 3 placebo Total n-3: 2.24 g 3. 9 fish oil Total n-3: 3.37 g	Olive oil 9 g	Lp(a) Hgb A1c Fibrinogen Apo A1 Apo B Factor VIII vWF
Djousse 2003	n3 Enrol: 395 n3 Enrol: 399 n3 Enrol: 387 Control enrol: 394 Age: 49±14 y SD % Male: 45 Race: Mostly white Country: US Sites: 4	Cross-sectional study	Members of randomly selected families Exclusion: CAD stroke hypertension kidney insufficiency DM	SBP: 113.2 /109.7 LDL: 3.07 / 3.17 mmol/L Tg: 1.64 / 1.40 mmol/L	ALA intake from FFQ: 0.58-0.75 g/d 0.76-0.97 g/d 0.98-3.48 g/d	Low ALA intake: 0.23-0.57 g/d	IMT

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Dunstan 1997	n3 Enrol: 14 n3 Enrol: 12 Control enrol: 23 Age: 53±7.2 y SD % Male: 75.5 Country: Australia Sites: ND	Randomized controlled trial (parallel) 8 wk	Sedentary nonsmoking diabetics treated by diet and/or hypoglycemics dyslipidemia Tg >1.8 mmol/L and/or HDL <1.0 mmol/L BMI < 36 kg/m^2 Exclusion: Insulin or hypolipidemic Tx hx of heart disease major diabetic complications fish oil intake	TC: 4.9 mmol/L LDL: 3.2 mmol/L HDL: 0.8 mmol/L Tg: 2.0 mmol/L BMI: 29.9 kg/m^2	Instructed to include one fish meal per day in their low-fat diet., including Greenland turbot fillets, canned sardines, tuna, salmon. ~ 3.6 g/d n3 FA	Low fat diet. No advice on fish	Hgb A1c Insulin Plt PL
Dunstan 1998	n3 Enrol: 14 n3 Enrol: 12 Control enrol: 23 Age: 53±7.2 y SD % Male: 75.5 Country: Australia Sites: ND	Randomized controlled trial (parallel) 8 wk	Sedentary nonsmoking diabetics treated by diet and/or hypoglycemics dyslipidemia Tg >1.8 mmol/L and/or HDL <1.0 mmol/L BMI < 36 kg/m^2 Exclusion: Insulin or hypolipidemic Tx hx of heart disease major diabetic complications fish oil intake	TC: 4.9 mmol/L LDL: 3.2 mmol/L HDL: 0.8 mmol/L Tg: 2.0 mmol/L BMI: 29.9 kg/m^2	Instructed to include one fish meal per day in their low-fat diet., including Greenland turbot fillets, canned sardines, tuna, salmon. ~ 3.6 g/d n3 FA	Low fat diet. No advice on fish	FBS

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Dunstan 1999	n3 Enrol: 14 n3 Enrol: 12 Control enrol: 23 Age: 53±7.2 y SD % Male: 75.5 Country: Australia Sites: ND	Randomized controlled trial (parallel) 8 wk	Sedentary nonsmoking diabetics treated by diet and/or hypoglycemics dyslipidemia Tg >1.8 mmol/L and/or HDL <1.0 mmol/L BMI < 36 kg/m^2 Exclusion: Insulin or hypolipidemic Tx hx of heart disease major diabetic complications fish oil intake	TC: 4.9 mmol/L LDL: 3.2 mmol/L HDL: 0.8 mmol/L Tg: 2.0 mmol/L BMI: 29.9 kg/m^2	Instructed to include one fish meal per day in their low-fat diet., including Greenland turbot fillets, canned sardines, tuna, salmon. ~ 3.6 g/d n3 FA	Low fat diet. No advice on fish	Fibrinogen Factor VII RBC PL
Durrington 2001	n3 Enrol: 30 Control enrol: 29 Age: 55±7.0 y SD % Male: 73 Country: UK Sites: 2	Randomized controlled trial (parallel) 24 wk	Patients with CHD ≤ 75 y Tg > 2.3 mmol/L; simvastatin on 10-40 mg ≥ 3 mo Exclusion: MI < 6 mo	TC: 5.6 mmol/L LDL: 3.5 mmol/L HDL: 1.1 mmol/L Tg: 4.6 mmol/L BMI: 28.8 kg/m^2 DM: 27% Prevalence	Omacor, 2 g bid EPA: 1.76 g DHA: 1.44 g	Corn oil 4 g	Lp(a) Apo A1 Apo B
Eritsland 1995a Shunt Occlusion Trial (SHOT)	n3 Enrol: 280 Control enrol: 269 Age: 60±8.7 y SD % Male: 87 Country: Norway Sites: ND	Randomized controlled trial (parallel) 6 mo	Stenosing CAD undergoing CABG	SBP: 144 DBP: 87 BMI: 25.3 kg/m^2	4 Omacor/ d EPA: 2.04 g DHA: 1.28 g	No oil	Lp(a)
Eritsland 1995b Shunt Occlusion Trial (SHOT)	n3 Enrol: 260 Control enrol: 251 Age:60±8.7 y SD % Male: 87 Country: Norway Sites: ND	Randomized controlled trial (parallel) 9 mo	Stenosing CAD undergoing CABG	BMI: 25.4 kg/m^2	4 Omacor /d EPA: 2.04 g DHA: 1.28 g	No oil	TC Tg LDL HDL FBS Apo A1 Apo B100 Insulin
Eritsland 1995c Shunt Occlusion Trial (SHOT)	n3 Enrol: 260 Control enrol: 251 Age: 60±8.7 y SD % Male: 87 Country: Norway Sites: ND	Randomized controlled trial (parallel) 9 mo	Stenosing CAD undergoing CABG	BMI: 25.4 kg/m^2	4 g/d Omacor Total n-3: 2.7 g Total n-6: 9.5 g (evaluation of factorial randomization to aspirin or warfarin included)	No oil	Fibrinogen Factor VII

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Finnegan 2003	n3 Enrol: 30 n3 Enrol: 31 n3 Enrol: 30 Control enrol: 30 Age: 54±2 y SE % Male: 58 Country: UK Sites: 1	Randomized controlled trial (parallel) 6 mo	Moderately hyperlipidemic adults 25-72 y (TC 4.6-8.0 mmol/L and Tg 0.8-3.2). Exclusion: CVD DM or FBS>6.5 mmol/L Liver or endocrine dysfunction pregnancy or lactation >15 cigs/d BMI <20 or >32 Hgb <130 g/L men <120 women. Lipid or antiinflammatory drugs FA or antioxidant supplements >2 oily fish /wk. Vegetarians non-consumers of margarine.	SBP: 118 DBP: 75 BMI: 26.1 kg/m^2	1 25 g day (21 g FA) fish oil margarine, sunflower oil based plus 3 placebo caps/d 2. 25 g day (21 g FA) fish oil margarine, sunflower oil based plus 3 fish oil caps/d 3. 25 g day (21 g FA) rapeseed and linseed oil margarine, sunflower oil based plus 3 placebo caps/d ALA: 4.5 g	25 g margarine (21 g FA) sunflower and safflower oil based plus 3 placebo capsules/day	TC Tg LDL HDL FBS Apo B Insulin Plasma PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Franzen 1993	n3 Enrol: 92 Control enrol: 83 Age: 57±8 y SD % Male: 82 Country: Germany Sites: 1	Randomized controlled trial (parallel) 4 mo	Elective PTCA Exclusion: Evolving MI, MI < 1 mo, PTCA of total coronary occlusions, PTCA of bypass grafts, prior fish oil, fish/fish oil allergy, > 80 y, anticoagulants, contraindication for aspirin, recent hx of peptic ulcer, malignant or systemic diseases, familial hypercholesterolemia chronic kidney failure requiring dialysis Insulin dependent DM HTN(SBP>180 or DBP>105 mmHg)	All on aspirin SBP: 127 DBP: 78 Wgt: 76 Kg DM: 6% Prevalence	9 Ameu ~33% omega-3 FA, Total n-3: 3.5 g	9 Olive oil	TC Tg LDL HDL Restenosis ETT
Freese 1994	n3 Enrol: 20 Control enrol: 20 Age: 29 y % Male: 100 Race: ND Country: Finland Sites: ND	Cross-over 6 wk	Healthy male university students and employees	TC: 4.3 mmpl/L BMI Men: 21.9	Low-erucic acid rapeseed oil diet containing similar amounts of SAFA, MUFA, & PUFA, but different proportions of linoleic and a-linolenic acids.	Trisun-sunflower oil diet containing similar amounts of SAFA, MUFA, & PUFA as control diet.	Plt Aggr
Freese 1997a	n3 Enrol: 16 n3 Enrol: 14 Age: 22-42 y % Male: 50 Country: Finland	Randomized controlled trial (parallel) 4 wk	Healthy students	TC: 4.94v 5.37 mmol/L Tg: 0.97 v 0.92 mmol/L Glucose: 4.71 v 4.69 mmol/L	1. Pikasol 12.2 g/d EPA: 3.04 g DHA: 2.45 g 18:2 n-6: 1.58 2. Linseed oil 11.9 g/d ALA: 6.21 g	No control	FBS Plt Aggr

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Freese 1997b	n3 Enrol: 24 n3 Enrol: 22 Age: 27.3 y % Male: 42 Country: Finland Sites: 1	Randomized controlled trial (parallel) 4 wk	Healthy students	TC: 5.36 mmol/L Tg: 0.78 Wgt: 63.7 Kg	1. Pikasol 12.2 g/d EPA: 3.04 g DHA: 2.45 g 18:2 n-6: 1.58 2. Linseed oil 11.9 g/d ALA: 6.21 g	No control	Fibrinogen Factor VII Plt PL
Gans 1990	n3 Enrol: 18 Control enrol: 19 Age: 66±10.4 y SD % Male: 69 Country: Netherlands Sites: 1	Randomized controlled trial (parallel) 4 mo	Age 18-80 y. Intermittent claudication due to atherosclerotic disease. Fontaine IIA or IIb (pain-free walking) Exclusion: UA or MI 3 mo prior, any illness with rapid evolution rest pain or gangrene DBP>100 poorly controlled DM (Hgb A1c>12%) vasculitis or thomboaniitis obliterans Plt> 500,000 or <90,000 Hct>55% fish allergy lipid or platelet-active Rx. DM (post hoc).	SBP: 146 DBP: 78 TC: 6.8 mmol/L LDL: 4.3 mmol/L HDL: 1.28 mmol/L Tg: 2.2 mmol/L	6 fish oil EPA: 1.8 g DHA: 1.2g	6 corn oil	Fibrinogen
GISSI 1999	n3 Enrol: 2836 n3 Enrol: 2830 Control enrol: 5668 Age: 59.4 y % Male: 85.3 Country: Italy Sites: 172	Randomized controlled trial (parallel) 3.5 y	Recent MI (≤ 3 mo) Exclusion: Unfavorable short-term outlook contraindications to dietary supplements	TC: 210.9 mg/dL LDL: 137.4 mg/dL HDL: 41.5 mg/dL Tg: 162.1 mg/dL BMI: 26.5 kg/m^2 DM: 14.8% Prevalence	850-882 mg EPA and DHA as ethyl esters in the average ratio of EPA:DHA of 1:2	No supplement	TC Tg LDL HDL

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Green 1990	n3 Enrol: 27 Control enrol: 27 Age: ND % Male: ND Country: Israel Sites: 1	Cross-over 8 wk	Tg >2.8 mmol/L, standard lipid-lowering diet Exclusion: prior to study - hypolipidemic meds ≥ 2 mo, or serious illness or operation < 3 mo	TC: IIB – 8.15 mmol/L IV – 6.45 mmol/L HDL: IIB – 0.85 mmol/L IV – 0.81 mmol/L Tg: IIB - 6.72 mmol/L IV - 6.24 mmol/L Htn: 37% Prevalence DM: 33.3% Prevalence	15 g fish oil EPAGIS 5.2 g n3 EPA: 2.72 g DHA: 1.6 g	15 g Corn & olive oil mixture	Apo A1 Apo B
Grigg 1989	n3 Enrol: 52 Control enrol: 56 Age: 53.5 y %Male: 82 Country: Australia Sites: 1	Randomized controlled trial (parallel) 4 mo	Consecutive patients undergoing angioplasty Exclusion: 1) the vessel dilated at angioplasty was not a native coronary artery 2) vessel was totally occluded before angioplasty. In addition if angioplasty was unsuccessful patients were withdrawn	Type IV angina: 34 vs 41%	10 fish oil/day EPA: 1.8 g DHA: 1.2 g	10 caps 50% olive oil and 50% corn oil	Restenosis
Grimsgaard 1997	n3 Enrol: 75 n3 Enrol: 79 Control enrol: 80 Age: 44 y % Male: 100 Country: Norway Sites: ND	Randomized controlled trial (parallel) 7 wk	Healthy nonsmoking males, serum chol < 8.0 mmol/L, DBP < 95 mmHg, SBP < 160 mmHg, during 4 mo run-in Tg < 5.0 mmol/L & chol <9.5 mmol/L Exclusion: CVD, liver, renal or bleeding disorder, DM, psychopatholgic disease, alcoholism, disease affecting BP or lipid metabolism, or hemostatis, meds, > 3 fish/wk, special diet	Wgt: 82.6 kg	4 capsules DHA 3.6 g, or EPA 3.8 g	4.0 g Corn oil	Tg TC LDL HDL Apo A1 Apg B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Grundt 1995	n3 Enrol: 28 Control enrol: 29 Age: 45±8.8 y SD % Male: 89 Country: Norway Sites: 1	Randomized controlled trial (parallel) 12 wk	Tg 2.0-15 mmol/L and TC > 6.0 mmol/L Exclusion: MI or other serious disease 3 mo prior, DM (FBS>7.0 mmol/L) serious psychological disease drug or alcohol abuse pregancy or lactation	SBP: 129.1 DBP: 84.2 BMI: 27.0 kg/m^2	4 capsules K85 EPA: 2.1 g DHA: 1.3 g	Corn oil 4 g	FBS Insulin Plasma PL
Grundt 1999	n3 Enrol: 28 Control enrol: 29 Age: 45±8.8 y SD % Male: 89 Country: Norway Sites: 1	Randomized controlled trial (parallel) 12 wk	Tg 2.0-15 mmol/L and TC > 6.0 mmol/L Exclusion: MI or other serious disease 3 mo prior to study, DM (FBS>7.0 mmol/L) serious psychological disease drug or alcohol abuse pregancy or lactation	SBP: 129.1 DBP: 84.2 BMI: 27.0 kg/m^2	4 capsules K85 EPA: 2.1 g DHA: 1.3 g	Corn oil 4 g	Fibrinogen Factor VII
Haines 1986	n3 Enrol: 19 Control enrol: 22 Age: 43±9.0 y SD % Male: 74 Race: 100% W Country: UK Sites: 1	Randomized controlled trial (parallel) 6 wk	IDDM Age 30-59 y Exclusion: Hyperlipidemia coagulation disorder.	SBP: 135 DBP: 81 TC: 4.73 mmol/L LDL: 2.43 mmol/L HDL: 1.66 mmol/L Tg: 0.82 mmol/L Wgt: 70.1 Kg Hgb A1c: 11.1%	MaxEPA 15 g EPA: 2.7 g DHA: 1.9	2 caps/Olive oil 0.6 g	BP Hgb A1c Fibrinogen Plt Aggr Factor VII Factor VIII RBC PL
Hamazaki 1996	n3 Enrol: 18 Control enrol: 17 Age: 22 y Median % Male: 42 Country: Japan Sites: 1	Randomized controlled trial (parallel) 13 wk	Healthy non-smoking students		DHA-rich fish oil containing 300 mg; 10 capsules if ≤50 kg 11 capsules 50 - 55 kg 12 capsules > 55 kg DHA: 1.48 - 1.77 g EPA: 0.20 - 0.24 g	97% soybean oil + 3% other fish oil (for taste)	Lp(a)

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Hanninen 1989	n3 Enrol: 20 n3 Enrol 21 n3 Enrol 22 n3 Enrol 19 Control enrol: 18 Age: 24±4 y SD % Male: 100 Country: Finland Sites: 1	Randomized controlled trial (parallel) 12 wk	Healthy male students Exclusion: Fish allergies	Wgt Men: 77 Kg	Actual Fish meals/wk: (Rainbow trout Vendace, perch Baltic herring) 1. 0.9 fish meals/wk DHA: 0.15 g EPA: 0.05g 2. 1.5 fish meals/wk EPA: 0.1 g DHA: 0.3 g 3. 2.3 fish meals/wk EPA: 0.15 g DHA: 0.35 g 4. 3.8 fish meals/wk EPA: 0.3 g DHA: 0.6 g	One fish meal every 2 wk	TC Tg Apo A Apo B
Hansen 1989	n3 Enrol: 40 Control enrol: 40 Age range: 20-40y % Male: 50 Country: Norway Sites: 1	Cross-over 8 wk	Healthy non-smoking persons. Age 20-40 years.		Cod liver oil 25 mL EPA: 2.1 g DHA: 3.7 g DPA: 0.2 g	No treatment	Fibrinogen Factor VII Plasma PL Monocyte
Hansen 1993a	n3 Enrol: 10 n3 Enrol: 11 Control enrol: 10 Age range: 21-47y % Male: 100 Country: Norway Sites: 1	Randomized controlled trial (parallel) 7 wk	Healthy Normolipemic Non-obese (<115% of desirable weight)	Diet: Typical Western Diet SBP: 122 DBP: 74 TC: 4.7 mmol/L Tg: 0.83 mmol/L	1. 4 g K85 Ethyl ester EPA: 2.2 g DHA: 1.2 g DPA: 0.2 g 2. 12 g ACTIVEPA triglycerides EPA: 2.2 g DHA: 1.4 g	Corn oil 4 g	Fibrinogen Factor VII vWF Plasma PL
Hansen 1993b	n3 Enrol: 34 Control enrol: 34 Age range: 20-40y % Male: 59 Country: Norway Sites: ND	Cross-over study 8 wk	Healthy nonobese nonsmoking subjects 20-40 y		25 ml cod liver oil 2.1 g EPA 3.2 g DHA	No oil	Plt Aggr

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Harris 1997	n3 Enrol: 22 Control enrol: 20 Age: 46±11 y SD % Male: 77 Country: US Sites: 2	Randomized controlled trial (parallel) 16 wk	Hypertriglyceridemia 5.65 - 22.60 mmol/l 18 -76 yr Exclusion: Tg > 22.60 mol/l cold water fish > 1/ wk type III hyperlipidemia MI < 6 mo serum alanine aminotransferase > 3 x upper normal value fasting serum glucose > 200 mg/dl Cr > 2 mg/dl platelet cnt < 60 x 10^9/L hemoglobin < 10 g/dL clincially significant disease pregnant or breastfeeding use of alcohol > 2 drinks per day drug abuse or condition associated with poor compliance	SBP: 127 DBP: 83 TC: 6.94 mmol/L LDL: 2.95 mmol/L HDL: 0.78 mmol/L Tg: 10.38 mmol/L BMI: 28 kg/m^2	4 Omacor /d	Corn oil 4 g	Hgb A1c Apo A1
Hendra 1990	n3 Enrol: 40 Control enrol: 40 Age: 56 y % Male: 69 Race: White 96% Country: UK Sites: 1	Randomized controlled trial (parallel) 6 wk	Adult NIDDM subjects Exclusion: pregnant taking OCP hypercholesterolemia AMI or stroke within past 12 months		10 MaxEPA EPA: 1.8 g DHA: 1.2 g	10 g olive oil	BP FBS Fibrinogen Plt. Aggr Factor VII Plt PL
Jain 2002	n3 Enrol: 25 Control enrol: 15 Age: 51±8.8 y SD % Male: 58 Country: India Sites: 1	Randomized controlled trial (parallel) 6 wk	Type 2 DM either sex with or w/o micro & macrovascular complications Exclusion: BMI > 27 kg/m^2 smokers previous antioxidant Rx	SBP: 126.9 DBP: 81.52 TC: 193 mg% LDL: 113.5 mg% HDL: 32.1 mg% Tg: 189.6 mg% BMI: 25.3 kg/m^2	1 Maxigard bid EPA: 0.36 DHA: 0.24 g	“Placebo”	BP Hgb A1c, FBS

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Jensen 1989	n3 Enrol: 18 Control enrol: 18 Age: 37 y % Male: 77.7% Country: Denmark Sites: 1	Cross-over study 8 wk	IDDM (onset before 31 y) albuminuria (>30 mg /24h urine albumin). Exclusion: kidney disease	SBP: 146 DBP: 90 TC: 5.72 mmol/L LDL: 3.89 mmol/L HDL: 1.20 mmol/L Tg: 1.08 mmol/L	21 ml cod liver oil Eskisol EPA: 2 g DHA: 2.6 g	21 ml cod-liver oil or 21 ml olive oil	Hgb A1c FBS Apo A1 Apo B
Johansen O 1999 CART	n3 Enrol: 196 Control enrol: 192 Age: 60 y % Male: 78 Country: Norway Sites: 1	Randomized controlled trial (parallel) 6 mo	Elective PTCA pts Exclusion: steroid or immunosuppressive Rx HTN pregancy; UA pectoris; bleeding disorder; serious illness with survival < 2 y; angiographic reasons: diffuse lesions (>2 cm long), Excessive tortuosity of proximal segment extremely angulated segments (> 90 deg) or chronic (>3 mo) total occlusions; stent implantation	Rx: Statin - Omacor 9.2% v Placebo 16.7 p<0.03	6 Omacor /d EPA: 2.7 g DHA: 2.34 g	Corn oil 6 g	Restenosis
Junker 2001	n3 Enrol: 18 Control enrol: 40 Age: 27±5.7 y SD % Male: 56 Country: Germany Sites: 1	Randomized controlled trial (parallel) 4 wk	BMI < 27 kg/m^2 TC < 300 Tg < 300. Exclusion: Obesity hyperlipidemia DM thyroid disease vitamin supplements hyperuricemia allergy drug or substance abuse malabsorption syndromes.	BMI: 23.3 kg/m^2	High fat diet containing refined rapeseed oil in margarine and bread 2.5% energy n-3 6.5% n-6.	1. High-fat diet containing refined sunflower oil 2. High fat diet containing refined olive oil.	CRP Fibrinogen Plt Aggr Factor VII

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Kaul 1992	n3 Enrol: 58 Control enrol: 49 Age: 56±11 y SD % Male: 85 Country: India Sites: 1	Randomized controlled trial (parallel) 6 mo	Pt undergoing coronary angioplasty Exclusion: Hx of bleeding disorder oral anticoagulants emergency angioplasty recent MI CABG inability to perform treadmill test	All on calcium channel blocker and aspirin	10 g MaxEPA EPA: 1.8 DHA: 1.2	No oil	Restenosis
Kwon 1991	n3 Enrol: 15 Control enrol: 13 Age: 60 Mean % Male: 100 Race: ND Country: US Sites: 1	Randomized controlled trial (parallel) 8 wk	Healthy males 21-50y TC 4.8-7.8 mmol/L Exclusion: hx of metabolic disease, regular use of Rx that affect platelet aggregation	ND	Canola oil diet 9.7% ALA	Safflower oil diet 0.5% ALA	Plt Aggr
Leigh-Firbank 2002	n3 Enrol: 55 Control enrol: 55 Age: 55±1 y SE % Male: 100 Country: UK Sites: 1	Cross-over 6 wk	Atherogenic lipoprotein phenotype (ALP) 30-70 y Exclusion: CVD liver dysfunction DM smoking BP > 160/95 mmHg hemoglobin < 130 g/l BMI > 35 kg/m^2 hypolipidemic Rx or Rx that interfere with lipid metabolism FA supplements wt reducing diets	Tg 1.5 - 4.0 mmol/l HDL: < 1.1 mmol/l LDL-3: > 40% totalLDL BMI: 28.0 kg/m^2	Six 1 g fish oil capsules approx 50% EPA & DHA enriched providing 279 mg EPA & 223 mg DHA/g oil EPA: 1.67 g DHA: 1.34 g	6 g olive oil	TC Tg LDL HDL Hgb A1c FBS Plt PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Leng 1998	n3 Enrol: 60 Control enrol: 60 Age: 65.0±0.94 y SE % Male: 68.3 Country: UK Sites: 1	Randomized controlled trial (parallel) 2 yr	Stable claudication > 6 mo; ankle brachial pressure index ≤ 0.9 in at least 1 limb Exclusion: Critical ischemia; previous or impending arterial surgery or angioplasty; UA or MI < 3 mo; severe disease (liver malignancy Epilepsy); anticoagulant Rx, lithium or phenothiazines; pregnant or trying to conceive	Rx: Aspirin BMI: 26.49 kg/m^2 Wgt: 72.92 Kg DM: 6.7% Prevalence	280 mg of GLA (18:3 n-6) + 45 mg EPA EPA: .27 g Total n-6: 1.68 g	Sunflower oil capsules containing 500 mg each; 4 cap/d first 2 wks followed by 6 cap/d	TC LDL HDL Fibrinogen vWF
Lungers-hausen 1994	n3 Enrol: 43 Control enrol: 43 Age: 61±3 y SE % Male: 69 Country: Australia Sites: 1	Cross-over 6 wk	HTN controlled by monotherapy: beta-blocker or diuretic or combination of both Exclusion: Hx unstable heart, kidney or liver disease DPB > 105 mmHg > 20 cigarettes or 40 g alcohol per day exercise erratically	BMI: 26.7 kg/m^2	4 Omacor EPA 1.9 g DHA 1.5g	Corn oil 4 g	TC Tg LDL HDL
Lungers-hausen 1997	n3 Enrol: 17 Control enrol: 17 Age: 55 combined % Male: 75 Country: Australia Sites: 2	Randomized controlled trial (parallel) 12 wk	DM clinic case notes identify IDDM or NIDDM UAE 20-200 mcg/min Exclusion: Proliferative retinopathy ACEI or NSAID use Hgb A1c>11% EtoH>40 g/d Cigarettes >20/day	SBP: 139 DBP: 81 Tg: 1.9 mmol/L BMI: 30 kg/m^2	4 Omacor EPA: 2.0 g DHA: 1.4 g	Corn oil 4 g	BP Hgb A1c

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Luo 1998	n3 Enrol: 12 Control enrol: 12 Age: 54±3 y SE % Male: 100 Country: France Sites: 1	Cross-over 2 mo	Type II DM men (FBS 7.84-14.0 mmol/L HgbA1c<10.5% Tg 1.72-4.6 mmol/L)	Baseline: Rx: HTN 2/10 Rx: Oral hypoglycemic ag - 8/10 sulfonylurea and/or metformin TC: 6.03 mmol/L Tg: 2.66 BMI Men: 28 kg/m^2 HbA%: 8.4	6 g fish oil in 1 g caps	Sunflower oil caps 6 g	Lp(a) Hgb A1c Apo A1 Apo B Insulin RBC PL
Mackness 1994	n3 Enrol: 47 Control enrol: 48 Age: 54.4 y % Male: 63 Country: UK Sites: 7	Randomized controlled trial (parallel) 14 wk	Primary type IIb or IV hyperlipidemia Age 18-70 Tg 2-10 mmol/L and TC > 5.2 Exclusion: DM hypothyroid serious illness in previous 3 mo (including MI) or severe concurrent illness drug or EtOH abusers pregnant or lactating women.	SBP: 140 DBP: 86 TC: 7.8 mmol/L LDL: ~4.8 HDL: ~1.0 Tg: 3.99 BMI: 26.8 kg/m^2	K-85 4 g	Corn oil 4g	FBS
Madsen 2001	n3 Enrol: 269 Age: 60±8 y SD % Male: 63.6 Country: Denmark Sites: 1	Single cohort study	Pt referred for elective coronary angiography with suspected IHD Exclusion: AMI cardiac surgery or angioplasty ≤ 6 mo significant heart valve disease nonischemic cardiomyopathy pacemaker permanent tachyarrhythmia CRP > 10 mg/L	Rx: Aspirin Rx: Statin BMI: 27.3 - 28.2 kg/m^2	FA data presented by consumption levels of fish from 0 per month to daily; cohort that could possibly be divided into control vs fish eaters based on fish intake.		CRP

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Madsen 2003	n3 Enrol: 20 Control enrol: 20 Age: 38 (21-57) y % Male: 60 Country: Denmark Sites: 1	Randomized controlled trial (parallel) 12 wk	Healthy volunteers	BMI: 25.1 kg/m^2 - n3 24.0 kg/m^2 - control	3 Pikasol capsules 2.0 g n3 & 7 olive oil capsules 4.9g EPA: 0.9 g	Olive oil 7g	CRP
Marckmann 1997	n3 Enrol: 23 Control enrol: 24 Age: 41±9 y SD % Male: 100 Country: Denmark Sites: 1	Randomized controlled trial (parallel) 4 wk	Non obese males Exclusion: Fish oil or regular pharma-ceuticals permanently raised CRP Intercurrent disease	TC: 4.75 combined mmol/L HDL: 1.14 Tg: 1.06 BMI Men: 24.1 kg/m^2	Margarine with 2 g of fish oil in 15 g (total) sunflower oil margarine. 30 g margarine eaten per day Total n-3: 0.91 g	Sunflower oil margarine 30 g/d	Lp(a) Fibrinogen Apo A1 Apo B Insulin Factor VII vWF

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Maresta 2002 ESPRIT	n3 Enrol: 169 Control enrol: 170 Age: 58.9±9.5 y SD % Male: 85.6 Country: Italy Sites: 17	Randomized controlled trial (parallel) 7 mo	PTCA (angina or ischemia not adequately responsive to medical Rx or silent ischemia after AMI in presence of a least 1 critical coronary artery stenosis (≥70% at visual inspection) amenable to PTCA Exclusion: Age <18 or >75 yrs; recent (<15 days) acute MI culprit lesions in left main coronary artery in a saphenous vein bypass graft or in previously dilated site (restenotic lesions) HTN; contraindication to omega-3 FA anticoagulant Tx presence of hepatic or kidney disease concomitant disease associated with limited life expectancy drug or alcohol abuse	SBP: 136.3 DBP: 80.7 Wgt: 76.4 Kg DM: Type 1: 4%; Type 2: 8% Prevalence	6 Esapent for 1 mo post-randomization; then half-dose 6 mo EPA: 3 g DHA: 2.1 g	Olive oil	Tg Restenosis
McVeigh 1993	n3 Enrol: 23 Control enrol: 23 Age range: 45-61y % Male: 87 Country: UK	Cross-over 6 wk	Type 2 DM controlled by diet alone or diet plus oral hypoglycemic Exclusion: Hx CVA IHD PVD BP>150/90 CCr<30 mL/min Taking CVD drugs	Baseline: MAP: 83 TC: 5.3 mmol/L Tg: 1.8 mmol/L HbA%: 9.6			Hgb A1c FBS Plt PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Mezzano 2001	n3 Enrol: 21 Control enrol: 21 Age: 21.2±1.7 y SD % Male: 100 Country: Chile Sites: 1	Semi-randomized trial (Some subjects chose treatment) 90 d	Healthy male students. Normal range lipids and glucose BP Exclusion: Clinical disease obesity alcohol use	TC: 4.42 mmol/L Tg: 1.13 mmol/L BMI Men: 23.4 kg/m^2	Meditteranean diet+. 32 mL/d of olive oil 675 g/d fruit and vegetables. White meat, fish, legumes 1.64 FAg/d During month 2: diets were isocalorically supplemented with 240 mL/d of red wine	High fat (red meat) diet 246 g/d fruit and vegetables 0.96 FAg/d	CRP Fibrinogen Factor VII FVIII
Milner 1989	n3 Enrol: 194 Control enrol: 99 Age: 59 y % Male: 70 Country: USA Sites: 1	Randomized controlled trial (parallel) 6 mo	Patients on PTCA if they had hx of chest pain characteristic of MI and <50% residual diameter narrowing after PTCA of all significant coronary narrowings Exclusion: Dilatation of total occlusion, presence of thrombus thrombolytic Tx Recent MI (7 d) Previous CABG Significant left main coronary narrowing or CHF	DM: 14 vs 16 % Hypertension: 43 vs 47 AMI 3 months: 18 vs 19	9 Promega Total n-3: 4.5 g EPA : 3.2 g DHA : 1.4 g	Placebo	Restenosis
Misso 1995	n3 Enrol: 12 Control enrol: 12 Age: 31 y % Male: 50 Country: Australia Sites: 1	Cross-over 4 wk	Normal healthy		12 MaxEPA EPA: 2.16 g DHA: 1.44 g	Olive oil 12 g	Fibrinogen Plt Aggr

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Mori 1994	n3 Enrol: 17 n3 Enrol: 17 n3 Enrol: 17 n3 Enrol: 16 Control enrol: 18 Age: 45±0.6 y SE % Male: 100 Country: Australia Sites: 1	Randomized controlled trial (parallel) 12 wk	Healthy males 30-60 y SBP 130-159 mm Hg & DBP 80-90 mm Hg TC 5.2 - 6.9 mmol/L BMI < 30 kg/m^2 Exclusion: smoking hx unstable heart kidney liver diseases hypercholesterolemia asthma & major allergies > 1 fish meal per wk > 3 mL ethanol per d	SBP: 136.5 DBP: 84.8 TC: 6.09 mmol/L LDL: 4.06 mmol/L HDL: 1.24 mmol/L Tg: 1.74 mmol/L BMI Men: 27.5 kg/m^2	7 groups: 5 assigned to diets supplying 40% total dietary energy, 2 30%. 1: placebo 2: fish (Greenland turbot, canned sardines, tuna, salmon) 3: fish oil caps 4: fish + fish oil caps 5: twice fish oil caps 6: control group 7: fish		TC Tg LDL HDL Apo B Plt PL
Mori 1999	n3 Enrol: 31 Control enrol: 32 Age: 53.7 ±: 1.7 y SD % Male: 66.7 Country: Austrialia Sites: ND	Randomized controlled trial (parallel) 16 wk	Overweight - BMI > 25 kg/m^2 nonsmoking 40-70 y antihypertensive Rx ≥ 3 mo SBP 125-180 mm Hg DBP < 110 mm Hg Exclusion: Lipid-lowering or antiinflammatory Rx 1 or less fish per wk < 175 g ethanol/wk	TC: 4.88 mmol/L LDL: 3.04 mmol/L HDL: 1.07 mmol/L Tg: 1.67 mmol/L BMI: 32.3 kg/m^2	1. Weight maintaining diet+ fish daily. Fish consisted of Greenland turbot (~200 g) canned sardines (~106 g) canned tuna (~102 g) canned salmon (~54 g) providing ~3.5, 4.1, 3.2, & 3.8 g n-3/d respectively. 2. Energy restricted diet + fish daily	1. Weight maintaining diet 2. Weight loss group	FBS Insulin Plasma PL
Mori 2000	n3 Enrol: 19 n3 Enrol: 17 Control enrol: 20 Age: 48.4 y Country: Australia Sites: 1	Randomized controlled trial (parallel) 6 wk	Healthy non-smoking men 20-65 yrs TC>6mmol/L Tg>1.8mmol/L BMI 25-30 kg/m^2 no symptoms of heart disease diabetes liver or kidney disease ≤1 fish meal w/ <210 ml ethanol/wk		1. 4 grams daily of purified EPA ethylester (~96%) 4 g daily of DHA ethyl ester (~91%)	4 grams daily of olive oil (~75% oliec acid ethyl ester)	FBS Insulin Plasma PL Plt PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Muller 1989	n3 Enrol: 40 Control enrol: 42 Age: 28.3 y % Male: 100 Country: Netherlands Sites: 3	Randomized controlled trial (parallel) 6 wk	Healthy males		Mackerel paste (135 g/d EPA: 1.7 g DHA: 3.0 g	Meat paste 135 g	Fibrinogen Factor VII vWF
Natvig 1968	n3 Enrol: 6690 Control enrol: 6716 Age: ND % Male: 100 Race: White/European - assumed 100 Country: Norway Sites: multiple	Randomized controlled trial (parallel) 1 yr	Male 50 - 59 yrs		Linseed oil with vitamin E added 10 ml per day	Sunflower seed oil (10 ml) and vitamin E	TC
Nenseter 2000	n3 Enrol: 34 Control enrol: 36 Age: 54±9 y SD % Male: 65 Country: Norway Sites: 1	Randomized controlled trial (parallel) 12 wk	Primary hypercholesterolemia 30-70 yrs non-smoker TC 5.5-8.5 mmol/L BMI < 30 kg/m^2 Exclusion: Heart kidney liver or malignant diseases Vegetarians alcoholics or drug abusers	Diet: Low fat diet - ALL SBP: 130 DBP: 83 TC: 6.6 mmol/L LDL: 4.5 HDL: 1.5 Tg: 1.43 BMI: 24.3 kg/m^2	Fish powder tablets 10 g (20 tablets) from whole Nowrwegian spring spawning herring (Clupea harengus) Total n-3: 0.279 g EPA: 0.075 g DHA: 0.169 g Total n-6: 0.040 g	20 tablets microcrystaline cellulose	Lp(a) Fibrinogen Apo B Factor VII Plasma PL
Nikkila 1991	n3 Enrol: 32 Control enrol: 32 Age: 54±7 y SD % Male: 100 Country: Finland Sites: 1	Cross-over 4 wk	Men with coronary heart disease Tg>1.7 mmol/L HDL<1.0	Wgt Men: 84.4 Kg	4 Almarin EPA: 1.4 DHA: 1.0	4 corn oil	Apo A1 Apo B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Nilsen 2001	n3 Enrol: 150 Control enrol: 150 Age: 64.4 y % Male: 79.3 Country: Norway Sites: 1	Randomized controlled trial (parallel) 24 mo	Pts with MI (WHO criteria (29) > 18 y discontinuation of regular fish oil supplements Exclusion: expected survival < 2 y by heart failure (NYHA class IV) or malignancy or other reasons GI bleeding or verified stomach ulcer thrombocytopenia or blood platelets <100 x 100 9/L liver insufficiency	BMI: 25.9 kg/m^2 DM: 12% Prevalence	2 Omacor-R bid; average ratio of EPA to DHA 1:2	Corn oil 4 g	TC Tg HDL
Nordoy 1998	n3 Enrol: 21 Control enrol: 20 Age: 46.8±9.2 y SD % Male: 71 Country: Norway Sites: 1	Randomized controlled trial (parallel) 5 wk	Hyperlipidemia Tg 2.0 - 15.0 mmol/L -1 TC > 5.3 mmol/L -1 Exclusion: Rx known to affect lipid metabolism	SBP: 132.9 DBP: 80.8 TC: 21.4 mmol/L HDL: 0.96 mmol/L Tg: 4.42 mmol/L BMI: 27.6 kg/m^2	Simvastatin 20 mg plus Omacor 4 g/d EPA (45%) & DHA (39%)	Simvastatin 20 mg plus corn oil 4 g	Hgb A1c Apo A1 Apo B Insulin
Nordoy 2000	n3 Enrol: 21 Control enrol: 20 Age: 46.8±9.2 y SD % Male: 70 Country: Norway Sites: 1	Factorial 5 wk	Women & men 25-60 yrs w/combined hyperlipidemia none taking lipid lowering Rx antioxidants fish oil	Glucose intolerant/diabetes:6/3 BMI: 28 kg/m^2	4 g/d omega-3 FA (45% EPA + 39% DHA) + simvastatin 20 mg/d EPA: 1.8 g DHA: 1.56 g	20 mg/d simvastatin + 4 g/d corn oil	Fibrinogen F VII vWF
Nye 1990	n3 Enrol: 108/99 Control enrol: 34 Age: 54 y % Male: 73 Country: New Zealand Sites: 1	Randomized controlled trial (parallel) 1 yr max	Patients with angina pectoris Exclusion: Post – CABG, anti-inflammatory drugs	Aspirin/ dipyridamole	12 fish oil EPA: 2.16 g	1. Aspirin (300 mg/day and dipyridamole 75 mg tds) 2: 12 olive oil	Restenosis

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Osterud 1995	n3 Enrol: 27 n3 Enrol::26 n3 enrol :27 n3 Enrol::26 Control enrol: 28 Age: 28 Median % Male: 50 Race: White/European - 100 Country: Norway Sites: 1	Randomized controlled trial (parallel) 10 wk	Healthy Norwegians living in Tromso		15 mL/day Harp seal blubber oil Total n-3: 3.8 g EPA: 0.9 g DHA: 1.5 g ALA: 0.2 g DPA: 0.07 g 15 mL/day cod liver oil Total n-3: 4.0 g EPA: 1.3 g DHA: 1.8 g ALA: 0.2 g DPA: 0.06 g 15 mL/day 1:1 volume mixture of Harp seal blubber oil and cod liver oil Total n-3: 3.9 g EPA: 1.1 g DHA: 1.7 g ALA: 0.2 g DPA: 0.06 g 15 mL/day Minke whale blubber oil Total n-3: 2.6 g EPA: 0.6 g DHA: 1.1 g ALA: 0.2 g DPA: 0.04 g	No oil	TC Tg HDL Fibrinogen Factor VII Plasma PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Pedersen 2003	n3 Enrol: 23 Control enrol: 21 Age: 63 (38-85) y Males: 56.8 Country: Denmark Sites: 1	Randomized controlled trial (parallel) 8 wk	Type II DM > 1 yr, fasting plasma Tg > 1.5 mmol/L, DM onset > 30 y Exclusion: lipid-lowering meds, antioxidant, fish oil or garlic supplements, high alcohol intake > 4 drinks/day, HRT, serum creatinin > 150 mmol/L	SBP: 151.8 mmHg DBP: 84.8 mmHg TC: 5.8 mmol/L HDL: 1.2 mmol/L LDL: 3.2 mmol/L Tg: 2.3 mmol/L BMI: 30.8 kg/m^2 Fasting glucose: 7.2 mmol/L	4 fish oil capules – 4 g daily EPA/ DHA: 2.6 g	4 corn oil capsules – 4 g daily	Hgb A1c
Prisco 1994	n3 Enrol: 10 Control enrol: 10 Age: 32±4 y SD Males: 100 Country: Italy Sites: 1	Randomized controlled trial (parallel) 4 mo	Healthy males TC < 5.5 mmol/L Tg < 2 mmol/L normal BP Exclusion: “extreme dietary habits”	Diet: "Mediterranean diet"	ESAPENT 4 g/d EPA: 2.04 g DHA: 1.4 g	Olive oil 4 g	Lp(a)
Radack 1989	n3 Enrol: 11 n3 Enrol: 9 Control enrol: 9 Age: ND Males: ND Country: US Sites: 1	Randomized controlled trial (parallel) 20 wk	Adults with hyperlipoproteinemia types IIb or IV Exclusion: Diseases dietary habits Rx requirements that would interfere with main outcomes.		2 1-g fish oil capsules + 1 1-g olive oil capsule TID EPA: 1.05 g DHA: 1.2 g 1 1-g fish oil capsules + 2 1-g olive oil capsule TID EPA: 0.525 g DHA: 0.6 g	Olive oil 9 g	Fibrinogen

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Radack 1990	n3 Enrol: 11 n3 Enrol: 9 Control enrol: 9 Age: 51±11.5 y SD Country: US Sites: 1	Randomized controlled trial (parallel) 20 wk	Age 21-65 y. Hyperlipidemia IIb (Tg>2.25 mmol/L LDL>4.15) or IV (Tg>2.25 LDL<4.15) Exclusion: Tg>8.46 Tx with lipid lowering agent IBW>140% Diet more restrictive than AHA Step I Diuretics Beta blockers Corticosteroids OCP anticoagulants antiplatelet drugs active CVD hepatobiliary pancreatic kidney endocrinologic hematologic or GI disorders. Abnormal blood chemistry levels (>20% above upper limit of normal) Except lipids) DM FBS>7.8 Drug or alcohol abuse		Fish oil capsules 2 different combinations of fish & olive oil capsules		LDL Apo B

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Radack 1991	n3 Enrol: 35 Control enrol: 35 Age: 44.3±9.5 y SD % Male: 53 Race: White/European – 65% Country: US Sites: 1	Cross-over 12 wk	Mild HTN (DBP 90-104) Age > 18 y Exclusion: Change in body weight >10% ≤ 1 mo NSAID use SBP>200 HTN due to endocrine or renovascular disease IBW>140% Steroids w/in 6 wks OCP anticoagulant or antiplatelet agent use CVD hepatobiliary pancreatic kidney endocrine hematologic GI disorder within 6 mo lipids thyroid liver kidney tests >20% above normal, abnormal platelet count DM or FBS>7.8 pregnancy EtOH or drug abuse	SBP: 136 DBP: 93 MAP: 107	6 g fish oil capsules Total n-3: 2.04 g EPA: ~1.1 g DHA: ~0.8 g	Safflower oil 6 g	LDL Apo B
Reis 1989	n3 Enrol: 124 Control enrol: 62 Age: 59 y % Male: 74.4 Country: USA Sites: 1	Randomized controlled trial (parallel) 6 mo	Pts undergoing PTCA Exc**lusion:** bleeding w/in 6 mo current Tx w/ anticoagulants (warfarin) emergency PTCA or AMI thrombolytic Tx allergy to fish & fish products inability to take aspirin or perform a standard treadmill exercise test	All patients were treated with aspirin 325 mg daily dipyridamole 50 mg qid	12 capsules fish oil /d Total n-3: 6 g	Olive oil	Restenosis

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Rivellese 1996	n3 Enrol: 8 Control enrol: 8 Age: 56±3 y SE % Male: 38 Country: Italy Sites: 1	Randomized controlled trial (parallel) 16 wk	Hypertryglyceridemic (IIb or IV Tg 2.25-5.56 mmol/L and TC<7.75 in absense of hypolipidemic drug) NIDDM (at least 2 yr) in diabetic clinic Near-stable metabolic control and weight for 3 mo Age 40-75 Exclusion: Premenopausal or on HRT HTN-control by other than calcium antagonist or ACE inhibitor Uncontrolled HTN Proliferative retinopathy vitreal hemorrhage hepatic or kidney failure bleeding disorder drugs	All on low fat diet TC: 6.27 mmol/L HDL: 0.88 Tg: 3.85 Wgt: 69 Kg Fasting glucose: 10.2 mmol/L	Fish oil capsules 3 g/day x 2 mo then 2 g/day x 1 mo Total n-3: 2.5 -> 1.7 g EPA: 0.96-> 0.64 g DHA: 1.59 -> 1.06 g	Olive oil capsules 3 g x 2 mo then 2 g	Insulin RBC PL
Rossing 1996	n3 Enrol: 18 Control enrol: 18 Age: 32.5±7 y SD % Male: 65.5 Country: Denmark Sites: 1	Randomized controlled trial (parallel) 1 yr	IDDM with persistent albuminuria (>300 mg/d) due to diabetic nephropathy 18-55 y Arterial blood pressure < 160/90 mmHg no antihypertensive Rx GFR >25 mL/min/ 1.73 m^2 diabetic onset < 40 y	Rx: Insulin - all BMI: 24 kg/m^2	Cod-liver oil given as Eskisol Fish Oil emulsion 4.6 g n-3 FA EPA: 2.0 DHA: 2.6 24.1% saturated FA 45.6% monosaturated FA 9.4% EPA 14.2% DHA 6.7% other FA	Olive oil which contained 15.1% saturated FA 76.9% MUFA & 8.0% other FA	BP Hgb A1c

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Sacks 1994 Trials of Hypertension Prevention	n3 Enrol: 175 Control enrol: 175 Age: 43±6.7 y SD % Male: 70 Race: White/European - 84-88 Country: US Sites: 7	Randomized controlled trial (parallel) 6 mo	Healthy 30-54 y DBP < 95 mmHg TC < 260 mg/dl non-fasting FBS <200 mg/dl	SBP: 122.9 DBP: 81.0 BMI: 28 kg/m^2 Wgt: 84 Kg	6 Promega/d Total n-3: 3 g EPA: 1.44 g DHA: 0.96 g DPA: 0.60 g	~50% subjects in the placebo gp (n=86 49%) on olive oil capsules half (n=89 on placebo K tablets.	TC HDL Plasma PL
Salachas 1994	n3 Enrol: 20 Control enrol: 19 Age: 54 y % Male: 95 Country: Greece Sites: 1	Randomized controlled trial (parallel) 12 wk			Fish oil 10 capsules		ETT
Salonen 1987	Enrol n-3: 27 Control enrol: 27 Age range: 30-49y % Male: 100 Country: Finland Sites: multiple	Randomized controlled trial (parallel) 12 wk	Healthy males BMI >24 kg DBP 95-109 mmHg Exclusion: hx of antihypertensive Rx		9 MaxEpa EPA 180 m DHA 120 mg	3 olive oil tid	Plt Aggr
Schaefer 1996	n3 Enrol: 11 Control enrol: 11 Age: 60±13 y SD % Male: 64 Country: US Sites: 1	Randomized controlled trial (parallel) 24 wk	LDL between 10th and 90th percentile for age & sex >40 y Women were post-menopausal Exclusion: Rx that affects lipids Endocrine liver kidney disease Smoking regular alcohol	Diet: Typical American diet TC: 5.64 mmol/L LDL: 3.72 HDL: 1.22 Tg: 1.51 mmol/L BMI: 25.6 kg/m^2	NCEP Step 2 High fish n-3 diet provided by center (all meals) 56% CHO 17% Protein 26% Fat 4% Sat fat 12% MUFA 10% PUFA 15 mg/mJ Cholesterol. Differed from low fish diet mainly in content of fish-derived n-3 FA (EPA+DHA) Derived from food composition tables	NCEP Step 2 Low fish n-3 diet provided by center (all meals). 58% CHO 16% Protein 26% Fat 4% Sat fat 11% MUFA 11% PUFA 11 mg/MJ Cholesterol	Lp(a)

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Schectman 1988	n3 Enrol: 13 Control enrol: 13 Age: 52±4 y SD % Male: 69 Country: US Sites: 1	Cross-over 1 mo	Treated for NIDDM Exclusion: CKD Liver disease uncompensated hypothyroidism Glu>220 mg/dL lipid lowering agents	All on low fish diet TC: 220 mg/dL Tg: 193 Wgt: 86 Kg Fasting glucose: 140 mg/dl	12 g fish oil (MaxEPA 12 capsules) Total n-3: 4.0 g EPA: 2.6 g DHA: 1.4 g	12 g safflower oil	Hgb A1c Apo A1 LDL apo B Apo B
Schectman 1989	n3 Enrol: 18 Control enrol: 18 Age: 50.1 y % Male: 78 Country: US Sites: 1	Cross-over 1 mo	Hypertryglyceridemic (fasting TC > 90th % for age & sex) Exclusion: CKD liver disease lipid meds uncompensated hypothyroidism Glu>220 mg/dL lipid lowering agents	Fasting TC: 245 mg/dL Fasting TG: 383 BMI: 24	12 g fish oil (MaxEPA 12 capsules) Total n-3: 4.0 g EPA: 2.6 g DHA: 1.4 g	12 g safflower oil	Apo A1 LDL apo B
Seljeflot 1998	n3 Enrol: 22 Control enrol: 19 Age: 49.5 Median % Male: 100 Country: Norway Sites: 1	Factorial 6 wk	Males with hyperlipidemia TC ≥ 6.0 mmol/L,fasting Tg ≥ 2.0 mmol/L smoke ≥ 10 cigarettes/d ≥ 40 y Exclusion: Heart kidney hepatic malignant diseases & vegetarians alcoholic & drug abusers also Rx fish oil and/or antioxidants < 3 mo	SBP: 132 DBP: 85 TC: 7.0 mmol/L HDL: 0.98 mmol/L Tg: 2.40 mmol/L BMI Men: 27.1 kg/m^2	n-3 FA adminisered as 60% 1 g ethyl ester capsules 4 caps bid providing 4.8 g EPA & DHA per day	n-3 FA placebo	vWF
Silva 1996	n3 Enrol: 20 Control enrol: 15 Age: 50.6±:2.8 y SE % Male: 71 Race: Portuguese Country: Portugal Sites: 1	Randomized controlled trial (parallel) 2 mo	18-70 yrs with Tg > 200 mg/dl +/- TC>200 mg/dl Exclusion: serum creatinine >1.5 mg/dl liver disease Insulin dependent DM MI or stroke in previous 6 months CHF	All on "Mediterranean diet" BMI: 28.9 kg/m^2	12 capsules/d fish oil (12 g/d) EPA: 2.2 g DHA: 1.4 g	Soya oil	Apo A1 Apo B-100

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Singh 2002	n3 Enrol: 499 Control enrol: 501 Age: 49±10 y SD % Male: 89.7 Race: Asian Country: India Sites: multiple	Randomized controlled trial (parallel) 2 yr	> 25 y; one or more of: hypercholesterolemia HTN or DM (based on WHO CVD risk factors); angina pectoris or MI Exclusion: Cancer chronic diarrhea or dysentery blood urea > 6.6 mmol/L arthritis	CVD: WHO criteria TC > 5.2 mmol/L HTN:SBP > 140 mm Hg DBP > 90 mm Hg FBS > 7.7 mol/ SBP: 132 DBP: 86 BMI: 24.3 kg/m^2 DM: 19% Prevalence	In addition to control diet daily recommendations 400-500 g vegetables fruits nuts (250-300 g fruit 125-150 g vegetables 25-50 g walnuts or almonds) 400-500 g whole grains legumes rice maize & wheat; 3-4 servings mustard seed or soybean oil. 1.79 (0.36) daily intake of n-3 FA	Similar diet to NCEP with step 1 prudent diet: < 30% energy from total fat < 10% safturated & < 300 mg cholesterol consumed per day	TC Tg LDL HDL BP FBS
Sirtori 1992	n3 Enrol: 12 Control enrol: 12 Age: ND % Male: ND Country: Italy Sites: 1	Cross-over 6 wk	Hypercholesterolemia Exclusion: Familial hypercholesterolemia. >20 cigarettes/day BMI>25.0 kg/m^2 male 23.5 kg/m^2 female >30 g EtOH/day MI within prior 12 mo	TC: 7.37 mmol/L LDL: 5.47 HDL: 1.34 Tg: 1.49	K85 6 g with corn oil diet EPA: 2.8 g DHA: 1.7 g	LA rich diet (corn oil). No additional oil.	Apo A1 LDL apo B Apo B Plt Aggr

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Sirtori 1998	n3 Enrol: 470 Control enrol: 465 Age: 58.2 ±:9.09 y SD % Male: 62 Country: Italy Sites: 63	Randomized controlled trial (parallel) 6 mo	Males 45-75 yr females 55-80 yr hyperlipoproteinemia-type IIb or IV one or more risk factors: impaired glucose tolerance NIDMM and/or arterial hypertension Exclusion: TC > 300 mg/dl Tg > 400 mg/dl severe intercurrent ailments kidney or kidney disease intestinal malabsorption duodenal ulcer non responsive to Tx including obese with BMI > 30 kg/m^2 hx vascular or non vascular brain disease (including epilepsy & alcoholism) severe hyperlipidemia severe HTNMI < 3 mo UA	Dyslipidemia: stable Tg > 200 mg/dl type IIb = TC > 270 mg/dl type IV = < 270 mg/dl HTN: past yr:SBP >= 160 mmHg DBP >= 95 mmHg independent of Tx BMI: 73.5 kg DM: 43% Prevalence	ESAPENT 1 capsule TID for 2 months followed by 1 capsule BID for 4 additional months [1] For 2 mo conventional tw + 1 cap TID of ESAPENT corresponding to a total 1530 mg of EPA & 1050 mg of DHA. After 2 mo ESAPENT reduced to 1 cap BID EPA: 1.53 / 1.02 g DHA: 1.05 / .70 g	Olive oil 1 capsule tid 2 mo then bid for 4 mo	TC Tg Hgb A1c FBS Insulin
Solomon 1990	n3 Enrol: 5 Control enrol: 5 Age: 55.7 y % Male: 80 Country: UK Sites: 1	Randomized controlled trial (parallel) 3 mo	"Typical history of angina pectoris" Exclusion: UA/recent MI heart failure uncontrolled HTN (ph V DBP > 100 mmHg) DM signif hepatic or kidney impairment unable to perform bicycle exercise uninterpretable ECG features	SBP: 144.8 DBP: 91.2	EPA-rich fish oil (MaxEPA) 15 capsules EPA: 2.8 g DHA: 1.8 g	Olive oil 15 capsules	ETT RBC PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Swahn 1998	n3 Enrol: 26 Control enrol: 27 Age: 57.5±9.6 y SD % Male: 79 Country: Sweden Sites: 1	Randomized controlled trial (parallel) 12 wk	Outpatient hx of MI > 3 mo fasting plasma Tg ≥ 2.0 mmol/L TC≤ 10 mmol/L Exclusion: Lipid-lowering Rx serious disease	Beta Blocker Rx: Aspirin SBP: 137 DBP: 88 BMI: 28.3 kg/m^2	N-3: 3.5 g/day EPA: 1.72 g DHA: 1.13 g DPA: .06 g	Corn oil 2 g bid	Lp(a)
Toft 1995	n3 Enrol: 42 Control enrol: 42 Age: 52.9±9.5 y SD % Male: 64 Country: Norway Sites: 1	Randomized controlled trial (parallel) 16 wk	58 patients who'd previously enrolled in Bonaa study + 26 hypertensives recruited from primary hearh care service Hypertension: SBP < 190 mmHg DBP 90-110 mmHg BMI < 32 kg/m^2	MAP: 115.2 TC: 6.21 mmol/L LDL: 4.24 mmol/L HDL: 1.40 mmol/L Tg: 1.19 mmol/L BMI: 26.1 kg/m^2	Omacor 4 g/d 85% EPA & DHA	Corn oil 4 g (56% LA)	Hgb A1c FBS Insulin
Toft 1997	n3 Enrol: 38 Control enrol: 40 Age: 52.9±9.5 y SD % Male: 64 Country: Norway Sites: 1	Randomized controlled trial (parallel) 16 wk	Patients who'd previously enrolled in Bonaa study + 26 hypertensives recruited from primary hearh care service	MAP: 115.2 TC: 6.21 mmol/L LDL: 4.24 mmol/L HDL: 1.40 mmol/L Tg: 1.19 mmol/L BMI: 26.1 kg/m^2	Omacor 4 g/d 85% EPA & DHA	Corn oil 4 g (56% LA)	ETT F VII
Toth 1995	n3 Enrol: 10 Control enrol: 0 Age: 50 ±9 y SD % Male: 100 Country: Hungary Sites: 1	Non-Randomized non-controlled study 2 mo	Presumably males only ischemic heart disease hyperlipopro-teinemia		10 caps/d Ameu (0.5 g salmon oil with 33% of n-3-FA) 2 mo Total n-3: 1.65 g		ETT
Verheugt 1986	n3 Enrol: 5 Control enrol: 0 Age: 51.6 % Male: 100 Country: Netherlands Sites: 1	Non-Randomized non-controlled study 6 mo	Presumably males only angiographically proven CAD moderate to severe exercise-induced angina pectoris	CVD: 50% luminal stenosis in one or more epicardial coronary arteries at angiography Rx: Beta Blocker TC: 7.6 mmol/L HDL: 0.92 mmol/L	12 caps/d Intradal fish oil concetrate Each capsule = 250 mg EPA/DHA/DPA		ETT

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Warren 1988	n3 Enrol: 7 Control enrol: 0 Age: 64 % Male: 57 Country: US Sites: 1	Non-Randomized non-controlled study 6 wk	Hx of chronic angina pectoris clinical stability of CAD	Rx: Oral Rx for angina SBP: 127 TC: 246 mg/dL LDL: 163 mg/dL HDL: 48 mg/dL Tg: 174 mg/dL	40 ml/d of cod liver oil containing approx 9% (3.1 g) EPA 780 IU/ml vit A 77.2 IU/ml vit D 306 mg cholesterol & 324 kcal EPA: 3.1 g		ETT
Wensing 1999	Enrol n-3: 13 Enrol n-3: 14 Control enrol: 11 Age: 65 % Male: 37 Race: ND Country: Netherlands Sites: 1	Randomized controlled trial (parallel)	>60 y TC < 8.0 mmol/L Tg < 3.0 mmol/L Exclusion: wt-reducing Rx/diet, Rx affecting lipids	BMI: 26	1.Diet enriched with a-linolenic acid via shortenings linseed oil (429 g/kg), ALA: 6.45 2.Diet enriched EPA/DHA via shortenings. EPA/DHA shortening menhaden oil (306 g/kg) EPA 1.02 DHA: 0.54	Diet enriched with oleic acid, a-linolenic acid, or EPA/DHA via shortenings (30 g). Other placebo: sunflower oil palm oil	Plt Aggr RBC PL
Westerveld 1993	n3 Enrol: 8 n3 Enrol: 8 Control enrol: 8 Age range: 37-71y % Male: 63 Country: Netherlands Sites: 1	Randomized controlled trial (parallel) 8 wk	NIDDM pts Exclusion: hepatic kidney GI or hematological diseases; CVD events in past 3 mo; Rx that modify plasma lipids or platelet function	Rx: Insulin	EPA-E 6 capsules EPA: 0.9 EPA-E 12 capsules EPA: 1.8	6 capsules containing 0.3 ml (276 mg) olive oil	Hgb A1c Plt agg

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Wilt 1989	n3 Enrol: 48 Control enrol: 48 Age range: 42 y % Male: 100 Country: US Sites: 1	Cross-over 12 wk	Vietnam Veterans serum chol 5.95 – 7.76 mmol/L, Tg <3.39 mmol/L Exclusion: signif co-morbidities (atherosclerotic CVD, malignancy, alcoholism, bleeding tendency); > 60 y; lipid-lowering meds; fish allergy		20 g fish oil (MaxEPA 20 capsules) EPA: 2.8 g DHA: 1.8 g	Safflower oil	Apo A1 Apo B
Woodman 2002	n3 Enrol: 17 n3 Enrol: 8 Control enrol: 16 Age: 60.9±8.2 y SD % Male: 72 Country: Australia Sites: 1	Randomized controlled trial (parallel) 6 wk	Men and post-menopausal women (40-75 y) non-smokers type 2 DM (on oral hypoglycemic or FBS>7.0 mmol/L or non-fasting BS > 11.1) HTN treated for ≥ 3 mo. Hgb A1c<9% SBP>115 <180 BBP <110 BMI<35 kg/m^2 TC and Tg < 7.5 mmol/L Exclusion: Insulin >2 fish meals/week fish oil supplement EtOH ≥ 40 g/day Tobacco ≤2 yrs Recent (<3 mo) heart disease angina major surgery Recent Hx (<6 mo) MI or stroke liver or kidney disease (Cr>130 mcmol/L macroproteinuria) symptomatic autonomic neuropathy	Rx: Beta Blocker - 18% Rx: Calcium Channel Bloc - 39% Rx: ACE Inhibitor 55% Rx: Diuretic - 14% Rx: ARB 24% Alpha blocker 6% Rx: Aspirin - 29% Rx: Statin - 31% Rx: Fibrate - 6% Rx: Oral hypoglycemic ag - Biguanides (53%) Sulfonylureas (49%) and alpha-2 glucosidase inhibitors (2%) Diet: Low fat diet - ≤ 2 fish meals/week SBP: 133 DBP: 71 TC: 4.5 mmol/L LDL: 2.7 HDL: 0.99 Tg: 1.6 BMI: 30.6 kg/m^2 Fasting glucose: 7.5 mmol/L	Capsules containing 4 g EPA (96%) EPA: 3.84 g Capsules containing 4 g DHA (92%) EPA: 0.02 g DHA: 3.68 g	Olive oil 4 g	BP Hgb A1c FBS Insulin Plasma PL

Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Cofactors	Intervention	Control	Outcomes Analyzed
Yamada 1997	n3 Enrol: 264 Control enrol: 212 Age: 58.9±8 y SE Race: Asian Country: Japan Sites: multiple	Non-Randomized multiple cohort trial	2 study populations: 264 citizens from Kamishima fishing Village, 212 citizens from Haze farming village	Diet: High fish diet SBP: 138 DBP: 79 TC: 208 mg/dL LDL: 130 mg/dL HDL: 58 mg/dL Tg: 97 mg/dL BMI: 23.3 kg/m^2 Fasting glucose: 93 mg/dl	Fishing village	Farming village	IMT

Appendix C. Evidence Table (Part 2)

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Agren 1988	**Apo A1**	Fish diet	1.26±0.16	g/L	SD	f/up	1.07±0.15	<.01	<.01	Dropouts because of inability to remain in area & other similar reasons. Control TC = 5.14+/-1.12 due to 2 subjects with TC>8.0 which decreased during study.
		Fish & low fat diet	1.23±0.15				1.15±0.16	<.05	NS	
		Control diet	1.27±0.17				1.22±0.13	NS		
	Apo B	Fish diet	0.70±0.12	g/L	SD	f/up	0.66±0.12	<.10	NS	
		Fish & low fat diet	0.63±0.1				0.58±0.1	<.05	NS	
		Control diet	0.69±0.07				0.67±0.1	NS		
Agren 1991	**Apo A1**	Fish	1.49±0.29	g/L	SD	f/up	1.52±0.34	NS	NS	Dropout: 6 fish eaters failed to follow diet.
		Fish Exercise	1.59±0.22				1.58±0.25	NS	NS	
		No intervention	1.53±0.29				1.48±0.34	NS		
		Exercise	1.58±0.29				1.57±0.33	NS		
	Apo B	Fish	0.64±0.11	g/L	SD	f/up	0.65±0.12	NS	NS	
		Fish Exercise	0.67±0.19				0.67±0.19	NS	NS	
		No intervention	0.64±0.11				0.63±0.11	NS		
		Exercise	0.7±0.17				0.65±0.16	NS		
Agren 1996	**Apo A1**	Fish diet	1.20±0.32	g/L	SD	f/up	1.25±0.21	NS	NS	4 excluded from analyses-high plasma Tg levels(1 from each arm), noncompliance to fish diet (1), very low platelet counts at beginning (1-fish oil arm)
		Fish oil	1.25±0.45				1.21±0.26	NS	NS	
		DHA oil	1.28±0.34				1.33±0.26	NS	NS	
		No oil	1.17±0.35				1.21±0.28	NS		
	Apo B	Fish diet	0.75±0.19	g/L	SD	f/up	0.79±0.2	NS	NS	
		Fish oil	0.72±0.19				0.73±0.19	NS	NS	
		DHA oil	0.71±0.17				0.72±0.17	NS	NS	
		No oil	0.81±0.23				0.85±0.23	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Agren 1997	**Factor VII**	Fish diet	94±5	%	SD	f/up	97±4	NS	NS	No funding source 4 excluded from analyses-high plasma Tg levels(1 from each arm), noncompliance (1-fish diet), very low platelet counts at start (1-fish oil arm)Incomplete population data. During study, intake of fish other than that consumed in study meals was 14 g/d. Therefore, actual increases of EPA & DHA from fish were about 0.05 and 0.15 g/d smaller than calculated on fish sample analyses. No data on definition of %T for platelet aggregation
		Fish oil	93±5				98±4	NS	NS	
		DHA oil	98±4				97±5	NS	NS	
		No oil	92±7				97±5	NS		
	Fibrinogen	Fish diet	3.4±0.5	g/L	SD	f/up	3.5±0.5	nd	NS	
		Fish oil	3.6±0.5				3.5±0.4	nd	NS	
		DHA oil	3.4±0.5				3.3±0.5	nd	NS	
		No oil	3.3±0.4				3.1±0.8	nd		
	Plt Aggr	PRP								
	ADP	Fish diet	35.1±27.3	%T	SD	f/up	39.7±20.9	nd	NS	
	2.0 μmol/L	Fish oil	49.9±22.5				44.1±20.3	nd	NS	
		DHA oil	37.2±25.2				44.7±25.6	nd	NS	
		No oil	41.5±27.0				41.5±26.9	nd		
	ADP	Fish diet	70.0±15.4	%T	SD	f/up	71.7±6.5	nd	NS	
	5.0 μmol/L	Fish oil	74.2±9.1				69.5±14.1	nd	NS	
		DHA oil	64.5±17.7				69.0±13.4	nd	NS	
		No oil	67.9±15.6				72.5±9.6	nd		
	Collagen	Fish diet	66.1±16.7	%T	SD	f/up	42.1±25.6	nd	<.05	
	50 μgmol/L	Fish oil	51.3±28.6				16.8±20.4	nd	<.05	
		DHA oil	39.3±23.9				49.7±27.5	nd	NS	
		No oil	48.7±26.0				45.4±28.0	nd		
Alaswad 1999	**Lp(a)**	Fish oil	7.8±4.0	mg/dL	SD	f/up	5.9±3.3	NS	NS	Reported single blind but subjects clearly not fully blinded
		Calcium gluconate	7.4±4				6.6±3.7	NS		
Allman-Farinelli 1999	**Factor VIIc**	Flaxseed	82.6±5.0	%	SE	f/up	86	NS	NS	Data approximated from figures 1 LA diet subject excluded from final results because of non-compliance Data approximated from figures
		Safflower	80.5±6.4				79	NS		
	Factor VIII	Flaxseed	82.4±7.3	%	SE	f/up	78	NS	NS	
		Safflower	78.4±3.3				78	NS		
	Fibrinogen	Flaxseed	2.09±0.10	g/L	SE	f/up	2.15±0.10	NS	NS	
		Safflower	2.38±0.14				2.34±0.14	NS		
	vWF	Flaxseed	96.4±9.1	%	SE	f/up	89	NS	NS	
		Safflower	85.8±6.5				85	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Angerer 2002	**HDL**	Fish oil	1.31±0.39	mmol/L	SD	Δ	-0.00±0.25	NS	.07	
		FA mixture	1.25±0.34				+0.09±0.31	NS		
	IMT Overall	Fish oil	1.26±0.41	mm	SD	Δ	+0.07±0.13	NS	NS	
		FA mixture	1.31±0.41				+0.05±0.11	NS		
	IMT CCA	Fish oil	0.86±0.29	mm	SD	Δ	+0.05±0.16	NS	NS	
		FA mixture	0.91±0.28				+0.03±0.10	NS		
	IMT CB	Fish oil	1.54±0.55	mm	SD	Δ	+ 0.06±0.13	NS	NS	
		FA mixture	1.65±0.62				+0.03±0.18	NS		
	IMT ICA	Fish oil	1.11±0.54	mm	SD	Δ	+0.11±0.29	NS	NS	
		FA mixture	1.10±0.59				+0.09±0.23	NS		
	LDL	Fish oil	4.07±1.25	mmol/L	SD	Δ	-0.25±0.20	.05	NS	
		FA mixture	3.87±1.04				-0.41±1.03	<.05		
	Tg	Fish oil	2.19±1.34	mmol/L	SD	Δ	-0.16±0.98	NS	NS	
		FA mixture	2.15±1.09				+0.09±1.19	NS		
Bairati 1992a	**Restenosis**	Fish oil				f/up	18/59		.05	
		Olive oil					29/60			
Bairati 1992b	**HDL**	MaxEPA	1.04±0.3	mmol/L	SD	Δ	+0.09±0.22	nd	<.05	
		Olive oil	1.09±0.34				-0.01±0.24	nd		
	LDL	MaxEPA	4.08±1.1	mmol/L	SD	Δ	+0.16±0.78	nd	<.05	
		Olive oil	4.20±1.02				-0.17±0.75	nd		
	TC	MaxEPA	6.24±1.24	mmol/L	SD	Δ	-0.09±0.90	nd	NS	
		Olive oil	6.28±1.13				-0.07±0.96	nd		
	Tg	MaxEPA	2.31±1.07	mmol/L	SD	Δ	-0.69±0.76	nd	<.0001	
		Olive oil	2.26±1.03				+0.21±0.94	nd		
Balestrieri 1996	**Apo A1**	Fish oil	116±47	mg/dL	SD	f/up	127±47	NS	NS	Dropout from each group- AMI (1), resection of abdominal aortic aneurism (1)
		Olive oil	112±27				125±42	NS		
	Apo B	Fish oil	205±44	mg/dL	SD	f/up	204±42	NS	NS	
		Olive oil	207±46				205±42	NS		
Bellamy 1992	**Restenosis**	Fish oil				f/up	19/60		NS	
		No oil					21/53			
Bemelmans 2002	**IMT**	ALA margarine	0.83±0.16	mm	SD	Δ	+0.05±0.11	<.01		Longitudinal cohort with no control
Berrettini 1996	**Factor VII**	Fish oil	116±25	%	SD	f/up	122	NS	NS	Data estimated from graph Dropout: 1 GI-placebo
		Corn oil	105±31				111	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Bonaa 1992	**Apo A1**	Fish oil	1.55±0.30	g/L	SD	f/up	1.54±0.31	NS	<.05	Dropout: 16 before baseline exam (ND on group distribution). About 92% completed study.
		Corn oil	1.56±0.24				1.62±0.27	<.01		
	Apo B	Fish oil	1.53±0.27	g/L	SD	f/up	1.49±0.23	NS	NS	
		Corn oil	1.54±0.29				1.51±0.28	NS		
	HDL	Fish oil	1.31±0.42	g/L	SD	f/up	1.36±0.46	<.05	NS	
		Corn oil	1.32±0.33				1.40±0.37	<.01		
	LDL	Fish oil	4.58±0.98	g/L	SD	f/up	4.68±0.93	NS	NS	
		Corn oil	4.54±0.79				4.47±0.85	NS		
	TC	Fish oil	6.51±1.02	g/L	SD	f/up	6.53±0.93	NS	NS	
		Corn oil	6.58±0.80				6.54±0.88	NS		
	Tg	Fish oil	1.40±0.77	g/L	SD	f/up	1.10±0.56	<.001	<.01	
		Corn oil	1.49±1.13				1.45±1.01	NS		
Bonnema 1995	**Hgb A1c**	Omega 3	8.0±2.0	%	SD	f/up	7.0±2.0	NS	NS	
		Olive oil	9.0±2.0				7.0±2.0	NS		
Borchgrevink 1966	**TC**	Linseed oil	.289	d/L		f/up	.277	nd	nd	
		Corn oil	.285				.260	nd		
Brox 2001	**Apo A1**	Seal oil	1.6±0.3	g/L	SD	f/up	1.8±0.4	NS	NS	Control data supplied directly by author via email.
		Cod liver oil	1.6±0.2				1.8±0.3	NS	NS	
		No oil	1.6±0.3				1.7±0.3	NS		
	Apo B100	Seal oil	2.0±0.3	g/L	SD	f/up	2±0.3	NS	NS	
		Cod liver oil	2±0.3				2±0.3	NS	NS	
		No oil	1.9±0.2				2±0.3	NS		
	HDL	Seal oil	1.3±0.3	mmol/L	SD	f/up	1.4±0.3	NS	NS	
		Cod liver oil	1.3±0.4				1.3±0.4	NS	NS	
		No oil	1.3±0.3				1.3±0.3	NS		
	Lp(a)	Seal oil	163±170	mg/L	SD	f/up	183±168	NS	NS	
		Cod liver oil	185±181				185±194	NS	NS	
		No oil	131±167				148±198	NS		
	TC	Seal oil	8.0±0.8	mmol/L	SD	f/up	8±0.7	NS	NS	
		Cod liver oil	8.3±0.8				7.8±0.9	NS	NS	
		No oil	7.9±0.9				7.9±0.8	NS		
Cairns 1996	**HDL**	Fish oil	1.04	mmol/L		f/up	1.04	nd	NS	Dropout: Bleeding (6), GI-# withdraws unknown Explicit statement pertaining to identical in appearance placebo capsules & test results performed by technologist blinded to treatment allocations.
		Corn oil	1.05				1.06	nd		
	LDL	Fish oil	3.83	mmol/L		f/up	3.71	nd	NS	
		Corn oil	3.87				3.67	nd		
	TC	Fish oil	5.91	mmol/L		f/up	5.59	nd	NS	
		Corn oil	5.98				5.75	nd		
	Tg	Fish oil	2.66	mmol/L		f/up	1.72	nd	<.05	
		Corn oil	2.52				2.30	nd		
	Restenosis	Fish oil				f/up	145/312		.6	
		Corn oil					140/313			

Δ = within cohort difference
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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Chan 2002	**Apo A1**	Fish oil	1180±40	mg/L	SE	f/up	1210±40	NS	NS	Incomplete reporting on design.
		Corn oil	1280±50				1260±40	NS		
	ApoB	Fish oil	1280±60	mg/L	SE	f/up	1180±60	NS	NS	CRP is Geometric mean and range
		Corn oil	1290±40				1230±30	NS		
	CRP	Fish oil	2.11(1.6, 3.2)	mg/L	SE	f/up	2.09(1.6, 3.2)	NS	NS	
		Corn oil	2.04(1.6, 3.1)				1.97(1.1, 4.0)	NS		
Chan 2003	**Insulin**	Fish oil	41±4	mU/L	SE	f/up	42±6	NS	NS	Not explicit inclusion/exclusion criteria.
		Corn oil	32±2				29±2	NS		
Christensen 1996	**HR var (SDNN)**	Fish oil	115±39	ms	SD	f/up	124±30	.04	.01	Dropout: FO-1 personal reasons, 1 poor Holter; Control-1 died, 1 personal reasons, 1 ventricular aneurysm, 1 Aflutter No demographic information.
		Olive oil	115±45				205±36	NS		
Christensen 1997	**HR var (SDNN)**	1 fish/week	122±48	ms	SD		--		NS	Cross-sectional evaluation of baseline data from Christensen, 1996. Dropout: Technically insufficient Holter recording (1) & platelet fatty acid analyses failed (2).
		2 fish/week	119±30				--		NS	
		No fish	103±43				--			
Christensen 1999	**HR var (SDNN)**	Fish oil 1.7 g	164±44	ms	SD	f/up	155±38	NS	NS	Exclusion criteria unclear
		Fish oil 5.9 g	136±27				136±33	NS	NS	
		Olive oil	170±43				157±36	NS		
Cobiac 1991	**Apo A1**	Fish	1.20±0.04	mmol/L	SE	Δ	-0.09±0.02	<.05	NS	Limited data on population
		Fish oil	1.17±0.04				-0.08±0.02	<.05	NS	
		Control diet	1.35±0.16				-0.09±0.02	<.05		
	Apo B	Fish	1±0.04	mmol/L	SE	Δ	-0.05±0.06	NS	NS	
		Fish oil	0.99±0.03				+0.02±0.03	NS	NS	
		Control diet	0.97±0.07				-0.04±0.12	NS		
	Fibrinogen	Fish	2.65±0.15	g/L	SE	Δ	-0.15±0.12	NS	<.05	
		Fish oil	2.35±0.2				+0.38±0.19	NS	NS	
		Control diet	1.96±0.14				+0.18±0.17	NS		
Conquer 1999	**Factor VIII**	Seal oil	0.85±0.06	u/mL	SD	f/up	1.01±0.10	NS	NS	Dropout: Poor compliance (1)
		Ev primrose oil	0.81±0.04				0.85±0.06	NS		
	Lp(a)	Seal oil	58.6±18.5	mmol/L	SD	f/up	43.2±13.7	NS	NS	
		Ev primrose oil	45.6±14.4				28.1±8.9	NS		
	vWF	Seal oil	6.9±0.7	mcmol/L	SE	f/up	5.7±0.7	NS	NS	
		Ev primrose oil	7.0±0.4				6.3±0.5	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
de Lorgeril 1994	**Apo A1**	Mediterranean diet	1.24±0.01	g/L	SE	f/up	1.34±0.02	nd	NS	Dropout: Failure to meet 2 consecutive appts given in percentages but failed to calculate appropriately. 584 randomized, 505 in final analyses. Only stable patients & without recurrent angina enrolled. Hospital contacts only.
		Regular diet	1.24±0.01				1.46±0.02	nd		
	Apo B	Mediterranean diet	1.52±0.02	g/L	SE	f/up	1.39±0.03	nd	NS	
		Regular diet	1.49±0.02				1.37±0.03	nd		
	HDL	Mediterranean diet	1.16±0.02	mmol/L	SE	f/up	1.28±0.03	nd	NS	
		Regular diet	1.17±0.01				1.32±0.03	nd		
	LDL	Mediterranean diet	4.52±0.07	mmol/L	SE	f/up	4.18±0.08	nd	NS	
		Regular diet	4.54±0.07				4.11±0.09	nd		
	Lp(a)	Mediterranean diet	0.28±0.02	g/L	SE	f/up	0.31±0.03	nd	NS	
		Regular diet	0.30±0.02				0.27±0.03	nd		
	TC	Mediterranean diet	6.50±0.08	mmol/L	SE	f/up	6.17±0.09	nd	NS	
		Regular diet	6.47±0.07				6.16±0.10	nd		
	Tg	Mediterranean diet	2.15±0.09	mmol/L	SE	f/up	1.85±0.12	nd	NS	
		Regular diet	2.00±0.07				1.92±0.13	nd		
Deck 1989	**LDL apo B**	Fish oil	0.957±0.308	g/L	SD	Δ	+0.150±0.236	NS	<.05	
		Corn oil	1.10±0.392				-0.0957±0.132	NS		
Dehmer 1988	**Restenosis**	Fish oil				f/up	8/43		.007	
		No oil				f/up	18/39			
DeLany 1990	**Apo B100**	Fish oil	0.62±0.12	g/L	SE	f/up	0.81±0.12	NS	NS	Unclear if randomized. Few demographic data. Industry funded.
		No oil	0.53±0.12				0.63±0.12	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Deslypere 1992	**Apo A1**	Fish oil 1.1g	137±25	mg/dL	SD	f/up	134±25	NS	NS	Very little traditional baseline data given. Baseline data given only for outcomes of interest
		Fish oil 2.2g	139±21				138±21	NS	NS	
		Fish oil 3.4g	137±20				126±17	NS	NS	
		Olive oil	136±25				142±29	NS		
	Apo B	Fish oil 1.1g	91±21	mg/dL	SD	f/up	95±22	NS	NS	
		Fish oil 2.2g	85±16				90±18	NS	NS	
		Fish oil 3.4g	89±22				87±19	NS	<.05	
		Olive oil	86±20				92±18	NS		
	Factor VIII	Fish oil 1.1g	80.7±36.4	%	SD	f/up	68.4±24.7	NS	NS	
		Fish oil 2.2g	73.1±37.5				55.6±23.1	NS	NS	
		Fish oil 3.4g	76.7±41.6				59.5±18.8	NS	NS	
		Olive oil	82.5±41.1				66.5±29.1	NS		
	Fibrinogen	Fish oil 1.1g	2.00±0.50	g/L	SD	f/up	1.90±0.44	NS	NS	
		Fish oil 2.2g	2.31±0.75				1.86±0.35	NS	NS	
		Fish oil 3.4g	2.33±0.65				2.03±0.51	NS	NS	
		Olive oil	2.29±0.48				2.13±0.55	NS		
	Hgb A1c	Fish oil 1.1g	4.86±0.57	%	SD	f/up	4.38±0.46	NS	NS	
		Fish oil 2.2g	4.76±0.62				4.57±0.42	NS	NS	
		Fish oil 3.4g	5.04±0.34				4.51±0.34	NS	NS	
		Olive oil	4.89±0.52				4.49±0.47	NS		
	Lp(a)	Fish oil 1.1g	22.1± 24.2	mg/dL	SD	f/up	28.5±25.9	NS	NS	
		Fish oil 2.2g	27.2±32.6				28.9±37.8	NS	NS	
		Fish oil 3.4g	22.5±33.3				32.2±32.9	NS	NS	
		Olive oil	35.1±26.3				34.5±28.3	NS		
	vWF	Fish oil 1.1g	137.2± 27.8	%	SD	f/up	154.5±47.2	NS	NS	
		Fish oil 2.2g	140.9±37.2				148.7±42.7	NS	NS	
		Fish oil 3.4g	132.5±26.6				141.5±34.7	NS	NS	
		Olive oil	130.7±36.9				140.9±40.4	NS		
Djousse 2003	**IMT CCA**	LA intake 1.2 g	0.64±0.03	mm	SE	ΔΔ	-0.06			Dropout: Missing data for- US data (125), smoking (17); preexisting condition that can influence CAD (CAD or stroke - 130), DM (86), hypertension (225), kidney insufficiency (11). Inconsistent pt selection. NHLBI Family Heart Study consist of smaller studies of pts at high CAD risk or at random
		LA intake 0.8 g	0.60±0.02				-0.10		.01	
		LA intake 0.6 g	0.63±0.02				-0.07		Trend	
		LA intake 0.4 g	0.70±0.03				-			
	IMT CB	LA intake 1.2 g	0.94±0.03	mm	SE	ΔΔ	-0.05			
		LA intake 0.8 g	0.86±0.03				-0.13		.0008	
		LA intake 0.6 g	0.91±0.03				-0.06		Trend	
		LA intake 0.4 g	0.99±0.03				-			
	IMT ICA	LA intake 1.2 g	0.71±0.01	mm	SE	ΔΔ	-0.01			
		LA intake 0.8 g	0.70±0.01				-0.02		NS	
		LA intake 0.6 g	0.70±0.01				-0.02		Trend	
		LA intake 0.4 g	0.72±0.01				-			

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Dunstan 1997	**Hgb A1c**	Fish/mod exercise	8.3±1.5	%	SD	Δ	+0.19±0.25 SE	nd	NS	Regression relative to control (no fish/lt exercise) adjusted for age, sex and change in body weight. 6 dropouts: either changes in medication or other commitments-assignment unknown Few details on low-fat diet
		Fish/lt exercise	8.0±1.5				+0.49±0.24 SE	nd	.05	
		No fish/mod exerc	8.8±2.7				+0.03±0.26	nd		
		No fish/lt exercise	8.1±1.4				nd	nd		
	Insulin	Fish/mod exercise	78.3±33.7	pmol/L	SD	Δ	-19.59±10.8 SE	nd	.08	
		Fish/lt exercise	78.2±47.2				-21.71±10.7 SE	nd	.05	
		No fish/mod exerc	89.5±97.2				-14.4±11.0	nd		
		No fish/lt exercise	100.3±53.2				nd	nd		
Dunstan 1998	**FBS**	Fish/mod exercise	10.0±3.4	mmol/L	SD	Δ	-0.72±0.15	nd	<.05	Regression adjusted for age, sex and change in body weight. 6 dropouts: either changes in medication or other commitments-assignment unknown Few details on low-fat diet
		Fish/lt exercise	8.9±2.6				+0.57±0.2	nd	.001	
		No fish/mod exerc	9.6±3.3				-0.52±0.2	nd		
		No fish/lt exercise	8.8±2.1				nd	nd		
Dunstan 1999	**Factor VII**	Fish/mod exercise	111.5± 19.7	%	SD	Δ	0.7±1.1	nd	NS	Estimates from graph. Compared to no fish light exercise, adjusted for age and sex. 6 dropouts: either changes in medication or other commitments-assignment unknown Few details on low-fat diet
		Fish/lt exercise	112.8±23.4				4.9±1.4	nd	.02	
		No fish/mod exerc	108.4±19.4				nd	nd		
		No fish/lt exerc	102.0±14.8				nd	nd		
	Fibrinogen	Fish/mod exercise	2.9±0.7	g/L	SD	Δ	+0.25	nd	NS	
		Fish/lt exercise	3.3±0.8				+0.14	nd	NS	
		No fish/mod exerc	3.1±0.8				+0.13	nd		
		No fish/lt exercise	3.3±1.0				nd	nd		
Durrington 2001	**Apo A1**	Fish oil	90±14	mg/dL	SD	f/up	84±13	NS	NS	
		Corn oil	89±15				89±13	NS		
	Apo B	Fish oil	96±31	mg/dL	SD	f/up	95±26	NS	NS	
		Corn oil	110±31				114±33	NS		
	Lp(a)	Fish oil	10.5 Median	mg/dL		f/up	16.2 Median	NS	NS	
		Corn oil	26 Median				38.5 Median	NS		
Eritsland 1995a	**Lp(a) ≥20**	Fish oil	29.7 Median	mg/dL		f/up	28.7 Median	nd	.023	Overall NS See Eritsland 1995b
		No oil	30.3 Median				30.8 Median	nd		
	Lp(a) <20	Fish oil	5.5 Median	mg/dL		f/up	5.7 Median	nd	NS	
		No oil	5.6 Median				6.0 Median	nd		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Eritsland 1995b	**Apo AI**	Fish oil	1240±250	mg/L	SD	f/up	1390±280	nd	NS	Dropouts: 610 enrolled: 12 died before 9 mo; 9 reinvestigated (angiography etc) before 9 mo; 11 started antidiabetic or lipid lowering agent (7 fish oil, 4 control, p=0.43); 66 deviated from assigned treatment (>28 d). Unclear whether adjusted or unadjusted results are presented in tables
		No oil	1230±230				1360±210	nd		
	Apo B100	Fish oil	1820±500	mg/L	SD	f/up	1910±440	nd	NS	
		No oil	1910±390				1970±460	nd		
	FBS	Fish oil	4.78±1.02	mg/L	SD	f/up	4.95±1.29	nd	NS	
		No oil	4.93±1.12				5.02±1.18	nd		
	HDL	Fish oil	1.06±0.31	mmol/L	SD	f/up	1.16±0.33	nd	NS	
		No oil	1.00±0.27				1.08±0.28	nd		
	Insulin	Fish oil	125±74	mg/L	SD	f/up	122±68	nd	NS	
		No oil	133±94				131±92	nd		
	LDL	Fish oil	4.59±0.97	mmol/L	SD	f/up	5.11±1.18	nd	NS	
		No oil	4.61±1.09				5.03±1.25	nd		
	TC	Fish oil	6.54±1.14	mmol/L	SD	f/up	6.98±1.29	nd	NS	
		No oil	6.55±1.16				7.04±1.34	nd		
	Tg	Fish oil	1.94±1.05	mmol/L	SD	f/up	1.57±0.86	nd	<.0001	
		No oil	2.09±1.07				2.08±1.26	nd		
Eritsland 1995c	**Factor VII**	Fish oil	108.8±26.2	%	SD	f/up	109.0± 22.9	nd	NS	Multivariate analysis See Eritsland 1995b
		No oil	104.9±24.7				110.9±25.3	nd		
	Fibrinogen	Fish oil	2.61±0.61	g/L	SD	f/up	2.72±0.55	nd	NS	
		No oil	2.61±0.55				2.78±0.58	nd		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Finnegan 2003	**Apo A1**	0.8 g EPA+DHA	1.74±0.05	mmol/L	SE	f/up	1.82±0.05	NS	NS	Unclear content of placebo capsules.
		1.7 g EPA+DHA	1.76±0.06				1.82±0.05	NS	NS	
		4.5 g ALA	1.78±0.07				1.84±0.05	NS	NS	
		Sunflower oil	1.75±0.05				1.8±0.05	NS		
	FBS	0.8 g EPA+DHA	5.4±0.14	mmol/L	SE	f/up	5.39±0.12	NS	NS	
		1.7 g EPA+DHA	5.36±0.14				5.38±0.09	NS	NS	
		4.5 g ALA	5.48±0.12				5.37±0.10	NS	NS	
		Sunflower oil	5.23±0.12				5.41±0.16	NS		
	HDL	0.8 g EPA+DHA	1.37±0.07	mmol/L	SE	f/up	1.45±0.07	NS	NS	
		1.7 g EPA+DHA	1.34±0.07				1.40±0.08	NS	NS	
		4.5 g ALA	1.29±0.06				1.31±0.06	NS	NS	
		Sunflower oil	1.35±0.06				1.35±0.05	NS		
	Insulin	0.8 g EPA+DHA	57.4±6.7	pmol/L	SE	f/up	51.7±5.1	NS	NS	
		1.7 g EPA+DHA	41.9±4.8				44.2±5.0	NS	NS	
		4.5 g ALA	49.3±5.6				42.8±5.6	NS	NS	
		Sunflower oil	37.1±4.6				39.2±5.2	NS		
	LDL	0.8 g EPA+DHA	3.41±0.17	mmol/L	SE	f/up	3.62±0.18	NS	NS	
		1.7 g EPA+DHA	3.42±0.14				3.96±0.16	NS	NS	
		4.5 g ALA	3.55±0.13				3.71±0.13	NS	NS	
		Sunflower oil	3.63±0.16				3.84±0.13	NS		
	TC	0.8 g EPA+DHA	5.50±0.16	mmol/L	SE	f/up	5.76±0.17	NS	NS	
		1.7 g EPA+DHA	5.40±0.15				5.99±0.18	NS	NS	
		4.5 g ALA	5.62±0.14				5.83±0.15	NS	NS	
		Sunflower oil	5.80±0.17				5.95±0.14	NS		
	Tg	0.8 g EPA+DHA	1.65±0.14	mmol/L	SE	f/up	1.63±0.12	NS	NS	
		1.7 g EPA+DHA	1.60±0.13				1.40±0.11	NS	NS	
		4.5 g ALA	1.66±0.13				1.83±0.16	NS	NS	
		Sunflower oil	1.69±0.11				1.60±0.11	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Franzen 1993	**ETT Ex Cap**	Fish oil	29±15	Kwatt-sec	SD	f/up	38±21	<.05	NS	Dropout: Fish - AE (6), subacute occlusion (1), refused followup angiogram (3), sudden death (1) Placebo - AE (7), inadequate angioplasty (1), subacute occlusion (2), refused followup angiogram (6), sudden death (2). 204 of 211 were randomized - 5 of placebo & 3 of fish arms were excluded because of periprocedural complications or unsuccessful angioplasty
		Olive oil	33±20				37±19	<.05		
	ETT ST Dep	Fish oil	2.0±2.3	mV	SD	f/up	1.1±1.6	<.05	nd	
		Olive oil	2.1±2.6				1.4±2.1	NS		
	HDL	Fish oil	42.6±11	mg/dL	SD	f/up	45.8±11	<.05	nd	
		Olive oil	40.9±10				42.4±13			
	LDL	Fish oil	151±37	mg/dL	SD	f/up	165±36	<.05	nd	
		Olive oil	157±36				162±37			
	Restenosis	Fish oil				f/up	30/92		nd	
		Olive oil				f/up	29/83			
	TC	Fish oil	219±43	mg/dL	SD	f/up	232±39	<.05	nd	
		Olive oil	222±40				233±41			
	Tg	Fish oil	158±71	mg/dL	SD	f/up	140±61	<.05	nd	
		Olive oil	156±81				172±78			
Freese 1994	**Plt Aggr**	PRP								
	ADP	Rapeseed oil	19.9±10.9	%/min	SD	f/up	21.0±8.7	NS		
	1 μmol/L	Sunflower oil	20.7±8.5				27.2±14.3	<.001	<.004	
	ADP	Rapeseed oil	43.4±11.2	%/min	SD	f/up	44.8±13.9	NS		
	2 μmol/L	Sunflower oil	43.1±2.5				54.0±13.6	<.001	<.002	
	ADP	Rapeseed oil	56.4±10.3	%/min	SD	f/up	59.4±11.2	NS		
	3 μmol/L	Sunflower oil	56.4±9.9				66.0±10.0	<.001	<.001	
	Thrombin	Rapeseed oil	20.7±14.0	%/min	SD	f/up	16.5±13.1	.06	NS	
	0.12 NIH/mL	Sunflower oil	23.4±16.9				20.2±12.8	NS		
	Thrombin	Rapeseed oil	33.5±16.7	%/min	SD	f/up	29.4±17.5	NS		
	0.15 NIH/mL	Sunflower oil	38.3±20.5				38.0±18.6	NS	.03	
	Thrombin	Rapeseed oil	36.7±20.6	%/min	SD	f/up	40.3±17.5	NS		
	0.18 NIH/mL	Sunflower oil	49.6±25.8				56.2±25.2	<.001	.02	

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Freese 1997a	**FBS**	Fish oil	4.69±0.32	mmol/L	SD	f/up	4.95±0.30	<.05	NS	Dropout: 4 (ND which arms): large changes in smoking habits, abnormally long bleeding time or difficulty blood sampling Randomization only implied
		Linseed oil	4.71±0.39				4.75±0.41	NS		
	Plt Aggr	PRP								
	ADP	Fish oil	34.4±13.3	%/min	SD	f/up	38.2±10.5	NS	NS	
	1 μmol/L	Linseed oil	34.8±12.5				34.1±17.4	NS		
	ADP	Fish oil	60.0±12.0	%/min	SD	f/up	64.6±7.5	<.05	NS	
	2 μmol/L	Linseed oil	56.3±10.8				54.7±18.1	NS		
	ADP	Fish oil	72.3 ±13.4	%/min	SD	f/up	71.6±9.0	NS	NS	
	3 μmol/L	Linseed oil	68.8±10.0				63.8±16.6	NS		
	Collagen	Fish oil	53.3±30.3	%/min	SD	f/up	31.1±20.2	<.05	NS	
	0.5 μgmol/L	Linseed oil	44.8±28.5				35.2±31.8	NS		
	Collagen	Fish oil	81.2±15.0	%/min	SD	f/up	79.0±20.4	NS	NS	
	1 μgmol/L	Linseed oil	78.6±23.4				76.8±24.1	NS		
	Collagen	Fish oil	99.6±12.8	%/min	SD	f/up	96.2±10.9	NS	NS	
	3 μgmol/L	Linseed oil	94.3±13.1				98.4±15.3	NS		
Freese 1997b	**Factor VII**	Linseed oil	90.4±17.1	%	SD	f/up	95.7±18.2	nd		NS between treatments for all outcomes
		Fish oil	89.3±16.1				95.6±15.2	nd		
	Fibrinogen	Linseed oil	3.11±0.63	g/L	SD	f/up	3.16±0.64	nd		
		Fish oil	3.14±0.55				3.08±0.57	nd		
Gans 1990	**Fibrinogen**	Fish oil	3.3±0.8	g/L	SD	f/up	3.6±0.7	NS	NS	Implied NS between groups Dropout: (2 DM, post hoc exclusion), eye surgery (1-fish oil). Corn oil- lumbar fracture(1), rapid progression of claudication (1). ND on weight of placebo capsules.
		Corn oil	3.5±0.6				3.7±0.6	NS		
Green 1990	**Apo A1**	Fish oil	113	g/L		Δ	+5	NS	NS	Estimates from graph. Carry-over effect from 1st phase after 4 wk washout for EPA, DHA, & DPA fatty acid concentration of erythrocytes
		Corn/olive oil	117				-5	NS		
	Apo B	Fish oil	122	g/L		Δ	+7	NS	NS	
		Corn/olive oil	129				+12	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
GISSI 1999	**HDL**	Omega-3	41.5±11.3	mg/dL	SD	Δ	+8.8%	nd	NS	Main effect Apparent error in data table: N of controls = 5658, not 5668 Few details for eligibility criteria. Both n3 arms combined in statistical analyses.
		Omega-3 / Vit E	41.6±11.5				+8.9%	nd		
		No oil / Vit E	41.7±12.0				+9.2%	nd		
		No oil	41.3±11.2				+9.4%	nd		
	LDL	Omega-3	137.3±39.1	mg/dL	SD	Δ	+9.9%	nd	NS	
		Omega-3 / Vit E	138.2±38.1				+10.8%	nd		
		No oil / Vit E	138.0±38.1				+7.2%	nd		
		No oil	138.5±37.6				+7.4%	nd		
	TC	Omega-3	210±42.1	mg/dL	SD	Δ	+7.9%	nd	NS	
		Omega-3 / Vit E	210.6±41.5				+8.9%	nd		
		No oil / Vit E	211.1±42.4				+7.1%	nd		
		No oil	211.6±42.3				+7.1%	nd		
	Tg	Omega-3	162.6±81.7	mg/dL	SD	Δ	-3.4%	nd	<.05	
		Omega-3 / Vit E	160.3±80.3				-0.9%	nd		
		No oil / Vit E	163.3±85.3				+2.9%	nd		
		No oil	161.9±94.5				+1.4%	nd		
Grigg 1999	**Restenosis**	Fish oil				f/up	19/56		NS	
		Olive/corn oil					19/61			
Grimsgaard 1997	**HDL**	DHA	1.36±0.30	mmol/L	SD	Δ	0.06±0.13	<0.001	0.001	Dropout: 251 enrolled but upon verification 7 did not meeting initial criteria, additional 10 left for personal reasons. Few demographic data.
		EPA	1.33±0.31				0.01±0.12	NS		
		Corn oil	1.41±0.28				-0.01±0.11	NS		
	LDL	DHA	4.06±0.86	mmol/L	SD	Δ	0.07±0.46	NS	NS	
		EPA	4.06±0.83				-0.08±0.48	NS		
		Corn oil	4.04±0.98				0.06±0.48	NS		
	TC	DHA	6.00±0.95	mmol/L	SD	Δ	0.03±0.49	NS	0.01	
		EPA	5.98±0.94				-0.15±0.55	<0.05		
		Corn oil	6.02±1.08				0.10±0.55	NS		
	Tg	DHA	1.24±0.58	mmol/L	SD	Δ	-0.22±0.31	<0.001	0.0001	
		EPA	1.23±0.57				-0.15±0.40	<0.01		
		Corn oil	1.22±0.55				0.11±0.34	<0.01		
	Apo A1	DHA	1.38±0.21	mmol/L	SD	Δ	0.02±0.13	NS	0.003	
		EPA	1.38±0.20				-0.04±0.10	<0.001		
		Corn oil	1.46±0.23				0.00±0.12	NS		
	Apo B	DHA	1.00±0.21	mmol/L	SD	Δ	-0.01±0.11	NS	0.05	
		EPA	1.01±0.23				-0.03±0.11	<0.05		
		Corn oil	1.02±0.28				0.02±0.11	NS		
Grundt 1995	**FBS**	Fish oil	4.7±0.7	mmol/L	SD	f/up	4.7±0.8	NS	NS	Dropout: "administrative reasons" (1)
		Corn oil	4.7±0.6				4.7±0.6	NS		
	Insulin	Fish oil	65.7±22.0	pmol/L	SD	f/up	67±31.2	NS	NS	
		Corn oil	70.3±31.1				82.5±46.4	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Grundt 1999	**Factor VII**	Fish oil	119.0±25.6	%	SD	f/up	114.0±22.6	NS	NS	Dropout: administrative reasons (1). Industry funded. Unclear if antihyperlipemia meds or other supplementation were exclusion criteria. Omega 3 info poor.
		Corn oil	117.0±24.6				117.0±29.3	NS		
	Fibrinogen	Fish oil	2.9±0.6	g/L	SD	f/up	2.8±0.5	NS	NS	
		Corn oil	2.8±0.4				2.8±0.8	NS		
Haines 1986	**DBP**	Fish oil	81.1	mmHg		f/up	76.2	nd	NS	ANOVA. Dropout: unable to swallow capsules (2- MaxEPA). Different # of capsules, low dose olive vs fish oil. Population from diabetic clinic. No statistics on pop. Platelet aggregation units are maximum change in light transmittance in arbitrary units.
		Olive oil	82.1				78.5	nd		
	Factor VII	Fish oil	79.2	%		f/up	84.6	nd	NS	
		Olive oil	85.1				85.2	nd		
	Factor VIII	Fish oil	123	%		f/up	123	nd	NS	
		Olive oil	119				111	nd		
	Fibrinogen	Fish oil	2.73	g/lL		f/up	2.92	nd	<.05	
		Olive oil	3.04				2.88	nd		
	Hgb A1c	Fish oil	11.1	%		f/up	11.1	nd	NS	
		Olive oil	10.6				10.4	nd		
	Plt Aggr									
	Collagen	Fish oil	49.3	U		Δ	44.2	nd	NS	
	1 mcg/mL	Olive oil	54.0				52.0	nd		
	Collagen	Fish oil	59.1	U		Δ	57.9	nd	NS	
	10 mcg/mL	Olive oil	60.8				57.4	nd		
	SBP	Fish oil	135	mmHg		f/up	131	nd	NS	
		Olive oil	136				131	nd		
Hamazaki 1996	**Lp(a)**	Fish oil	0.11±0.06	g/L	SD	Δ	+0.01±0.03	NS	NS	Dropout: Control (1), capsule damage from improper storage (1), dyslipidemia (2), body weight changes (2) DHA: body weight changes (1), smoking (1), decrease in serum DHA (2) Few details on population / study characteristics
		Corn oil	0.13±0.13				-0.01±0.04	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Hanninen 1989	**Apo A1**	0.9 fish/week	1.18±0.08	g/L	SD	f/up	1.19±0.19	NS	nd	Dropout: 100 total from 5 groups. ND on group assignments. n-3:n-6 of FA in the phosphatidylethanolamine of RBC ghosts about 0.54. No FA data
		1.5 fish/week	1.21±0.19				1.13±0.13	NS	nd	
		2.3 fish/week	1.17±0.16				1.2±0.11	NS	nd	
		3.8 fish/week	1.13±0.15				1.14±0.16	NS	nd	
		0.4 fish/week	1.23±0.13				1.24±0.13	NS		
	Apo B	0.9 fish/week	0.86±0.18	g/L	SD	f/up	0.89±0.23	NS	nd	
		1.5 fish/week	0.80±0.23				0.74±0.18	<.10	nd	
		2.3 fish/week	0.78 ±0.18				0.75±0.18	<.10	nd	
		3.8 fish/week	0.93±0.23				0.83±0.24	<.05	nd	
		0.4 fish/week	0.78±0.20				0.77±0.18	NS		
	TC	0.9 fish/week	4.41± 0.71	mmol/L	SD	f/up	4.50± 0.66	NS	nd	
		1.5 fish/week	4.12±1.03				3.94±0.73	NS	nd	
		2.3 fish/week	4.09±0.71				4.15±0.70	NS	nd	
		3.8 fish/week	4.58±0.70				4.38±0.77	NS	nd	
		0.4 fish/week	4.05±0.69				4.05±0.63	NS		
	Tg	0.9 fish/week	0.78±0.26	mmol/L	SD	f/up	0.81±0.34	NS	nd	
		1.5 fish/week	0.68±0.24				0.58±0.20	<.10	nd	
		2.3 fish/week	0.92±0.48				0.77±0.31	<.10	nd	
		3.8 fish/week	0.91±0.47				0.74±0.33	< .02	nd	
		0.4 fish/week	0.76±0.27				0.75±0.30	NS		
Hansen 1989	**Factor VII**	Fish oil	90±6	%	SE	f/up	91±4	NS	NS	8 week washout. Poor design, possible bias. Unclear if randomized.
		No oil	88±5				87±4	NS		
	Fibrinogen	Fish oil	2.4±0.1	g/L	SE	f/up	2.2±0.1	NS	NS	
		No oil	2.2±0.1				2.1±0.1	NS		
Hansen 1993a	**Factor VII**	4 g omega-3 FA	83±3	%	SE	Δ	+3±4	NS	nd	Industry funded. "Controlled cross-over study" with 8 wk wash-out, not specifically stated randomized; further divided by sex
		12 g omega-3 FA	87±3				+4±4	NS	nd	
		Corn oil	86±4				+5±4	nd		
	Fibrinogen	4 g omega-3 FA	2.4±0.2	g/L	SE	Δ	-0.4±0.2	.03	nd	Fibrinogen results: p=0.09 between 2 omega-3 fatty acid groups
		12 g omega-3 FA	2.4±0.1				0.0±0.2	NS	nd	
		Corn oil	2.4±0.1				-0.3±0.2	.11		
	vWF	4 g omega-3 FA	121±20	%	SE	Δ	-6±9	NS	nd	
		12 g omega-3 FA	100±21				-3±9	NS	nd	
		Corn oil	105±21				+10±9	nd		

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Hansen 1993b	**Plt Aggr**	PRP								No data reported for control arm results, only net change.
	Collagen 0.5 µg/mL			%	SE	ΔΔ				
	Women	Fish oil v No oil	47.0±5.7				1.2±5.6	nd	NS	
	Men	Fish oil v No oil	56.0±6.0				-24.7±7.1	nd	<.01	
	Collagen 4 µg/mL			%	SE	ΔΔ				
	Women	Fish oil v No oil	95.0±1.4				1.4±2.0	nd	NS	
	Men	Fish oil v No oil	95±1.2				-2.6±2.4	nd	NS	
	ADP 2.5 µmol/L			%	SE	ΔΔ				
	Women	Fish oil v No oil	81.0±3.1				-4.3±8.3	nd	NS	
	Men	Fish oil v No oil	76.0±4.6				-5.9±6.1	nd	NS	
Harris 1997	**Apo A1**	Fish oil	1.32±0.41	g/L	SD	f/up	1.31±0.34	nd	NS	Dropout: One placebo group on advice from personal physician. Statistical analyses on population not completed
		Corn oil	1.28±0.26				1.26±0.27	nd		
	Hgb A1c	Fish oil	5.3±0.6	%	SD	f/up	4.9±0.4	nd	nd	
		Corn oil	5.4±0.9				5.0±0.8	nd		

Δ = within cohort difference
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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Hendra 1990	**DBP**	Fish oil	84.8	mmHg		f/up	81.4	nd	.86	Dropout: one patient in control group died from asthmatic exacerbation, one patient in MaxEPA group withdrew due to flatulence and abdominal pain. 2 from each arm withdrew due to difficulty in swallowing capsules. Platelet aggregation units are percent platelets remaining after aggregation.
		Corn oil	81.1				78.0	nd		
	Factor VII	Fish oil	93.7	%		f/up	109	nd	.02	
		Corn oil	106.2				99.7	nd		
	FBS	Fish oil	11.2	mmol/L		f/up	12.5	nd	.17	
		Corn oil	10.8				11.3	nd		
	Fibrinogen	Fish oil	3.176	g/lL		f/up	3.182	nd	.3	
		Corn oil	3.310				3.308	nd		
	Plt Aggr	Whole blood								
	Spontaneous	Fish oil	77.3 (75.3, 79.2)	%	95% CI	f/up	80.6 (78.6 82.7)	nd	.06	
	10 min	Corn oil	77.5 (75.5, 79.6)				77.6 (75.0, 80.1)	nd		
	Spontaneous	Fish oil	70.3 (67.9, 72.7)	%	95% CI	f/up	73.9 (71.2, 76.5)	nd	.02	
	20 min	Corn oil	71.6 (69.1, 74.0)				70.8 (67.1, 74.6)	nd		
	Spontaneous	Fish oil	67.4 (64.6, 70.2)	%	95% CI	f/up	70.7 (68.0, 73.4)	nd	.02	
	30 min	Corn oil	68.0 (64.9, 71.0)				66.6 (62.8, 70.4)	nd		
	Spontaneous	Fish oil	62.9 (59.6, 66.3)	%	95% CI	f/up	66.5 (63.4, 69.6)	nd	.02	
	60 min	Corn oil	64.1 (60.7, 67.6)				63.5 (59.6, 67.5)	nd		
	SBP	Fish oil	145.2	mmHg		f/up	140.7	nd	.93	
		Corn oil	140.7				134.7	nd	.93	
Jain 2002	**DBP**	Fish oil	81.52±5.26	mmHg	SD	f/up	79.1±4.32	<.001	.0003	Potential bias - ND on type, source, or appearance of placebo capsules
		"Placebo"	80.27±3.10				80.0±2.5	.33		
	FBS	Fish oil	139±34.88	mg%	SD	f/up	123.2±35.5	<.05	.004	
		"Placebo"	121.7±23.27				115.5±23.9	<.01		
	Hgb A1c	Fish oil	8.02±1.2	%	SD	f/up	7.84±1.07	<.001	.009	
		"Placebo"	7.59±0.56				7.54±0.59	.013		
	SBP	Fish oil	126.9±8.2	mmHg	SD	f/up	123.9±8.0	<.001	.0003	
		"Placebo"	124.8±6.22				124.5±6.0	.16		
Jensen 1989	**Apo A1**	Cod liver oil	1.34±0.04	g/L	SE	f/up	1.27±0.03	NS	NS	Crossover study with eight weeks of intervention & 8 week washout. Inadequate description of exclusion, inclusion criteria. Potential bias / uncovering of blinding from taste of oils, & in unequal distribution of baseline patient characteristics. No stratification of patient reported.
		Olive oil	1.34±0.04				1.33±0.04	NS		
	Apo B	Cod liver oil	1.09±0.07	g/L	SE	f/up	1.16±0.09	NS	NS	
		Olive oil	1.09±0.07				1.1±0.08	NS		
	FBS	Cod liver oil	9.9±1.1	mmol/L	SE	f/up	11.0±1.1	NS	NS	
		Olive oil	9.9±1.1				12.6±0.9			
	Hgb A1c	Cod liver oil	9.5±0.3	%	SE	f/up	9.6±0.3	NS	NS	
		Olive oil	9.5±0.3				9.5±0.4			

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Johansen 1999	**Restenosis**	Fish oil				f/up	90/196		NS	Design included 2 wk enrollment before angioplasty with 20% exclusion rate calculated. 108 of 500 enrolled disqualified & 4 deaths (22.4%). Excluded evenly distributed between 2 groups.
		Corn oil					86/192			
Junker 2001	**CRP**	Rapeseed oil	0.5 Median	mg/L		f/up	0.44	NS	NS	Dropout: Intercurrent illness (6) & noncompliance of diet (5). Randomized unclear
		Olive oil	0.71 Median				0.52	NS		
		Sunflower oil	0.90 Median				0.75	NS		
	Factor VII (Act)	Rapeseed oil	101.1±12.4	%		f/up	101.4±12.0	NS	nd	
		Olive oil	107.3±17.0				101.9±11.5	<.01		
		Sunflower oil	110.3±27.0				107.6±27.4	NS		
	Factor VII (Ag)	Rapeseed oil	45.2 Median	mU/mL		f/up	44.4	NS	nd	
		Olive oil	46.1 Median				38.6	NS		
		Sunflower oil	40.8 Median				44.7	NS		
	Fibrinogen	Rapeseed oil	2.298±0.266	g/L	SD	f/up	2.334±0.39	NS	NS	
		Olive oil	2.598±0.864				2.43±0.462	NS		
		Sunflower oil	2.507±0.413				2.451±0.433	NS		
	Plt Aggr	PRP								
	ADP	Rapeseed oil	7.8 Median	%		f/up	27.3	NS	NS	
	0.5 µmol/L	Olive oil	15.6 Median				17.6	NS		
		Sunflower oil	15.0 Median				12.6	NS		
	ADP	Rapeseed oil	27.1 Median	%		f/up	55.9	NS	NS	
	2 µmol/L	Olive oil	78.2 Median				73.0	NS		
		Sunflower oil	73.6 Median				73.7	NS		
	Adrenaline	Rapeseed oil	82.3±5.1	%	SD	f/up	82.2±8.3	NS	NS	
	1 µmol/L	Olive oil	94.3±16.1				81.2±8.0	NS		
		Sunflower oil	89.1±6.3				82.3±11.4	NS		
	Adrenaline	Rapeseed oil	85.1±3.6	%	SD	f/up	87.6±6.1	NS	NS	
	4 µmol/L	Olive oil	95.2±12.5				86.6±8.2	NS		
		Sunflower oil	90.7±8.3				88.7±7.6	NS		
	Spontaneous	Rapeseed oil	7.2 Median	%		f/up	8.2	NS	NS	
		Olive oil	8.8 Median				11.4	NS		
		Sunflower oil	14.6 Median				11.4	<.05		
Kaul 1992	**Restenosis**	Fish oil				f/up	19/58		NS	Few details on population.
		No oil					13/49			

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Kwon 1991	**Plt Aggr**	Whole blood								Maximum aggregation
	Collagen	Canola oil	43.5±3.0	Ω	SE	f/up	45.5±2.9	NS	nd	
	1 mg/L	Corn oil	47.9±3.2				49.9±2.0	NS	nd	
	Collagen	Canola oil	43.5±3.0	Ω	SE	f/up	49.0±1.7	NS	nd	
	2 mg/L	Corn oil	47.9±3.2				52.5±0.7	NS	nd	
Leigh-Firbank 2002	**FBS**	Fish oil v Olive oil	5.49±0.09	mmol/L	SE	ΔΔ	+3.3%±2.2	nd	NS	Only net difference reported. No data on olive oil cohort.
	HDL	Fish oil v Olive oil	0.95±0.02	mmol/L	SE	ΔΔ	-0.3%±3.2	nd	NS	
	Hgb A1c	Fish oil v Olive oil	71.7±7.0	mmol/L	SE	ΔΔ	-0.8%±12.0	nd	NS	
	LDL	Fish oil v Olive oil	4.53±0.12	pmol	SE	ΔΔ	+7.6±3.1	nd	0.03	
	TC	Fish oil v Olive oil	6.60±0.11	mmol/L	SE	ΔΔ	-0.7%±2.0	nd	NS	
	Tg	Fish oil v Olive oil	2.50±0.11	mmol/L	SE	ΔΔ	-33.3±5.0	nd	<.001	
Leng 1998	**Fibrinogen**	Fish oil (w/GLA)	3.43	g/L		f/up	3.90	nd	NS	Dropout: Unclear how many were actual dropouts/withdraws (someoverlaping #). FA: all cause death(3), CVD deaths(2), nonfatal CVD-MI(3), nonfatal all coronary events(6), nonfatal stroke/TIA(3), angioplasty/bypass surgery(3), other serious AE(17), GI(30), Respiratory & other infections(5), musculoskeletal(12), other(9); Placebo: all cause death(3), CVD deaths(2), nonfatal CVD-MI(4), nonfatal all coronary events(9), nonfatal stroke/TIA(1), critical ischemia/amputation(1), angioplasty/bypass surgery(1), other serious AE(21), GI(19), Respiratory & other infections(7), musculoskeletal(6), other(1). Voluntary withdrawal: FA(6), placebo(11). Potential bias on dosage/ compliance. Geometric mean for fibrinogen
		Sunflower oil	3.48				3.91	nd		
	HDL	Fish oil (w/GLA)	44.5±1.4	mg/dL	SE	f/up	52.6±1.5	NS	NS	
		Sunflower oil	46.9±1.5				54.9±2.4	NS		
	LDL	Fish oil (w/GLA)	107.1±3.5	mg/dL	SE	f/up	120.0±5.3	NS	NS	
		Sunflower oil	103.4±4.3				115.7±6.3	NS		
	TC	Fish oil (w/GLA)	233.2±5.0	mg/dL	SE	f/up	237.2±6.6	NS	NS	
		Sunflower oil	226.7±6.1				229.0±8.1	NS		
	vWF	Fish oil (w/GLA)	118.4± 03.2				138.8± 04.3	nd	NS	
		Sunflower oil	123.0± 03.2				136.6± 04.6	nd		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Lungershausen 1994	**HDL**	Fish oil	1.03±0.04	mmol/L	SE	f/up	1.06±0.05	nd	NS	Dropout: Poorly controlled blood pressure 4 wk run-in prior to intervention Tg data approximated from figures/graphs
		Corn oil	1.03±0.04				1.04±0.04	nd		
	LDL	Fish oil	4.04±0.19	mmol/L	SE	f/up	4.21±0.19	nd	NS	
		Corn oil	4.04±0.19				4.04±0.18	nd		
	TC	Fish oil	5.74±0.21	mmol/L	SE	f/up	5.83±0.20	nd	NS	
		Corn oil	5.74±0.21				5.78±0.19	nd		
	Tg	Fish oil	1.7	mmol/L	SE	f/up	1.38	nd	<.01	
		Corn oil	1.7				1.6	nd		
Lungershausen 1997	**DBP**	Fish oil	81±3	mmHg	SE	f/up	80±3	nd	NS	Dropout: unrelated illness (1) GI from consumption of oil (1), group assignment unknown. Post hoc change in eligibility criteria Possible reporting error for SBP outcome data for placebo group
		Corn oil	75±2				73±2	nd		
	Hgb A1c	Fish oil	8.5±0.3	%	SE	f/up	+0.88±0.24	<.01	NS	
		Corn oil	8.5±0.3				+0.69±0.22	<.01		
	SBP	Fish oil	139±5	mmHg	SE	f/up	133±4	nd	.039	
		Corn oil	140±4				138±4	nd		
Luo 1998	**Apo A1**	Fish oil	1.48±0.05	g/L	SE	f/up	1.43±0.07	nd	NS	Dropout: "Misunderstanding of experimental design" (1); discontinued oral antidiabetic medicine in error at study start (1).
		Sunflower oil	1.54±0.08				1.48±0.08	nd		
	Apo B	Fish oil	1.38±0.08	g/L	SE	f/up	1.43±0.09	nd	NS	
		Sunflower oil	1.55±0.16				1.5±0.11	nd		
	Hgb A1c	Fish oil	8.8±0.6	%	SE	f/up	8.7±0.5	nd	NS	
		Sunflower oil	8.6±0.5				8.9±0.6	nd		
	Insulin	Fish oil	84±6	pmol/L	SE	f/up	83±7	nd	NS	
		Sunflower oil	91±12				76±10	nd		
	Lp(a)	Fish oil	0.17±0.04	g/L	SE	f/up	0.14±0.03	nd	<.02	
		Sunflower oil	0.16±0.04				0.16±0.03	nd		
Mackness 1994	**FBS**	Fish oil	5.03±0.63	mmol/L	SD	f/up	4.85±0.74	NS	NS	Dropout: Tx arm- 1 endometrial CA, 1 head injury, 1 cataract surgery, 3 personal reasons; Control arm-1 CABG, 1 MI, 3 unstable angina, 2 non-compliance, 3 personal reasons
		Corn oil	4.86±0.59				4.59±0.75	NS		
Madsen 2001	**CRP**	Fish score 2-4	0.86±0.97	mg/L	SD		na	na	NS	Cross-sectional study
		Fish score 5-6	0.83±0.90				na	na	NS	
		Fish score 7-8	0.64±0.88				na	na	NS	
		Fish score 9-10	0.73±0.89				na	na	NS	
		Fish score 11-12	0.80±0.92				na	na	NS	

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Madsen 2003	**CRP**	Fish oil	0.69 Median	mg/L		f/up	0.67	NS	NS	Recruits from medical staff, bloodbank employees, students
		Olive oil	0.67 Median				0.63	NS		
Marckmann 1997	**Apo A1**	Fish oil	1.49±0.04	g/L	SE	f/up	1.51±0.04	NS	NS	Dropout: Intercurrent disease (2), permanently raised serum concentrations of CRP (1)
		Sunflower oil	1.48±0.04				1.52±0.04	<.001		
	Apo B	Fish oil	1.13±0.06	g/L	SE	f/up	1.12±0.06	NS	NS	
		Sunflower oil	1.07±0.04				1.05±0.04	NS		
	Factor VII (act)	Fish oil	104±3.6	%	SE	f/up	103±4.9	NS	NS	
		Sunflower oil	96±3.7				95±3.6	NS		
	Factor VII (ag)	Fish oil	117±3.6	%	SE	f/up	115±4.4	NS	NS	
		Sunflower oil	115±4.1				116±3.4	NS		
	Fibrinogen	Fish oil	7.10±0.25	mcmol/L	SE	f/up	6.71±0.27	NS	NS	
		Sunflower oil	6.57±0.22				6.33±0.26	NS		
	Insulin	Fish oil	9.2±1.0	mU/L	SE	f/up	8.7±0.8	NS	NS	
		Sunflower oil	7.7±0.9				8.4±0.8	NS		
	Lp(a)	Fish oil	36 Median	mg/L	SE	f/up	54	NS	NS	
		Sunflower oil	76 Median				64	NS		
	vWF	Fish oil	86 Median	%	SE	f/up	84	NS	NS	
		Sunflower oil	85 Median				89	NS		
Maresta 2002	**Restenosis**	Omega-3				f/up	39/125		.05	Dropout: no 6 month angiogram available; QCA not possible; unevaluable. Method of allocation concealment not reported. Unclear on volume of olive oil Uncertain if Tg tested between control vs. treatment
		Olive oil					54/132			
	Tg	Omega-3	160±84	mg/dL	SD	f/up	151±72	NS	NS	
		Olive oil	196±142				182±114	NS		
McVeigh, 1993	**FBS**	Fish oil	10.2	mmol/L		f/up	11.4	.06	NS	
		Olive oil	10.2				11.0	NS		
	Apo A1	Fish oil	1.19(1.01, 1.37)	g/l	95% CI	f/up	1.12(0.95, 1.29)	NS	NS	
		Olive oil	1.19(1.01, 1.37)				1.10(0.93, 1.27)	NS		
	Apo B	Fish oil	0.95(0.78, 1.12)	g/l	95% CI	f/up	0.95(0.77, 1.13)	NS	NS	
		Olive oil	0.95(0.78, 1.12)				0.94(0.77, 1.11)	NS		
	Hgb A1c	Fish oil	9.6	%		f/up	9.9	NS	NS	
		Olive oil	9.6				9.7	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Mezzano 2001	**CRP**	Mediterranean diet	0.49±0.19	mg/dL	SD	f/up	0.59±0.53	NS	NS	ANOVA including 1, 2, and 3 month data. 30 subjects randomized. 12 subjects (30%) allowed to choose diet. Unclear if some data part of eligibility.
		High fat diet	0.49±0.25				0.42±0.11	NS		
	Factor VII	Mediterranean diet	78±19	%	SD	f/up	79±15	nd	.03	
		High fat diet	78±15				83±16	nd		
	Factor VIII	Mediterranean diet	68±27	%	SD	f/up	64±35	nd	.006	
		High fat diet	74±29				75±28	nd		
	Fibrinogen	Mediterranean diet	228±56	mg/dL	SD	f/up	231±54	nd	.03	
		High fat diet	218±38				252±64	nd		
Milner 1989	**Restenosis**	Fish oil r				f/up	16/84		nd	
		No oil					35/99			
Misso 1995	**Fibrinogen**	Fish oil	2.99±0.24	g/L	SE	f/up	2.67±0.28	NS	nd	Randomization implied. Minimal data on eligibility criteria.
		Olive oil	2.99±0.2				2.52±0.14	<.01		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Mori 1994	**Apo B**	Control diet 40% fat			SE	Δ	+1	nd		Regression controlled for wt; ANOVA difference between all arms; 40% fat except for 2 arms (30% fat). Outcomes data estimated from graphs. 120 of 138 enrolled completed 12-wk intervention & were included in analyses.
		Fish diet 40% fat					+7	nd	NS	
		Fish oil 2.6 g 40%					+13	nd	<.05	
		Fish & fish oil 2.6g	1.43±0.02	mmol/L			+6	nd	NS	
		Fish oil 5.2 g 40%					+10	nd	<.05	
		Control diet 30%					-6	nd		
		Fish diet 30% fat					-5	nd	NS	
	HDL	Control diet 40% fat			SE	Δ	+0.01	nd		
		Fish diet 40% fat					+0.10	nd	<.001	
		Fish oil 2.6 g 40%					+0.11	nd	<.01	
		Fish & fish oil 2.6g	1.24±0.02	mmol/L			+0.08	nd	<.01	
		Fish oil 5.2 g 40%					+0.07	nd	<.05	
		Control diet 30%					+0.08	nd		
		Fish diet 30% fat					+0.01	nd	<.05	
	LDL	Control diet 40% fat			SE	Δ	+0.09	nd		
		Fish diet 40% fat					+0.36	nd	NS	
		Fish oil 2.6 g 40%					+0.50	nd	<.05	
		Fish & fish oil 2.6g	4.06±0.06	mmol/L			+0.37	nd	NS	
		Fish oil 5.2 g 40%					+0.64	nd	<.01	
		Control diet 30%					-0.4	nd		
		Fish diet 30% fat					-0.1	nd	<.05	
	TC	Control diet 40% fat			SE	Δ	-0.05	nd		
		Fish diet 40% fat					+0.29	nd	NS	
		Fish oil 2.6 g 40%					+0.49	nd	<.05	
		Fish & fish oil 2.6g	6.09±0.06	mmol/L			+0.13	nd	NS	
		Fish oil 5.2 g 40%					+0.43	nd	NS	
		Control diet 30%					-0.32	nd		
		Fish diet 30% fat					-0.29	nd	NS	
	Tg	Control diet 40% fat			SE	Δ	0	nd		
		Fish diet 40% fat					-0.36	nd	<.001	
		Fish oil 2.6 g 40%					-0.24	nd	<.05	
		Fish & fish oil 2.6g	1.74±0.07	mmol/L			-0.74	nd	<.001	
		Fish oil 5.2 g 40%					-0.63	nd	<.01	
		Control diet 30%					+0.04	nd		
		Fish diet 30% fat					-0.38	nd	<.01	

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Mori 1999	**FBS**	1 fish/d	5.13±0.08	mmol/L	SE	Δ	+0.14	NS	NS	Dropout: 6 unable to make lab visits or compliance with diet, ND on group assignment. NS for type or number of antihypertensive meds. Data approximated from figures/graphs.
		1 fish/d & wt loss	5.20±0.14				-0.1	NS	NS	
		No fish & wt loss	5.29±0.12				-0.06	NS		
		No fish diet	5.28±0.22				-0.08	NS		
	Insulin	1 fish/d	12.11±1.53	pmol/L	SE	Δ	+2.3	nd	.05	
		1 fish/d & wt loss	13.40±4.51				-3.9	nd	.05	
		No fish & wt loss	11.41±1.50				-1.3	nd		
		No fish diet	12.81±1.99				+0.7	nd		
Mori 2000	**FBS**	EPA	5.03±0.09	mmol/L	SE	Δ	5.24±0.08	nd	.062	Dropout: 56 of 59 completed study. 3 WD-unable to make lab visits (2) & GI (1), group assignment unknown.
		DHA	5.15±0.13				5.08±0.09	nd	NS	
		Olive oil	4.95±0.12				5.03±0.08	nd		
	Insulin	EPA	8.78±0.83	pmol/L	SE	Δ	10.34±0.52	nd	.04	
		DHA	9.59±0.99				11.38±0.55	nd	.001	
		Olive oil	9.79±1.24				8.76±0.51	nd		
Muller 1989	**Factor VII (act)**	Mackerel paste	99±1.4	%	SE	Δ	+1.5±1.63	NS	NS	Dropout: 2 unaccounted for. Limited data on eligibility criteria.
		Meat paste	99±1.4				+2±1.25	NS		
	Fibrinogen	Mackerel paste	2.7±0.11	g/L	SE	Δ	+0.10±0.09	NS	NS	
		Meat paste	2.6±0.1				+0.12±0.09	NS		
	vWF	Mackerel paste	1.0±0.08	U/L	SE	Δ	0±0.08	NS	NS	
		Meat paste	1.1±0.07				0±0.06	NS		
Natvig 1968	**TC all subjects**	Linseed oil	245.9	mg/dL		f/up	237.8	nd	NS	Dropout: 70 % completed study. 13,578 randomized, 150 additional men given sunflower oil after linseed oil supply ran out. Limited data on eligibility criteria. No demographic data nor comparison data
		Sunflower oil	245.0				236.1	nd		
	TC diabetics	Linseed oil	249.9	mg/dL		f/up	240.4	nd	NS	
		Sunflower oil	253.4				238.7	nd		
Nenseter 2000	**Apo B**	Fish powder tablet	1.33±0.24	g/L	SD	f/up	1.37±0.23	nd	NS	Industry funded
		Cellulose	1.36±0.19				1.38±0.22	nd		
	Factor VII	Fish powder tablet	121±27	%	SD	f/up	123±23	nd	NS	
		Cellulose	116±28				117±31	nd		
	Fibrinogen	Fish powder tablet	3.0±0.5	g/L	SD	f/up	2.9±0.5	nd	NS	
		Cellulose	3±0.6				3.1±0.8	nd		
	Lp(a)	Fish powder tablet	135 Median	mg/L		f/up	151	nd	NS	
		Cellulose	258 Median				282	nd		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm		Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Nikkila 1991	**Apo A1**	Fish oil		1.09±0.13	g/L	SD	f/up	1.07±0.14	nd	NS	4 week randomized, blinded cross over of 4 capsules fish oil vs corn oil followed by 6 fish oil capsules for all subjects- unblinded. Eligibility criteria vague.
		Corn oil		1.09±0.13				1.09±0.13	nd		
	Apo B	Fish oil		1.22±0.28	g/L	SD	f/up	1.21±0.30	nd	NS	
		Corn oil		1.22±0.28				1.18±0.25	nd		
Nilsen 2001	**HDL**	Fish oil		1.08±0.30	mmol/L	SD	Δ	+19.10%	<.05	<.05	
		Corn oil		1.16±0.35				+7.22%	<.05		
	TC	Fish oil		5.53±0.99	mmol/L	SD	Δ	-0.01%	nd	NS	
		Corn oil		5.48±0.96				-4.42%	nd		
	Tg	Fish oil	Men	1.58±0.93	mmol/L	SD	Δ	-13.94%	<.05	<.05	
			Women	1.39±0.56				-1.18%	nd		
		Corn oil	Men	1.43±0.75				+22.26%	nd	nd	
			Women	1.41±0.58				+58.05%	nd		
Nordoy 1998	**Apo A1**	Fish oil		1.42±0.05	g/L	SE	Δ	-0.07±0.02	<.05	.8	No dropouts/WD. All subjects had run-in with simvastatin 20 mg for 5-10 weeks.
		Corn oil		1.42±0.05				-0.08±0.04	NS		
	Apo B	Fish oil		1.08±0.05	g/L	SE	Δ	-0.09±0.03	<.01	.8	
		Corn oil		1.15±0.05				-0.08±0.03	<.05		
	Hgb A1c	Fish oil		5.8±0.1	%	SE	Δ	+0.2±0.1	NS	.3	
		Corn oil		5.9±0.2				0.0±0.1	NS		
	Insulin	Fish oil		11.6±2.6	pmol/L	SE	Δ	-0.3±3.1	NS	.4	
		Corn oil		9.2±1.1				+2.3±1.4	NS		
Nordoy 2000	**Factor VII_c**	Fish oil		132.3±4.1	%	SD	Δ	+0.9±3.8	NS	NS	Unclear whether subjects were convenient sample or randomly selected from a larger population.
		Corn oil		133.5±4.9				+2.8±2.6	NS		
	Fibrinogen	Fish oil		3.0±0.2	g/L	SD	Δ	+0.4±0.1	<.05	.8	
		Corn oil		3.0±0.2				+0.3±0.2	NS		
	vWF	Fish oil		101.4±7.4	%	SD	Δ	-4.3 %±3.5	NS	.3	
		Corn oil		107.7±8.1				+0.9 %±4.0	NS		
Nye 1990	**Restenosis**	EPA					f/up	7/61		<.05	
		Olive oil						19/63			

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Osterud 1995	**Factor VII**	Seal blubber oil	1.23±0.09	U/mL	SE	f/up	1.14±0.08	NS	NS	Those taking oil were blinded as to oil type, controls took no oil. Exclusion criteria not defined.
		Cod liver oil	1.16±0.06				1.15±0.10	NS	NS	
		Seal oil/CLO	1.21±0.06				1.23±0.07	NS	NS	
		Minke whale oil	1.20±0.07				1.18±0.06	NS	NS	
		No oil	1.08±0.07				1.07±0.07			
	Fibrinogen	Seal blubber oil	2.8±0.2	g/L	SE	f/up	2.6±0.2	NS	NS	
		Cod liver oil	2.6±0.1				2.4±0.1	NS	NS	
		Seal oil/CLO	2.5±0.1				2.4±0.1	NS	NS	
		Minke whale oil	2.6±0.1				2.3±0.1	NS	NS	
		No oil	2.6±0.1				2.4±0.1	NS		
	HDL	Seal blubber oil	1.31±0.04	mmol/L	SE	f/up	1.37±0.04	nd	NS	
		Cod liver oil	1.25±0.05				1.32±0.07	nd	NS	
		Seal oil/CLO	1.36±0.07				1.46±0.08	nd	<.05	
		Minke whale oil	1.27±0.06				1.41±0.07	nd	<.005	
		No oil	1.36±0.09				1.36±0.09	nd		
	TC	Seal blubber oil	5.18±0.22	mmol/L	SE	f/up	5.04±0.23	nd	NS	
		Cod liver oil	5.29±0.22				5.12±0.22	nd	NS	
		Seal oil/CLO	5.30±0.21				5.35±0.21	nd	NS	
		Minke whale oil	5.12±0.21				5.18±0.24	nd	NS	
		No oil	4.94±0.23				4.75±0.23	nd		
	Tg	Seal blubber oil	1.20±0.10	mmol/L	SE	f/up	1.06±0.11	nd	NS	
		Cod liver oil	1.28±0.16				0.98±0.05	nd	<.05	
		Seal oil/CLO	1.29±0.15				1.07±0.11	nd	NS	
		Minke whale oil	1.10±0.08				1.02±0.08	nd	NS	
		No oil	1.18±0.12				1.20±0.08	nd		
Pedersen 2003	**Hgb A1c**	Fish oil	8.2±0.3	%	SD	f/up	8.2±0.3	NS	NS	Dropout: 49 recruited 2 left study during run-in period, personal reasons (1), hospitalization (1), pneumonia (1)
		Corn oil	8.4±0.4				8.4±0.4	NS		
Prisco 1994	**Lp(a)**	Fish oil	289±67	mg/dL	SD	f/up	281±52	nd	NS	Limited data on population. Sample size small
		Olive oil	288±61				280±50	nd		
Radack 1989	**Fibrinogen**	Fish oil 2.2 g	3.16±0.45	g/L	SD	f/up	2.45±0.37	<.01	<.05	P<0.05 between treatments Dropout: work schedule (3), intolerance to olive oil (1). ND on group assignment. Industry funded. Eligibility criteria vague
		Fish oil 1.1 g	2.86±0.36				2.68±0.37	<.01	NS	
		Olive oil	3.18±0.72				3.03±0.42	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Radack 1990	**LDL apo B**	Fish oil 6 g	1.00±0.179	g/L	SD	Δ	+0.297	<.05	<.05	Dropout: work conflict (1), started diuretic (1). Industry funded.
		Fish oil 3 g	0.953±0.118				+0.138	NS	<.05	
		Olive oil	1.00±0.303				-0.152	NS		
Radack 1991	**LDL apo B**	Fish oil	2.49±0.57	g/L	SD	Δ	+0.04	NS	NS	Dropout: work conflict (1), weight gain of 28 kg (1).
		Safflower oil	2.34±0.58				+0.10	NS		
Reis 1989	**Restenosis**	Fish oil				f/up	44/124		NS	Subjects subgroup of larger fish oil trial for prevention of restenosis after cornary angioplasty (Reis Lancet 1989; 2:177-181)
		Placebo					14/63			
Rivellese 1996	**Insulin**	Fish oil	75±9	pmol/L	SE	Δ	+31±9	<.01	NS	
		Olive oil	121±18.4				+15±22	NS		
Rossing 1996	**Hgb A1c**	Cod liver oil	8.8±0.4	mmHg	SE	f/up	8.8±0.4	NS	NS	Dropout: Nausea (17% receiving Tx), pregancy (1-placebo), glomerulonephritis (1-placebo), breast cancer (1-Tx)
		Olive oil	9.2±0.3				9.5±0.2	NS		
	SBP	Cod liver oil	141±2	%	SE	f/up	142±2	NS	NS	
		Olive oil	140±2				144±3	NS		
Sacks 1994	**HDL**	Fish oil	46±13	mg/dL	SD	Δ	+0.1±8.1	NS	NS	Baseline DBP/SBP data for fish oil cohort only
		Olive oil	189±32				-1.7±7.4	NS		
	TC	Fish oil	190±29	mg/dL	SD	Δ	+5.6±20.8	NS	NS	
		Olive oil	189±32				+1.5±18.0	NS		
Salachas 1994	**ETT Ex duration**	Fish oil	8.2	min		f/up	10.1	<.01	nd	Maximum heart rate x maximum systolic pressure; likely divided by 1000
		Olive oil	8.9				9.1	>.1		
	Max double product	Fish oil	16.5			f/up	20.8	<.01	nd	
		Olive oil	15.4				13.4	>.1		
Salonen 1987	**Plt Aggr**	PRP								Platelet aggregation measured as aggregation extent and aggregation velocity by optical density
	ADP extent	Fish oil	16.2±2.5	mV	SE	Δ	-10.0±2.9	<.001	NS	
	2.3-9.0 µmol/L	Olive oil	17.4±7.4				-6.7±1.6	<.001		
	ADP velocity	Fish oil	0.16±0.03	mV/sec	SE	Δ	-0.13±0.04	<.01	NS	
	2.3-9.0 µmol/L	Olive oil	0.17±0.02				-0.08±0.02	<.05		
Schectman 1988	**Apo A1**	Fish oil	114±7	mg/dL	SE	f/up	111±7	NS	NS	Additional non-controlled 1 month on 7.5 g n-3 not included. Unclear if 2 studies by Schectman et al. (1988 and 1989) are independent of each other. Possible overlap of up to 6 subjects with NIDDM and hypertriglyceridemia.
		Safflower oil	114±7				112±12	NS		
	Apo B	Fish oil	99±7	mg/dL	SE	f/up	116±8	<.05	NS	
		Safflower oil	99±7				109±9	NS		
	Hgb A1c	Fish oil	7.9±0.4	%	SE	f/up	8.5±0.3	<.05	NS	
		Safflower oil	7.9±0.4				8.4±0.4	NS		
	LDL apo B	Fish oil	82±8	mg/dL	SE	f/up	104±7	<.05	<.05	
		Safflower oil	82±8				93±6	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Schectman 1989	**Apo A1**	Fish oil	117±6	mg/dL	SE	f/up	117±8	NS	NS	Unclear if 2 studies by Schectman et al. (1988 and 1989) are independent of each other. Possible overlap of up to 6 subjects with NIDDM and hypertriglyceridemia.
		Safflower oil	123±6				128±8	NS		
	LDL apo B	Fish oil	92±10	mg/dL	SE	f/up	115±7	<.05		
		Safflower oil	105±11				108±7	NS		
Seljeflot 1998	**vWF**	Fish oil	127 (95, 143) Median	%		f/up	115 (90, 126)	nd	.03	Dropout: Nonfatal MI (1) Unclear on difference between arms for n-3 in serum phospholipids Insufficient detail on placebo composition
		Control fatty acids	112 (97, 152) Median				117 (95, 143)	nd		
Silva 1996	**Apo A1**	Fish oil	159±8.0	mg/dL	SE	f/up	131±6.5	.0001	nd	Dropout: 5 AE WD from control arm. 1 acute pancreatitis others: eructations, nausea, sensation of repletion, meterorism and epigastralgias Design: Also subanalysis of baseline fish intake Unclear whether glucose was fasting or not. Unclear whether premenopausal women were excluded (inclusion age criteria was 18-70) No p-value given for groups at baseline
		Soya oil	184±8.9				151±9.2	.0001		
	Apo B100	Fish oil	188±10	mg/dL	SE	f/up	185±9.4	NS	nd	
		Soya oil	222±11				217±14	NS		

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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Singh 2002	**FBS**	Omega-3 diet	5.99±1.39	mmol/L	SD	ΔΔ	-0.27	nd	<.0001	Dropout: LTF: intervention(15), control (16); dropouts: intervention (9), control (11); non-cardiac deaths: intervention (6), control (5). Data based on food recall/diary - possible recall bias FA val: 1.79 (0.36) daily intake of n-3 FA at 2 yr - unclear if % or grams
		Control diet	5.94±1.55				-	nd		
	SBP	Omega-3 diet	132±17	mmHg	SD	f/up	127±16	nd	<.0001	
		Control diet	131±17				129±15	nd		
	DBP	Omega-3 diet	86±10	mmHg	SD	f/up	83±9	nd	<.0001	
		Control diet	86±9				85±8	nd		
	Tg	Omega-3 diet	1.84±0.38	mmol/L	SD	ΔΔ	-0.25	nd	<.0001	
		Control diet	1.85±0.28					nd		
	TC	Omega-3 diet	5.74±0.98	mmol/L	SD	ΔΔ	-0.52	nd	<.0001	
		Control diet	5.77±0.98					nd		
	HDL	Omega-3 diet	1.16±0.26	mmol/L	SD	ΔΔ	0.06	nd	<.0001	
		Control diet	1.14±0.15					nd		
	LDL	Omega-3 diet	3.64±0.78	mmol/L	SD	ΔΔ	-0.49	nd	<.0001	
		Control diet	3.54±0.67					nd		
Sirtori 1992	**Plt Aggr**	PRP					±			Platelet aggregation: AC_{50}: Concentration of collagen giving a 50% decrease in optical density IC_{50}: Concentration of Iloprost resulting in 50% inhibition of platelet aggregation
	Collagen	Fish oil	0.35±0.05	mg/L	SE	f/up	0.48±0.13	NS	NS	
	AC_{50}	Corn oil	0.35±0.10				0.53±0.09	NS		
	Iloprost	Fish oil	0.65±0.15	mg/L	SE	f/up	0.66±0.16	NS	NS	
	IC_{50}	Corn oil	0.69±0.14				0.77±0.13	NS		
	LDL apo B	Fish oil	1.57±0.10	g/L	SE	f/up	1.54±0.10	NS	NS	
		Corn oil	1.60±0.09				1.55±0.12	NS		
	Apo B	Fish oil	1.67±0.09	g/L	SE	f/up	1.61±0.05	NS	nd	
		Corn oil	1.69±0.09				1.63±0.08	<.05		
	Apo A1	Fish oil	1.32±0.06	g/L	SE	f/up	1.30±0.06	NS	nd	
		Corn oil	1.36±0.05				1.38±0.06	NS		
Sirtori, 1998	**Insulin**	Fish oil	115.9±64.0	pmol/L	SD	f/up	112.0±50.7	NS	NS	Data also reported on lipids in diabetic and hyperlipidemia type subgroups. Lipid data estimated from graphs. Dropout: 67 from 935 original enrolled: Fish oil (28), placebo (39) 6 month RCT with subsequent 6 month open study including all remaining subjects Subanalyses for insulin outcomes only for NIDDM.
		Olive oil	111.6±57.2				119.7±84.5	NS		
	FBS	Fish oil	148.8±39.0	mg/dL	SD	f/up	147.2±36.9	NS	NS	
		Olive oil	146.7±37.2				142.9±37.0	NS		
	Hgb A1c	Fish oil	7.25±1.6	%	SD	f/up	7.05±1.6	NS	NS	
		Olive oil	7.14±1.6				6.88±1.4	NS		
	TC	Fish oil	233.9	mg/dL		f/up	233.8	nd	NS	
		Olive oil	233.8				232.8	nd		
	Tg	Fish oil	294.3	mg/dL		f/up	231	nd	<.0001	
		Olive oil	297.5				277.5	nd		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Solomon, 1990	**ETT Work load producing angina**	Fish oil	18.87±12.20	Kwatt-sec	SD	f/up	20.09±11.03	nd	NS	Dropout: Exhaustion w/o angina (9), lower limb claudication (1), syncope (1), absence of dx ECG changes (1) 22 were initially assessed 2 wk prior to randomization. Small sample sz for statistical comparison
		Olive oil	19.53±9.81				22.22±11.45	nd		
Swahn, 1998	**Lp(a)**	Fish oil	308	mg/L		f/up	296	nd	NS	SD not applicable - skewed data. Confusing math: patients randomized to receive 2 g of n-3s or 2 g of corn oil twice daily for 12 weeks . . . "thus, the patients allocated to n-3 took 3.5 g of n-3 fatty acids each day"; calculations of specific FA intake based on 3.5 g
		Corn oil	280				275	nd		
Toft, 1995	**Insulin**	Fish oil	52±6	pmol/L	SE	Δ	7±7	.10	.06	Dropout: Fish oil-angina (F1), DBP>110 (1), personal reasons (2); Control-personal reasons (2). Non-randomized, uncontrolled cohort study Few details on population/study characteristics
		Corn oil	64±7		SE		9±6	.53		
	FBS	Fish oil	5.5±0.1	mmol/L	SE	Δ	0.1±0.1	.001	.16	
		Corn oil	5.7±0.1		SE		0.0±0.1	.001		
	Hgb A1c	Fish oil	5.7±0.1	%	SE	Δ	0.3±0.1	.28	.83	
		Corn oil	5.7±0.1		SE		0.2±0.1	.10		
Toft, 1997	**Fibrinogen**	Fish oil	2.2±0.1	g/L	SE	Δ	0.6±0.1	.0001	NS	See Toft 1995 for study design
		Corn oil	2.2±0.1				0.4±0.1	.0002		
	Factor VII	Fish oil	105±6	%	SE	Δ	6±5	NS	NS	
		Corn oil	103±4				5±4	NS		

Δ = within cohort difference
ΔΔ = net difference from the reference group

Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Toth, 1995	**ETT Ex TPR**	Fish oil	730 *		SE	Δ	-40 *	<.01		* Values were estimated from graph Non-randomized, cohort only. Ex TPR = Total peripheral resistance during exercise, measured using impedance-cardiography Ex CI = Cardiac index during exercise, measured using impedance-cardiography.
	ETT Ex CI	Fish oil	6.3 *			Δ	+1.0 *	<.05		
	ETT Relative aerobic capacity	Fish oil	70 *	%		Δ	+10 *	<.01		
	ETT ST score	Fish oil	1.2 *			Δ	-0.4 *	<.05		
Verheugt, 1986	**ETT Exercise duration**	Fish oil	6.8	min	SE	Δ	-0.2	NS		Non-randomized, cohort only. Few details for eligibility criteria.
	ETT ST Dep	Fish oil	2.6	min		Δ	+0.2	NS		
Warren, 1988	**ETT Ex RPP**	Cod liver oil	18,800			Δ	+300	NS		Non-randomized, cohort study. Part funding listed. Rate-pressure product; equivalent to work load.
	ETT Ratio resting/exercise RPP	Cod liver oil	0.45			Δ	-0.08	<.05		
	ETT Time to ischemia	Cod liver oil	7.6	min		Δ	+0.9	NS		
Wensing, 1999	**Plt Aggr**	PRP								
	ADP	Fish oil shortening	48.2±2.8	%	SE	f/up	+6.1±7.8	NS	NS	
	1.5 µmol/L Va	Linseed oil	52.9±4.2				-2.5±6.1	NS	NS	
	Aggr velocity	Sunflower oil	50.7±5.8				-0.6±8.9	NS		
	ADP	Fish oil shortening	69.6±5.1	%	SE	f/up	+9.2±5.8	NS	NS	
	1.5 µmol/L Imax	Linseed oil	73.3±7.3				-8.6±11.1	NS	NS	
	Maximum velocity	Sunflower oil	68.5±9.4				+7.0±12.1	NS		
	Collage	Fish oil shortening	46.5±2.4	%	SE	f/up	+3.7±8.6	NS	NS	
	1.0 µmol/L Va	Linseed oil	40.2±6.1				+6.1±5.4	NS	NS	
	Aggr velocity	Sunflower oil	42.8±5.8				+9.9±11.0	NS		
	Collagen	Fish oil shortening	65.7±3.0	%	SE	f/up	-0.1±7.4	NS	NS	
	1.0 µmol/L Imax	Linseed oil	50.2±6.9				+7.5±4.2	NS	NS	
	Maximum velocity	Sunflower oil	63.9±6.0				-2.9±9.2	NS		
Westerveld, 1993	**Hgb A1c**	1800 mg EPA-E	8.2±2.8	%	SD	f/up	7.9±2.1	.30	NS	Discrepancy b/w reported baseline data in table and in text. Table data: 8.6 +/- 2.7 range (4.9-13). Demographic data given, no baseline analyses.
		900 mg EPA-E	7.6±2.9	%			8.1±2.8	.37	NS	
		Olive oil	9.2±2.7	%			9.3±3.0	.90		

Δ = within cohort difference
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Study	Outcome	Study Arm	Base			Follow-up / Change		*P* W/in	*P* Btw	Comments/Biases
Wilt, 1989	**Apo A1**	Fish oil	0.01(0.20)	g/L	SD	Δ	0.04 (-0.4, 0.12)	NS	NS	
		Safflower oil	0.05(0.16)					NS		
	Apo B	Fish oil	0.03(0.24)	g/L	SD	Δ	-0.05 (-0.15, 0.05)	NS	NS	
		Safflower oil	-0.02(0.20)					NS		
Woodman, 2002	**DBP**	EPA	75.8± 2.2	mmHg	SE	f/up	74.6±1.9	nd	NS	Dropout: 8 of 59 WD. ND for group assignment. 5 because of medication change, 2 because of time commitment, 1 illness unrelated to protocol. Difference from the control group, after adjustment for baseline values for outcomes Hgb A1c, FBS, insulin.
		DHA	71.8± 2.4				71.9±1.8	nd	NS	
		Olive oil	73.0±1.5				72.1±1.3	nd		
	SBP	EPA	137.1±4.1	mmHg	SE	f/up	133.7±3.4	nd	NS	
		DHA	138.5±3.9				142.7±4.8	nd	NS	
		Olive oil	135.9±3.6				132.5±2.8	nd		
	Hgb A1c	EPA	7.14±0.25	%	SE	ΔΔ	0.18±0.14	nd	NS	
		DHA	7.48±0.17				0.03±0.15	nd	NS	
		Olive oil	7.14±0.15				-	nd		
	FBS	EPA	7.46±0.44	mmol/L	SE	ΔΔ	1.40±0.29	nd	.002	
		DHA	8.25±0.23				0.98±0.29	nd	.002	
		Olive oil	7.96±0.40				-	nd		
	Insulin	EPA	14.16±1.76	mU/L	SE	ΔΔ	-0.47±1.29	nd	NS	
		DHA	16.54±2.11				-0.75±1.28	nd	NS	
		Olive oil	14.57±1.94				-	nd		
Yamada, 1997	**IMT**	Fishing village	nd	mm	SE	f/up	0.70±0.01	nd	<.05	Data is 'all cases' combined. Cross-sectional study No inclusion/exclusion criteria; no baseline data. Potential bias: larger proportion of diabetics in "comparison" group. Age is the only confounder addressed. No individual FA data.
		Farming village	nd				0.73±0.01	nd		

Δ = within cohort difference
ΔΔ = net difference from the reference group

APPENDIX D. Peer Reviewers

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