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Number 89

Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis

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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 Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis was 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. 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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Chapter 1 was written in collaboration with the Tufts-New England Medical Center Evidence-based Practice Center.

Structured Abstract

Context: Clinical trials report differing effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease (IBD), rheumatic arthritis, renal disease, systemic lupus erythemosus (SLE), and osteoporosis.

Objectives: To assess the effect of omega-3 fatty acids on 1) total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and insulin resistance in type-II diabetes and the metabolic syndrome, 2) clinical score, sigmoidoscopic score, histologic score and requirement for immunosuppressive therapy in IBD, 3) pain, swollen and tender joint counts, acute phase reactants, patient global assessment, and requirement for anti-inflammatory or immunosuppressive therapy in rheumatoid arthritis, 4) renal function, progression to end-stage renal disease, hemodialysis graft patency, mortality, and requirement for immunosuppressive therapy in renal disease, 5) disease activity, damage, patient's perception of disease activity, and requirement for immunosuppressive therapy in SLE, and 6) bone mineral density and fracture rates.

Data Sources: We searched on-line databases to identify potentially relevant studies and contacted industry experts for unpublished data.

Study Selection: We screened 4,212 titles, reviewed 1,097 articles, and included 83 articles. We restricted to randomized controlled trials (RCTs), but included case-control and cohort studies for bone/fracture. We had no language restrictions.

Data Extraction: We abstracted data on study design, study population, and outcomes; source, amount, and duration of omega-3 fatty acid consumption; and randomization, dropouts, blinding, and allocation for RCTs.

Data Synthesis: We performed meta-analyses for diabetes, rheumatoid arthritis, and IBD; and qualitative analyses for the other conditions.

For diabetes, omega-3 fatty acids had a favorable effect on triglyceride levels but no significant effect on total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood sugar, or glycosylated hemoglobin. There was no effect on plasma insulin or insulin resistance in type II diabetics or the metabolic syndrome.

For IBD, omega-3 fatty acids had variable effects on clinical score, sigmoidoscopic score, histologic score, induced remission, and relapse, and no effect on the relative risk of relapse in ulcerative colitis. There was a statistically non-significant reduction in requirement for corticosteroids. No studies evaluated requirement for other immunosuppressive agents.

For rheumatoid arthritis, omega-3 fatty acids had no effect on patient report of pain, swollen joint count, Erythrocyte Sedimentation Rate, and patient's global assessment. There was no effect on joint damage, contrary to a previous meta-analysis. There was a reduced requirement for anti-inflammatory drugs or corticosteroids. No studies assessed requirements for disease modifying antirheumatic drugs.

For renal disease, omega-3 fatty acids had varying effects on serum creatinine and creatinine clearance. Single studies respectively demonstrated reduced progression to end-stage renal disease and improvements on hemodialysis graft patencyrelative. No studies assessed requirements for corticosteroids or other immunosuppressive drugs.

For SLE, omega-3 fatty acids had variable effects on clinical activity. No studies assessed the effect on end organ damage, patient perception of disease, or requirements for other immunosuppressive drugs. One study showed no effect on corticosteroid requirements.

For bone mineral density, the effect of omega-3 fatty acids was variable. No studies assessed the effect on fracture.

Conclusions: The evidence for effects of omega-3 fatty acids on outcomes in the conditions assessed varies greatly. Omega-3 fatty acids appear to reduce serum triglycerides among type II diabetics, but have no effect on total cholesterol, HDL cholesterol, and LDL cholesterol. There appears to be no effect on most clinical outcomes in rheumatoid arthritis, although tender joint count may be reduced. There are insufficient data to draw conclusions about IBD, renal disease, SLE, bone density or fractures, requirement for anti-inflammatory or immunosuppressive drugs, or insulin resistance among type II diabetics.

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Summary

Introduction

This report was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It is one of several reports focusing on the role of omega-3 fatty acids in the prevention or treatment of various diseases. Three Evidence-based Practice Centers (EPCs) produced this series of reports: the Southern California EPC, based at RAND, the Tufts-New England Medical Center EPC, and the University of Ottawa EPC. This particular report focuses on the effects of omega-3 fatty acids on immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases.

Over the past 40 years, an increasing number of physiological functions have been attributed to omega-3 fatty acids, including movement of calcium and other substances into and out of cells, relaxation and contraction of muscles, inhibition and promotion of clotting, regulation of secretion of substances that include digestive enzymes and hormones, control of fertility, cell division, and growth.[1] In addition, omega-3 fatty acids may play an important role in brain development and function. Some evidence has suggested that omega-3 fatty acids in the diet may protect against heart attack and stroke, as well as certain inflammatory diseases like arthritis, lupus, and asthma.[1] The major dietary sources of omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements.

Methods

Key Questions

We consulted with three technical expert panels (TEPs) on this project. The respective panels focused on the following conditions:

- Rheumatoid arthritis, systemic lupus erythematosis (SLE), and bone density/osteoporosis
- Renal disease and diabetes
- Gastrointestinal diseases

The TEPs advised us on refining the preliminary questions posed to us by AHRQ, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

Based on the original questions that we received from AHRQ and input from our TEPs, we addressed the following questions in this study:

Diabetes

What is the evidence in adults or children with a) type II diabetes, or b) insulin resistance/the metabolic syndrome for an effect of omega-3 fatty acids on:

- Total cholesterol
- HDL cholesterol
- LDL cholesterol
- Triglycerides

What is the evidence in adults and children for an effect of omega-3 fatty acids on insulin sensitivity in a) type II diabetes, or b) the metabolic syndrome?

Inflammatory Bowel Disease

What is the evidence for the efficacy of omega-3 fatty acids in treatment of Crohn's disease and ulcerative colitis?

What is the evidence in adults or children with inflammatory bowel disease that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of inflammatory bowel disease?

Rheumatoid Arthritis

What is the evidence in adults or children with rheumatoid arthritis that omega-3 fatty acids affect:

- Pain
- Number of swollen joints
- Disease activity
- Patients' global assessment
- Joint damage

What is the evidence in adults or children with rheumatoid arthritis that omega-3 fatty acids can replace other more potent anti-inflammatory or immunosuppressive drugs such as steroids and nonsteroidal anti-inflammatory drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of rheumatoid arthritis?

Renal Disease

What is the evidence for the efficacy of omega-3 fatty acids in treatment of renal inflammation and glomerulosclerosis?

What is the evidence in adults or children with immune-mediated renal disease that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of immune-mediated renal disease?

Systemic Lupus Erythematosus

What is the evidence in adults or children with SLE that omega-3 fatty acids affect disease activity, damage, or patient perceptions of outcomes in SLE?

What is the evidence in adults or children with SLE that omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids in the treatment of SLE are influenced by the concomitant administration of various immunosuppressive agents?

Bone Density/Osteoporosis

What is the evidence that omega-3 fatty acids help maintain bone mineral status?

For each of the study questions, we also assessed:

- The effect of omega-3 fatty acids on subpopulations
- The effects of covariates, dose, source, and exposure duration on the outcomes of interest
- The sustainment of effect

In addition to answering these questions, we evaluated the data on adverse events, including clinical bleeding, gastrointestinal complaints or nausea, diarrhea, headache, dermatological problems, and withdrawal from study due to an adverse event.

Search Strategy

We searched the following online databases to identify literature: MEDLINE® (1966-July 2003), PreMEDLINE® (July 8, 2003), EMBASE (1980-Week 27, 2003), Cochrane Central Register of Controlled Trials (2nd Quarter, 2003), CAB Health® (1973-June 2003), and Dissertation Abstracts (1861-December 2002). We developed a core search strategy and applied it to each relevant disease category: rheumatoid arthritis, bone density, SLE, renal disease, diabetes, and gastrointestinal diseases. We also reviewed the reference lists of all applicable articles and contacted our technical expert panel as well as industry experts to identify unpublished data.

Selection Criteria

Two reviewers independently reviewed each article considered for inclusion in the study. Any disagreements between the reviewers were resolved through consensus. We included any articles pertaining to the effects of omega-3 fatty acids on diabetes mellitus, inflammatory bowel disease (ulcerative colitis and Crohn's disease), rheumatoid arthritis, SLE, renal disease, osteoporosis, or bone mineral status. We included only articles that presented research on human subjects and those that reported the results of randomized clinical trials or controlled clinical trials; we accepted observational studies only for bone mineral status. Language was not a barrier to inclusion.

Data Extraction and Analysis

For each article included in the study, two reviewers independently extracted data about the trial design; the outcomes of interest; the quality of the trial; the number and characteristics of the patients; details on the intervention, such

as the dose, frequency, and duration; the types of outcome measures; adverse events; and the elapsed time between the intervention and outcome measurements. Any disagreements between the reviewers were resolved through consensus. For each article, we then evaluated the quality of the design and execution of trials using a system developed by Jadad; determined a combined applicability grade based on applicability to the U.S. population and health state; performed a meta-analysis of those studies that sufficiently assessed interventions, populations, and outcomes to justify pooling; and performed a qualitative analysis of the remaining studies.

Results

We screened 4,212 article titles. From these article titles, we reviewed the 1,097 full-text articles relevant to our topics. Of these full-text articles, 115 met our selection criteria and underwent detailed review; among these, 83 articles met our inclusion criteria (34 for diabetes/metabolic syndrome, 13 for inflammatory bowel disease, 21 for rheumatoid arthritis, 9 for renal disease, 3 for SLE, and 4 for bone density and fractures). All of these 83 articles were randomized controlled trials, except for one observational study of bone density. We had a sufficient number of articles to perform quantitative meta-analyses for rheumatoid arthritis, inflammatory bowel disease, and diabetes. Due to the limited number of articles we identified for renal failure, SLE, and bone mineral metabolism, we performed qualitative analyses for these conditions.

Overall, our analyses yielded variable results both within and among disease categories. Our findings are summarized for each condition studied.

Diabetes/Metabolic Syndrome. Among 18 studies of type II diabetes or the metabolic syndrome, omega-3 fatty acids had a favorable effect on triglyceride levels relative to placebo (pooled random effects estimate: -31.61; 95% CI, -49.58, -13.64) but had no effect on total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood sugar, or glycosylated hemoglobin, by meta-analysis. Omega-3 fatty acids had no effect on plasma insulin or insulin resistance in type II diabetics or patients with the metabolic syndrome, by qualitative analysis of four studies.

Inflammatory Bowel Disease. Among 13 studies reporting outcomes in patients with inflammatory bowel disease, variable effects of omega-3 fatty acids on clinical score, sigmoidoscopic score, histologic score, induced remission, and relapse were reported. In ulcerative colitis, omega-3 fatty acids had no effect on the relative risk of relapse in a meta-analysis of three studies. There was a statistically non-significant reduction in requirement for corticosteroids for omega-3 fatty acids relative to placebo in two studies. No studies evaluated the effect of omega-3 fatty acids on requirement for other immunosuppressive agents.

Rheumatoid Arthritis. Among nine studies reporting outcomes in patients with rheumatoid arthritis, omega-3 fatty acids had no effect on patient report of pain, swollen joint count, Erythrocyte Sedimentation Rate (ESR), and patient's global assessment by meta-analysis. A previously performed meta-analysis[2] reached the same conclusions for swollen joint count, ESR, and patient's global assessment. That meta-analysis found a statistically significant improvement in tender joint count compared to placebo (rate difference = -2.9, 95% CI, -3.8, -2.1). The one study that assessed the effect on joint damage found no effect. In a qualitative analysis of seven studies that assessed the effect of omega-3 fatty acids on anti-inflammatory drug or corticosteriod requirement, six demonstrated reduced requirement for these drugs. No studies assessed the effect on requirements for disease modifying anti-rheumatic drugs. None of the studies used a composite score that incorporates both subjective and objective measures of disease activity, such as the American College of Rheumatology response criteria.

Renal Disease. In a qualitative analysis of nine studies that assessed the effect of omega-3 fatty acids in renal disease, there were varying effects on serum creatinine and creatinine clearance and no effect on progression to end stage renal disease. In a single study that assessed the effect on hemodialysis graft patency, graft patency was significantly better with fish oil than with placebo. No studies assessed the effects of omega-3 fatty acids on requirements for corticosteroids

Systemic Lupus Erythematosis. Among three studies that assessed the effects of omega-3 fatty acids in SLE, variable effects on clinical activity were reported. No studies were identified that assessed effect on damage or patient perception of disease. Omega-3 fatty acids had no effect on corticosteroid requirements in one study. No studies were identified that assessed the effects of omega-3 fatty acids on requirements for other immunosuppressive drugs for SLE. None of the studies used a measure of disease activity that incorporates both subjective and objective measures of disease activity.

Bone Mineral Density/Fracture. Among five studies described in four reports the effect of omega-3 fatty acids on bone mineral density was variable. No studies that assessed the effect of omega-3 fatty acids on fracture were identified.

The quantity and strength of evidence for effects of omega-3 fatty acids on outcomes in the conditions assessed varies greatly. The findings of many studies among type II diabetics provide strong evidence that omega-3 fatty acids reduce serum triglycerides but have no effect on total cholesterol, HDL cholesterol, and LDL cholesterol. For rheumatoid arthritis, the available evidence suggests that omega-3 fatty acids reduce tender joint counts and may reduce requirements for corticosteroids, but does not support an effect of omega-3 fatty acids on other clinical outcomes. There are insufficient data available to draw conclusions about the effects of omega-3 fatty

acids on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics.

Discussion

We offer the following observations and recommendations regarding future research on the effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, SLE, and osteoporosis.

- Additional research on the effects of omega-3 fatty acids needs to be performed on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics before recommendations regarding the use of omega-3 fatty acids for these conditions can be made.
- Studies of inflammatory bowel disease that include patients with both Crohn's disease and ulcerative colitis should report data separately for these groups.
- Studies that assess the effects of omega-3 fatty acids should use standard validated instruments to assess clinical outcomes.
- Trials that assess the effects of omega-3 fatty acids should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 fatty acid consumption.
- Studies of omega-3 fatty acids should explicitly define both the quantity of the omega-3 fatty acid source and of the specific omega-3 fatty acids present in a study dose of that source.
- Trials of omega-3 fatty acids should include a baseline assessment of dietary omega-3 and omega-6 fatty acid intake.
- In controlled trials that assess the effects of omega-3 fatty acids, analysis should include and report explicit testing of the effects of the omega-3 fatty acid relative to the control substance.
- In studies that use a crossover design, outcome data for all study arms should be reported at the end of each treatment period.

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 Southern California/RAND Evidence-based Practice Center, Los Angeles, CA, under Contract No. 290-02-0003. The full report is expected to be available in March 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 89, *Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis*. 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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References

1. Innis S. Essential dietary lipids. In: Ziegler EE, Filer, LJ Jr, editors. Present knowledge in nutrition. Washington, DC: International Life Sciences Institute; 1996.
2. Fortin P, Lew R, Liang M, et al. Validation of a meta-analysis: The effects of fish oil in rheumatoid arthritis. J Clin Epidemiol 1995;48(11):1379-90.

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Evidence Report

Chapter 1. Introduction

This report is one of a group of evidence reports prepared by three Agency for Healthcare Research and Quality (AHRQ)-funded Evidence-Based Practice Centers (EPCs) on the role of omega-3 fatty acids (both from food sources and from dietary supplements) in the prevention or treatment of a variety of diseases. These reports were requested and funded by the Office of Dietary Supplements, National Institutes of Health. The three EPCs – the Southern California EPC (SCEPC, based at RAND), the Tufts-New England Medical Center (NEMC) EPC, and the University of Ottawa EPC – have each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of these reports is to summarize the current evidence on the effects of omega-3 fatty acids on prevention and treatment of cardiovascular diseases, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, immune-mediated diseases, tissue/organ 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.

This report focuses on the effects of omega-3 fatty acids on immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases. Subsequent reports from the SCEPC will focus on cancer and neurological diseases and conditions.

This chapter provides a brief review of the current state of knowledge about the metabolism, physiological functions, and sources of omega-3 fatty acids.

The Recognition of Essential Fatty Acids

Dietary fat has long been recognized as an important source of energy for mammals, but in the late 1920s, researchers demonstrated the dietary requirement for particular fatty acids, which came to be called essential fatty acids. It was not until the advent of intravenous feeding, however, that the importance of essential fatty acids was widely accepted: Clinical signs of essential fatty acid deficiency are generally observed only in patients on total parenteral nutrition who received mixtures devoid of essential fatty acids or in those with malabsorption syndromes. These signs include dermatitis and changes in visual and neural function. Over the past 40 years, an increasing number of physiological functions, such as immunomodulation, have been attributed to the essential fatty acids and their metabolites, and this area of research remains quite active.[1, 2]

Fatty Acid Nomenclature

The fat found in foods consists largely of a heterogeneous mixture of triacylglycerols (triglycerides)--glycerol molecules that are each combined with three fatty acids. The fatty acids can be divided into two categories, based on chemical properties: saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room

temperature. The term “saturation” refers to a chemical structure in which each carbon atom in the fatty acyl chain is bound to (saturated with) four other atoms, these carbons are linked by single bonds, and no other atoms or molecules can attach; unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond, which allows the attachment of additional atoms to those carbons (resulting in saturation). Despite their differences in structure, all fats contain approximately the same amount of energy (37 kilojoules/gram, or 9 kilocalories/gram).

The class of unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Monounsaturated fatty acids (the primary constituents of olive and canola oils) contain only one double bond. Polyunsaturated fatty acids (PUFAs) (the primary constituents of corn, sunflower, flax seed and many other vegetable oils) contain more than one double bond. Fatty acids are often referred to using the number of carbon atoms in the acyl chain, followed by a colon, followed by the number of double bonds in the chain (e.g., 18:1 refers to the 18-carbon monounsaturated fatty acid, oleic acid; 18:3 refers to any 18-carbon PUFA with three double bonds).

PUFAs are further categorized on the basis of the location of their double bonds. An omega or n notation indicates the number of carbon atoms from the methyl end of the acyl chain to the first double bond. Thus, for example, in the omega-3 (n-3) family of PUFAs, the first double bond is 3 carbons from the methyl end of the molecule. The trivial names, chemical names and abbreviations for the omega-3 fatty acids are detailed in Table 1.1.

Finally, PUFAs can be categorized according to their chain length. The 18-carbon n-3 and n-6 short-chain PUFAs are precursors to the longer 20- and 22-carbon PUFAs, called long-chain PUFAs (LCPUFAs).

Table 1.1. Nomenclature of omega-3 fatty acids.

Names		Abbreviations		
Trivial	IUPAC*	Carboxyl-reference	Omega-reference	Other
Linolenic acid	9,12,15-octadecenoic acid	$18{:}3\Delta^{9\,12\,15}$	18:3n-3 18:3 (ω-3)	ALA α-LA LNA α-LNA
Docosahexaenoic acid	4,8,12,15,19- docosahexaenoic acid	$22{:}6\Delta^{4\,8\,12\,15\,19}$	22:6n-3 22:6 (ω-3)	DHA
Docosapentaenoic acid	7,10,13,16,19- docosapentaenoic acid	$22{:}5\Delta^{7\,10\,13\,16\,19}$	22:5n-3 22:5 (ω-3)	DPA
Eicosapentaenoic acid Icosapentaenoic acid Timnodonic acid	5,8,11,14,17- eicosapentaenoic acid	$20{:}5\Delta^{5\,8\,11\,14\,17}$	20:5n-3 20:5 (ω-3)	EPA

*IUPAC=International Union of Pure and Applied Chemistry

Fatty Acid Metabolism

Mammalian cells can introduce double bonds into all positions on the fatty acid chain except the n-3 and n-6 position. Thus, the short-chain alpha-linolenic acid (ALA, chemical abbreviation: 18:3n-3) and linoleic acid (LA, chemical abbreviation: 18:2n-6) are essential fatty acids. No other fatty acids found in food are considered ‘essential’ for humans, because they can all be synthesized from the short chain fatty acids.

Following ingestion, ALA and LA can be converted in the liver to the long chain, more-unsaturated n-3 and n-6 LCPUFAs by a complex set of synthetic pathways that share several enzymes (Figure 1). LC PUFAs retain the original sites of desaturation (including n-3 or n-6).

The omega-6 fatty acid LA is converted to gamma-linolenic acid (GLA, 18:3n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the longer-chain omega-6 fatty acid, arachidonic acid (AA, 20:4 n-6). AA is the precursor for certain classes of an important family of hormone-like substances called the eicosanoids (see below).

The omega-3 fatty acid ALA (18:3n-3) can be converted to the long-chain omega-3 fatty acid, eicosapentaenoic acid (EPA; 20:5 n-3). EPA can be elongated to docosapentaenoic acid (DPA 22:5n-3), which is further desaturated to docosahexaenoic acid (DHA; 22:6n-3). EPA and DHA are also precursors of several classes of eicosanoids and are known to play several other critical roles, some of which are discussed further below.

The conversion from parent fatty acids into the LC PUFAs - EPA, DHA, and AA - appears to occur slowly in humans. In addition, the regulation of conversion is not well understood, although it is known that ALA and LA compete for entry into the metabolic pathways.

Physiological Functions of EPA and AA

As stated earlier, fatty acids play a variety of physiological roles. The specific biological functions of a fatty acid are determined by the number and position of double bonds and the length of the acyl chain.

Both EPA (20:5n-3) and AA (20:4n-6) are precursors for the formation of a family of hormone-like agents called eicosanoids. Eicosanoids are rudimentary hormones or regulating - molecules that appear to occur in most forms of life. However, unlike endocrine hormones, which travel in the blood stream to exert their effects at distant sites, the eicosanoids are autocrine or paracrine factors, which exert their effects locally – in the cells that synthesize them or adjacent cells. Processes affected include the movement of calcium and other substances into and out of cells, relaxation 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.[3]

The eicosanoid family includes subgroups of substances known as prostaglandins, leukotrienes, and thromboxanes, among others. As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA (20:4n-6), is the precursor of a group of eicosanoids that include series-2 prostaglandins and series-4 leukotrienes. The omega-3 fatty acid, EPA (20:5n-3), is the precursor to a group of eicosanoids that includes series-3 prostaglandins and series-5 leukotrienes. The AA-derived series-2 prostaglandins and series-4 leukotrienes are often synthesized in response to some emergency such as injury or stress, whereas the EPA-derived series-3 prostaglandins and series-5 leukotrienes appear to modulate the effects of the series-2 prostaglandins and series-4 leukotrienes (usually on the same target cells). More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate the effects of excessive levels of series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins seems to protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma.[3]

EPA (22:6 n-3) also affects lipoprotein metabolism and decreases the production of substances – including cytokines, interleukin 1ß (IL-1ß), and tumor necrosis factor a (TNF-a) –

that have pro-inflammatory effects (such as stimulation of collagenase synthesis and the expression of adhesion molecules necessary for leukocyte extravasation [movement from the circulatory system into tissues]).[2] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs remains unknown, although suppression of omega-6-derived eicosanoid production by omega-3 fatty acids may be involved, because the omega-3 and omega-6 fatty acids compete for a common enzyme in the eicosanoid synthetic pathway, delta-6 desaturase.

DPA (22:5n-3) (the elongation product of EPA) and its metabolite DHA (22:6n-3) are frequently referred to as very long chain n-3 fatty acids (VLCFA). Along with AA, DHA is the major PUFA found in the brain and is thought to be important for brain development and function. Recent research has focused on this role and the effect of supplementing infant formula with DHA (since DHA is naturally present in breast milk but not in formula).

Dietary Sources and Requirements

Both ALA and LA are present in a variety of foods. LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA is present in some commonly used oils, including canola and soybean oil, and in some leafy green vegetables.

Thus, the major dietary sources of ALA and LA are PUFA-rich vegetable oils. The proportion of LA to ALA as well as the proportion of those PUFAs to others varies considerably by the type of oil. With the exception of flaxseed, canola, and soybean oil, the ratio of LA to ALA in vegetable oils is at least 10 to 1. The ratios of LA to ALA for flaxseed, canola, and soy are approximately 1: 3.5, 2:1, and 8:1, respectively; however, flaxseed oil is not typically consumed in the North American diet. It is estimated that on average in the U.S., LA accounts for 89% of the total PUFAs consumed, and ALA accounts for 9%. Another estimate suggests that Americans consume 10 times more omega-6 than omega-3 fatty acids.[4] Table 1.2 shows the proportion of omega 3 fatty acids for a number of foods.

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.

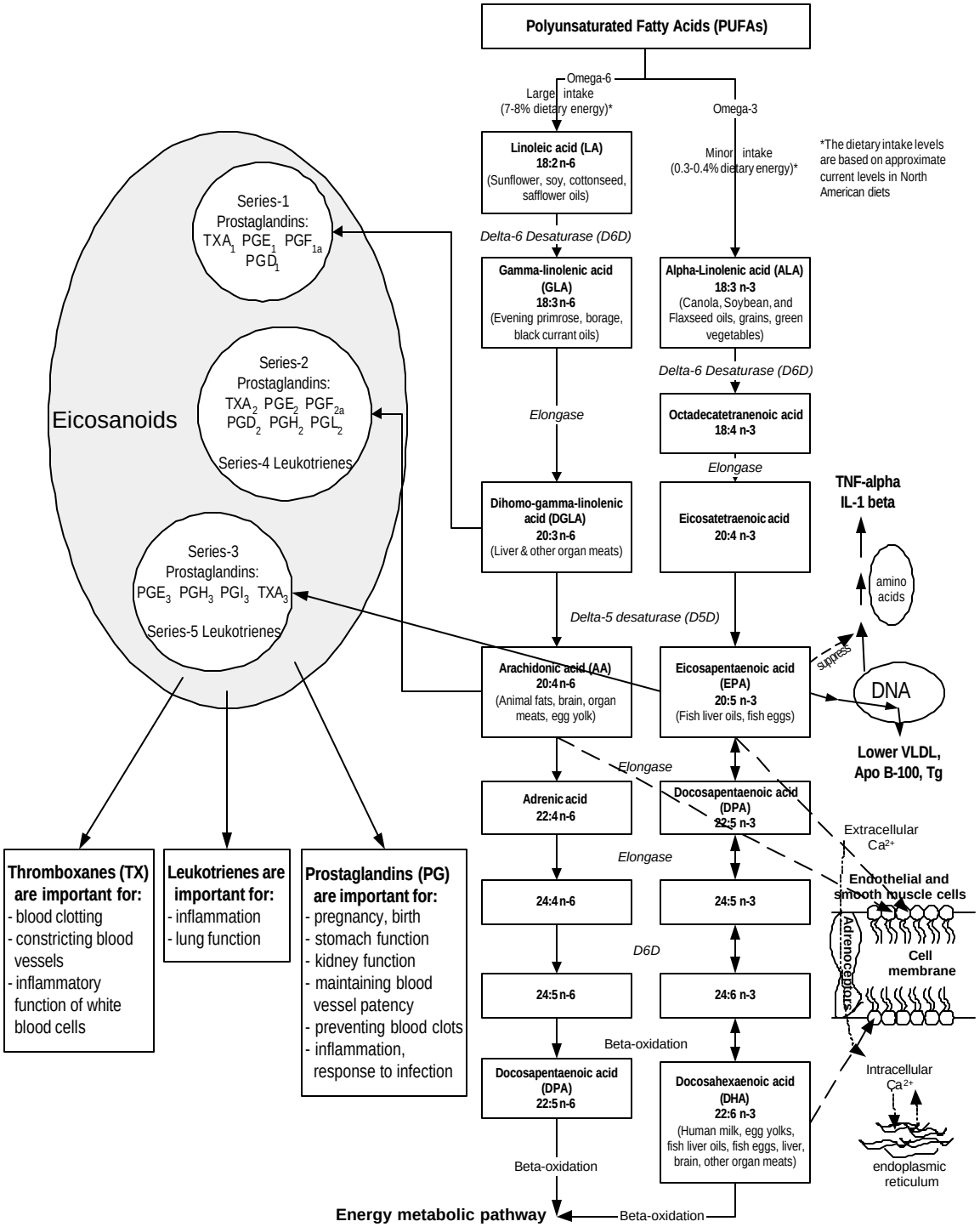


Table 1.2. Sources and proportions of omega-3 fatty acids in common foods and supplements.

Food/supplement	EPA 20:5n-3	DHA 22:6n-3	DPA 22:5n-3	ALA 18:3n-3
Foods in which Total Omega-3 Fatty Acids account for more than 50% of Total PUFA				
Fish				
Anchovy	✔	✔	✔	
Halibut	✔	✔	✔	
Herring	✔	✔	✔	
Mackerel	✔	✔	✔	
Salmon	✔	✔	✔	
Sardine	✔			
Tuna		✔	✔	
Canned, waterpacked	✔	✔	✔	
Fresh Bluefin				
Oils/Supplements				
Cod liver oils	✔	✔	✔	
Coromega *	✔	✔		
Fish oil capsules*	✔	✔		
*Flaxseed/linseed oil**				✔
Herring oil	✔	✔	✔	
MaxEPA*	✔	✔		
Menhaden oil	✔	✔	✔	
Neuromins*		✔		
Omacor*	✔	✔		
Ropufa*	✔	✔	✔	
Salmon oil	✔	✔	✔	
Sardine oil	✔	✔	✔	
Seeds				
Flaxseeds/Linseeds				✔
Foods/Supplements in which total Omega 3 fatty acids are 10-50% of total PUFA				
Oils				
Black currant oil				✔
Canola oil**				✔
Mustard seed oils				✔
Soybean oil				✔
Walnut oil				✔
Wheat germ oil				✔
Other foods				
Wheat germ				✔
Human milk				✔
Foods/Supplements in which total Omega 3 fatty acids are less than 10% of total PUFA				
Efamol Marine*****	✔	✔		
Soybeans				✔
Walnuts				✔

* Dietary Supplement

** Also called rapeseed oil

Several lines of research have suggested that the high ratio of omega 6s to omega 3s currently consumed in the U.S. promotes a number of chronic diseases.[4] Because of the slow rate of elongation and further desaturation of the essential FA, the importance of LC PUFAs to many physiological processes, and the overwhelming ratio of omega 6s to omega 3s in the average U.S. diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of omega 3 LC PUFAs by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of LC omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements, and the primary dietary sources of omega-6 LC PUFAs are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main sources of dietary intake data for the U.S. population. The CSFII has the advantage of collecting dietary recall data over a period of several days, which may permit estimates of omega-3 intake that more accurately reflect individual intakes than do those of NHANES. However, NHANES intake data have the advantage of being able to be linked to health outcomes. Table 1.3 provides a list of food sources of omega-3 fatty acids.

Table 1.3. Good food sources* of omega 3 fatty acids.

	EPA+DHA	ALA		EPA+DHA	ALA
Fish (3oz. Cooked)			**Oils (1 Tbs.)**		
Anchovy	✔		Canola		✔
Halibut	✔		Cod liver	✔	
Herring, Atlantic	✔		Flaxseed/linseed		✔
Pacific	✔		Herring	✔	
Mackerel, Atlantic	✔		Menhaden	✔	
Pacific	✔		Salmon	✔	
Salmon, Atlantic**	✔		Sardine	✔	
Sardines	✔		Soybean		✔
Trout, Rainbow	✔		Walnut		✔
Tuna, Albacore	✔		Wheat germ		✔
Canned light, water-packed	✔				
Canned white, water-packed	✔				
Fresh Bluefin	✔				
Organ Meats (3 oz. Cooked)			**Seeds**		
Brain, lamb	✔		Flaxseeds/linseeds (1 Tbs.)		✔
Brain, pork	✔				
Thymus, calf		✔			
Other Foods					
Caviar (1 oz.)#	✔				
Human breast milk (1c)#		✔			
Soybeans, cooked (1/2c)		✔			
Tofu, regular (1/2c)		✔			
Walnuts (1/4c)		✔			
Wheat germ (1/4c)#		✔			

Source: Figures adapted from USDA, 2003; *Foods that provide (per serving) 10% or more of the Adequate Intake (AI) for ALA or the Acceptable Macronutrient Distribution Range (AMDR) for EPA and DHA (10% of the AMDR for ALA); an AI is a recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people (thus, assumed to be adequate) when an RDA cannot be determined; an AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[5]

Standard serving size not established; **Farm-raised Atlantic salmon have nearly identical omega-3 fatty acid levels to wild Atlantic salmon and significantly more omega-3 fatty acids than wild Pacific salmon.

Table 1.4 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by NHANES III.[1] Table 1.5 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by CSFII.

Table 1.4. Estimates of the mean intake of LA, ALA, EPA, and DHA in the U.S. Population from analysis of NHANES III data.*

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

*Based on analysis of a single 24-hour dietary recall from NHANES III data; **Distributions are not adjusted for the over-sampling of Mexican –Americans, non-Hispanic African Americans, children 5 years old and under, and adults 60 years and over in the NHANES III dataset.

Table 1.5. Mean, range, and median usual daily Intakes (ranges) of n-6 and n-3 PUFAs, in the U.S. population, from analysis of CSFII data (1994 to 1998).*

	Mean (gms/d) (± SEM)**	Range of Means (gms/d) (±SEM)	Median (gms/d) (± SEM)**
LA (18:2n-6)	13.0 ± 0.1	6.7 ± 0.1-17.6 ± 0.5	12.0 ± 0.1
Total n-3 FA	1.40 ± 0.01	0.72 ± 0.02 - 1.86 ± 0.04	1.30 ± 0.01
ALA (18:3n-3)	1.30 ± 0.01	0.72 ± 0.02 - 1.73 ± 0.04	1.21 ± 0.01
EPA (20:5n-3)	0.028	0.002 - 0.049	0.004
DPA (22:5n-3)	0.013	0.001 - 0.019	0.005
DHA (22:6n-3)	0.057 ± 0.018	< 0.0005 ± 0.001	0.046 ± 0.013

Source: Adapted from Dietary Reference Intakes Report;[5] *Estimates are based on respondents' intakes on the first day of survey and were adjusted using the Iowa State University method; **For all individuals.

Lacking sufficient evidence from research on the effects or correction of dietary deficiencies to establish Recommended Dietary Allowances (RDAs) for the essential fatty acids, the Food and Nutrition Board (FNB) of the Institute of Medicine[5] has set adequate intakes[2] (AI) for the essential fatty acids, based on the average intakes of healthy CSFII participants. The AIs for the essential fatty acids vary by age group and sex, as well as for particular conditions such as pregnancy and breastfeeding. For ALA, the AI for men 19 and older, is 1.6 grams/day and the AI for (non-pregnant, non-breastfeeding) women is 1.1 grams/day. The AI for LA is 17 grams/day for men and 11 grams/day for women.

Based on evidence suggesting a role in prevention or treatment of some chronic diseases, the FNB has also established Acceptable Macronutrient Distribution Ranges (AMDR) for the essential fatty acids. An AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of

[1] The population represented by NHANES III includes individuals ages 2 months and older. Mexican Americans and non-Hispanic African-Americans, children 5 years old and younger, and adults 60 years of age and over 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 data. The NHANES III also included a physical examination and health survey of each participant.

[2] An Adequate Intake (AI) is defined as "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people, that are assumed to be adequate – used when a recommended dietary allowance cannot be determined."[5] An AI is set when data are insufficient or inadequate to establish an Estimated Average Requirement, on which the RDA is based, and indicate the need for more and better research. The EAR is "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group," based on a specific indicator or criterion of adequacy.

essential nutrients."[5] The AMDR is expressed as a percentage of total energy intake: The AMDR for LA is set at 5 to 10 percent of usual energy intake, and the AMDR for ALA is 0.6 to 1.2 percent of energy intake. Of this amount, up to 10 percent can be consumed as EPA and/or DHA, the omega-3 LC PUFAs. For a person who consumes 2000 kcal/day, ALA intake should range from 1.3 to 2.6 grams/day, and EPA/DHA intake can substitute for 0.13 to 0.26 of that quantity. Table 1.3 lists foods that provide 10 percent or more of these recommended intakes per serving, which may be referred to as "good sources." [3] Table 1.6 provides the actual omega-3 content per 100 gm for a variety of foods.

Rationale for and Organization of this Report

Studies show that tissue levels of AA and EPA-derived eicosanoids influence many physiological processes, including platelet aggregation, vessel wall constriction, and immune cell function (IOM), resulting in protection against heart attack and stroke as well as certain inflammatory diseases like arthritis, systemic lupus erythematosus, and asthma. Epidemiological studies have suggested that groups of people who consume diets high in omega 3 FAs may experience a lower prevalence of these conditions, and many small trials have attempted to assess the effects of adding omega 3 fatty acids to the diet, either as omega-3 FA-rich foods or as dietary supplements (primarily fish oils). In addition, dietary omega 3FA have been found to increase calcium absorption, rates of bone formation, and bone strength in rodents and birds. In response to this evidence, a number of omega-3 FA-containing dietary supplements that claim to protect against a variety of conditions have appeared on the market. Thus, AHRQ and the NIH Office of Dietary Supplements have requested a synthesis of the research to date on the health effects of diets rich in omega-3 FA.

The remainder of this report is organized into four chapters. Chapter Two describes the methods we used to identify and review studies related to the role of omega-3 fatty acids in immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases. Chapter Three presents our findings related to the effects of omega-3 fatty acids on those diseases/conditions. Chapter Four presents our conclusions and recommendations for future research in this area.

[3] Identifying a food as a "good source" of a nutrient strictly means that one standard serving of the food supplies 10 to 19 percent of the Daily Value for that nutrient. The Daily Values are based on the FDA's Daily Reference Values, standards for the macronutrients (fats, protein, carbohydrates, and dietary fiber), which are similar, although not identical to the DRIs (RDAs) and are based on the amount of energy consumed per day (2000 kcal/d is the reference for calculating DVs). In the case of the PUFAs, no DVs have been established: For this report, the FNB's AIs and AMDRs, have been used instead.

Table 1.6. 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.

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	Wolf fish, 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

Chapter 2. Methodology

Objectives

The topic of this report was nominated by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). The three participating Evidence-Based Practice Centers (EPCs) were asked to examine the effects of omega-3 fatty acids, in general, and on the following conditions: Cardiovascular Disease, Transplantation, Immune-Mediated Diseases, Gastrointestinal/Renal Diseases, Cancer, Neurology, Asthma, Child/Maternal Health, Eye Health, and Mental Health. The Southern California EPC (SCEPC) was responsible for examining Immune-Mediated Diseases and Gastrointestinal/Renal Diseases in Year 1 of the project and Cancer and Neurology in Year 2 of the project.

Scope of Work

The methodology that we used for this study included the following:

- Refining the preliminary questions provided by AHRQ,
- Convening a technical expert panel to advise the SCEPC on the study,
- Identifying sources of evidence in the scientific literature,
- Establishing inclusion/exclusion criteria for the articles identified in the scientific literature,
- Identifying potential evidence with attention to controlled clinical trials using omega-3 fatty acids,
- Evaluating potential evidence for methodological quality and relevance,
- Extracting data from studies meeting methodological and clinical criteria,
- Synthesizing the results,
- Performing further statistical analysis on selected studies,
- Performing pooled analyses where appropriate,
- Submitting the results to technical experts for peer review,
- Incorporating reviewers' comments into a final report for submission to AHRQ.

Original Proposed Key Questions

Preliminary questions for the project were developed by ODS in collaboration with the following NIH Institutes: (a) National Cancer Institute (NCI); (b) National Eye Institute (NEI); (c) National Heart, Lung, and Blood Institute (NHLBI); (d) National Institute of Alcohol Abuse and Alcoholism (NIAAA); (e) National Institute of Allergy and Infectious Diseases (NIAID); (f) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); (g) National Institute of Child Health and Human Development (NICHD); (h) National Institute of Diabetes

and Digestive and Kidney Diseases (NIDDK); (i) National Institute of Mental Health; and (j) National Institute of Neurological Disorders and Stroke (NINDS).

The general and disease-specific questions that were originally proposed are detailed in Appendix A.1, "Methodologic Approach."

Technical Expert Panel

Each AHRQ evidence report is guided by a Technical Expert Panel (TEP). The TEP advises the SCEPC on refining the preliminary questions, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

We convened three TEPs that focused on the following conditions: 1) rheumatoid arthritis (RA), systemic lupus erythematosis (SLE), and bone density/osteoporosis; 2) renal disease and diabetes; and 3) gastrointestinal (GI) diseases. The TEPs were composed of distinguished basic scientists and clinicians, with established expertise in the following areas: omega-3 fatty acids, human nutrition, dietary assessment methods, gastroenterology, nephrology, diabetes, osteoporosis, immunology, and rheumatology. In addition to the experts that we identified, AHRQ and the relevant NIH Institute(s) recommended a number of industry experts. The members of our technical expert panels and a summary of their key comments and recommendations are listed in Appendix A.2.

Key Questions Addressed in this Report

Based on input from our three TEPs, the preliminary disease-specific questions were revised. Additionally, in consultation with the Task Order Officer and the other participating EPCs, we added several questions to our scope of work that had previously been assigned to the NEMC/EPC because they were related to topics we were reviewing. Similarly, a question that had been assigned to the SCEPC for year two was reassigned to the NEMC-EPC. Lastly, one additional question (pertaining to rheumatoid arthritis – number of tender joints) was suggested by a TEP member after reviewing the draft report and was assessed post-hoc. The questions that are addressed in this report are as follows:

Diabetes

What is the evidence in adults or children with a) type II diabetes, or b) insulin resistance/the metabolic syndrome for the efficacy of omega-3 fatty acids in treatment of:

- *total cholesterol*
- *HDL cholesterol*
- *LDL cholesterol*

- *Triglycerides*

What is the evidence in adults and children for an effect of omega-3 fatty acids on insulin sensitivity in a) type II diabetes, or b) the metabolic syndrome?

Inflammatory Bowel Disease

What is the evidence for the efficacy of omega-3 fatty acids in treatment of Crohn's disease and ulcerative colitis?

What is the evidence that in adults or children with inflammatory bowel disease, omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of inflammatory bowel disease?

Rheumatoid Arthritis

What is the evidence that in adults or children with rheumatoid arthritis, omega-3 fatty acids affect:

- *pain*
- *number of swollen joints*
- *disease activity*
- *patient's global assessment*
- *joint damage*
- *number of tender joints*

What is the evidence that in adults or children with rheumatoid arthritis, omega-3 fatty acids can replace other more potent anti-inflammatory or immunosuppressive drugs such as steroids and NSAIDs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of rheumatoid arthritis?

Renal Disease

What is the evidence for the efficacy of omega-3 fatty acids in treatment of renal inflammation and glomerulosclerosis?

What is the evidence that in adults or children with immune-mediated renal disease, omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of immune-mediated renal disease?

Systemic Lupus Erythematosus

What is the evidence that in adults or children with systemic lupus erythematosus, omega-3 fatty acids affect disease activity, damage, or patient perceptions of outcomes?

What is the evidence that in adults or children with systemic lupus erythematosus, omega-3 fatty acids can replace steroids or other immunosuppressive drugs?

What is the evidence that the benefits of omega-3 fatty acids are influenced by the concomitant administration of various immunosuppressive agents in the treatment of systemic lupus erythematosus?

Bone Density/Osteoporosis

What is the evidence that omega-3 fatty acids help maintain bone mineral status?

For each of the study questions we also assessed 1) the effect of omega-3 fatty acids on sub-populations, 2) the effects of covariates, dose, source, and exposure duration on the outcomes of interest, and 3) the sustainment of effect.

Assessment of Adverse Events

In addition to assessing the efficacy of omega-3 fatty acids as specified above, we evaluated the data on adverse events that were reported in the studies we reviewed. We recognized, a priori, that adverse events are not reported in a standard way across clinical trials either in terms of the specific adverse events assessed or in the reporting of these adverse events. Hence, the purpose of this analysis was to define in general terms adverse events that occur with omega-3 fatty acids in order to identify specific adverse events that might warrant further investigation.

From each study, we extracted the number of adverse events reported for both intervention and placebo groups. We grouped the adverse events into the following categories:

- Clinical bleeding
- Gastrointestinal complaints or nausea

- Diarrhea
- Headache
- Dermatological
- Withdrawal due to adverse event

We calculated rates of adverse events within the intervention and placebo groups. Adverse event rates were calculated as the percentage of patients pooled across all conditions who had one of the adverse events. Reporting of adverse events varied greatly across studies. Many studies did not report on adverse events. If a study did not report on an adverse event (i.e. missing value), it was not used in that adverse event calculation. If a study reported not having an adverse event (i.e. adverse event rate of 0%), it was used in the calculation. Studies that did not specify the group allocation of the adverse events were excluded. We also excluded studies that reported the number of adverse events but did not report the group sample sizes.

Identification of Literature Sources

Potential evidence for our study came from three sources: on-line library databases, the reference lists of all relevant articles, and industry experts.

Jessie McGowan, Senior Information Scientist, and Nancy Santesso, Knowledge Translation Specialist, at the University of Ottawa were responsible for developing a common search strategy for omega-3 fatty acids for the 3 participating EPCs. Nancy Santesso developed a core omega-3 search strategy in collaboration with project librarians, biochemists, nutritionists, and clinicians, who also provided biochemical names, abbreviations, food sources, and commercial product names for omega-3 fatty acids. The literature search was not restricted by language of publication or by study design, except with the MeSH term, "dietary fats," in order to increase specificity. When possible, the searches were limited to studies involving human subjects. The core search strategy is detailed in Appendix A.3.

For the SCEPC, this core search strategy was incorporated into 6 specific searches that focused on our relevant disease categories: rheumatoid arthritis, bone density, SLE, renal disease, diabetes, and gastrointestinal diseases. The strategies for these searches are detailed in Appendix A.3.

The following databases were searched: Medline (1966-July, 2003), Premedline (July 8, 2003), Embase (1980-Week 27, 2003), Cochrane Central Register of Controlled Trials (2nd Quarter, 2003), CAB Health (1973-June 2003), Dissertation Abstracts (1861-to December 2002). All of these databases were searched using the Ovid interface, except CAB Health, which was searched through SilverPlatter. Any duplicate records were identified and removed within each search question using Reference Manager software, except for the last update, which was imported into EndNote. The citations obtained from these literature searches were sent to the SCEPC via e-mail.

The citations were transferred to a secured Internet-based software system (termed D2D) that enabled us to view article titles and abstracts electronically. Two reviewers, Walter Mojica and James Pencharz, used the computerized software system to independently evaluate the citations and abstracts using the review form in Figure B.1, Appendix B, which was loaded onto the computerized system.

The reviewers flagged article titles that focused on omega-3 fatty acids and any of the following disease conditions: diabetes mellitus, inflammatory bowel disease (ulcerative colitis and Crohn's disease), rheumatoid arthritis, SLE, renal disease, osteoporosis, or bone mineral status. In addition, they flagged article titles that pertained to the disease conditions of the other participating EPCs (i.e., cardiovascular disease or asthma). Language was not a barrier to inclusion. Articles that either reviewer flagged were ordered, as well as those articles in which it was unclear from the title or abstract whether the article was relevant. The articles were ordered from the RAND library, the UCLA library, or Kessler-Hancock, a San Francisco-based literature retrieval firm with contacts around the world. The literature was tracked using ProCite and Access software.

In addition, we sent letters to industry experts recommended by the Office Dietary Supplements to obtain any unpublished data (Figure A.3.1).

Evaluation of Evidence

Two reviewers independently reviewed each article that was ordered to determine whether it should be accepted for further study using a structured screening form (shown in Figure B.2, Appendix B) that included a defined set of inclusive/exclusive criteria (Table A.4.1, Appendix A.4). Walter Mojica reviewed all of the articles; James Pencharz and Jennifer Grossman each reviewed a portion of the articles. The reviewers resolved any disagreements by consensus.

Extraction of Data

For the articles that passed our screening criteria, two reviewers independently abstracted detailed data onto a specialized quality review form (QRF) (Figure B.3, Appendix B). Walter Mojica and Jennifer Grossman reviewed all of the articles except those pertaining to diabetes, which were reviewed by Walter Mojica and Puja Khanna. We consulted with several outside scientists to complete QRFs for foreign-language articles. The reviewers resolved differences through consensus, and a senior physician researcher resolved any disagreements that could not be resolved through this method.

The QRF included questions about the trial design; the outcomes of interest; the quality of the trial; the number and characteristics of the patients; details on the intervention, such as the dose, frequency, and duration; the types of outcome measures; adverse events; and the elapsed time between the intervention and outcome measurements.

Grading Evidence

Methodologic Quality of Randomized Controlled Trials

To evaluate the quality of the design and execution of trials, we also collected information on the QRF about the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts, and concealment of allocation.[6,113] A score for quality was calculated

for each trial using a system developed by Jadad (Appendix A.5, Figure A.5.1). The Jadad score rates studies on a scale of 0 to 5. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.[114,115] Thus, studies with a Jadad score of 3 or more are referred to as "high quality," and studies scoring 2 or less are referred to as "poor quality." For our purposes, if a trial was associated with more than one study, its quality score was equal to the maximum score calculated across its associated studies. Additionally, a generic summary quality score (A, B, C) was assigned to each study based upon the combination of its Jadad score and reporting of concealment of allocation (Appendix A.5, Table A.5.1).

Applicability

In this report, the focus is on the U.S. population. To capture the potential applicability of studies to the different populations of interest as defined in the scope of work (namely Americans with inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus or osteoporosis), we categorized the populations in the studies we reviewed in terms of 1) applicability to the U.S. population and 2) health state (Appendix A.5, Table A.5.2). In the summary tables, each study receives a combined applicability grade consisting of the applicability and health state.

Data Synthesis

We performed both a qualitative and quantitative synthesis of the evidence. We performed a meta-analysis for those studies that sufficiently assessed interventions, populations, and outcomes to justify pooling. For the remaining studies, we performed a qualitative analysis.

Meta-Analysis

Our meta-analytic methods are sufficiently comparable across conditions and outcomes that we describe them in general in this section. Individual approaches and decisions are discussed as necessary and appropriate in the discussion of results for particular conditions and outcomes.

Selection of Trials for Descriptive Analysis or Meta-Analysis

For each condition, we identified a set of relevant outcomes, e.g., cholesterol outcomes for the condition of diabetes, based on input from our TEP. Trials were considered for further analysis if they contained information on a chosen outcome collected within a follow-up interval for which measures were considered clinically comparable.

For some trials, several publications presented the same outcome data. In these cases, we picked the most informative of the duplicates; for example, if one publication was a conference abstract with preliminary data and the second was a full journal article, we chose the latter. The publications dropped for duplicate data do not appear in the evidence table but are noted in the

results text. We note that multiple citations of the same article were removed at the title screening stage of the project.

In order for a trial to be included in further analysis, the associated publication(s) had to report on the outcome, and contain sufficient statistical information for the calculation of a summary statistic. A trial also had to provide data prior to the crossover point if the trial was a crossover design to mirror the data available from a non-crossover trial, i.e., to enable the inclusion of a treatment effect uncontaminated by other treatments. Had data been included after the cross-over, the uncontaminated placebo or control group outcome would not have been available for example.

Trial Summary Statistics

Each trial contained one control or placebo group. Some trials contained more than one treatment (omega-3) group. In order not to double-count patients, we chose the most clinically relevant treatment group to enter our analysis, or in some cases combined treatment groups. For those outcomes that were dichotomous, the summary statistic was a risk ratio, that is, the risk of the outcome in the treatment (omega-3) group divided by the risk of the outcome in the control or placebo group. A risk ratio greater than one indicates that the risk of the outcome in the treatment group is larger than that in the control or usual care arm. For example, if the risk ratio is 1.10, then patients in the treatment group are 1.10 times as likely to have the outcome as those in the control or placebo group.

For each study, we estimated the log risk ratio and its standard deviation. We conducted the analysis on the logarithmic scale for variance-stabilization reasons.[7] We then back-transformed to the risk ratio scale for interpretability.

For those outcomes that were continuous, we extracted the follow-up means and standard deviations for the treatment and control or placebo groups respectively. If a study did not report a follow-up mean, or a follow-up mean could not be calculated from the given data, the study was excluded from analysis. For studies that did not report a standard deviation or for which a standard deviation could not be calculated from the given data, we imputed the standard deviation by using those studies and groups that did report a standard deviation and weighting all groups equally, or we assumed that the standard deviation was 0.25 of the theoretical range for the specific measure in the study. For example, if a study measured pain on a 0-100 scale, we assumed the standard deviation was 25.

If all studies measured the outcome on the same scale or the measures could all be converted to the same scale, e.g., cholesterol measurements measured in mg/dL or mmol/L which could all be converted to mg/dL, the summary statistic was the *mean difference* (MD) between the treatment group follow-up mean and the control or placebo group follow-up mean:

Mean difference = treatment follow-up mean – control follow-up mean

We estimated the standard deviation for that mean difference.[8] If the studies used different measurements of the same outcome and we could not convert them all to the same scale, the summary statistic was an effect size. The effect size is the mean difference at follow-up divided by the pooled standard deviation. This summary statistic is unitless and indicates the number of standard deviations by which the treatment and control or placebo group means differ. We estimated an unbiased estimate[9] of Hedges' g effect size[10] and its standard deviation. A negative

mean difference or effect size indicates that the treatment is associated with a decrease in the outcome at follow-up as compared with the control or usual care group.

Stratification of Trials

For each condition, we performed, as permissible given available data, stratified analyses on subgroups of studies defined by patient population, type of omega-3, and dose of omega-3. We will discuss the particular strata definitions for each condition in the relevant results sections in Chapter 3. In general, a paucity of available data precluded us from pooling data separately in most strata. However, we do discuss the results qualitatively in each stratum when possible.

Performance of Meta-Analysis

In some cases, the trials were judged too clinically heterogeneous to combine. Furthermore, for each outcome, condition, and trial stratum combination, we required that at least three trials be available for pooling. In heterogeneous settings and those with insufficient data, we conduct only a descriptive analysis and present the study-level summary statistics but do not estimate a pooled effect.

For those conditions for which trials were determined to be clinically comparable and for which there were at least three trials, we estimated a pooled random-effects estimate[11] by combining summary statistics across trials. We also report the chi-squared test of heterogeneity p-value.[9]

Forest plots were constructed for each setting. Each individual trial summary statistic is shown as a box whose area is inversely proportional to the estimated variance of the summary statistic in that trial. The trial's confidence interval is shown as a horizontal line through the box. The pooled estimate and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate value. A vertical solid line at one for dichotomous outcomes or at zero for continuous outcomes indicates no treatment effect.

Sensitivity Analyses

We conducted post hoc sensitivity analysis for meta-analyses that exhibited significant ($p<0.05$) heterogeneity based on the chi-squared test of heterogeneity. In these sensitivity analyses, we removed the most outlying study chosen based on a visual inspection of the forest plot of the original meta-analysis, and estimated a new pooled estimate. We compared this pooled estimate to the original result as well as observed whether significant heterogeneity still remained.

Publication Bias

We assessed the possibility of publication bias by evaluating a funnel plot of summary statistics for asymmetry, which can result from the nonpublication of small trials with negative results. These funnel plots include a horizontal line at the fixed-effects pooled estimate and pseudo–95% confidence limits.[9] If bias due to nonpublication exists, the distribution is asymmetric or skewed. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test[10] and a regression asymmetry test[9] as formal statistical tests for publication bias. The correlation approach tests whether the correlation between the effect sizes and their variances is significant, and the regression approach tests whether the intercept of a regression of the effects sizes on their precision differs from zero; that is, both formally test for asymmetry in the funnel plot. We acknowledge that other factors, such as differences in trial quality or true study heterogeneity, could produce asymmetry in funnel plots.

Interpretation of the Results

The mean difference pooled results are readily interpretable as they are measured in a clinically interpretable metric. To aid in interpreting the pooled effect size and risk ratio, whenever possible we back-transformed each pooled estimate to a specific metric. In order to do this, we multiplied each pooled effect size estimate by the average standard deviation of the most clinically relevant outcome measured across the trials, e.g., pain on the VAS scale, included in the pooled estimate. For each pooled risk ratio, we estimated a number needed to treat (NNT) or number needed to harm (NNH) depending on whether the risk ratio was less than or greater to one, by assuming that the population outcome risk was equal to the average control group risk observed across the trials. By average in either calculation, we mean a simple average across relevant placebo/control and/or treatment groups in the relevant studies. We note these back-transformations require assuming a particular underlying standard deviation or outcome risk. Readers may wish to apply their own standard deviation or underlying risk, based on the particular patient population to which they wish to apply the results. We conducted all analyses and drew all graphs using the statistical package Stata.[11]

Peer Review

This draft report was sent for review to a select group of experts in omega-3 fatty acids, epidemiology, nutrition, rheumatoid arthritis, SLE, IBD, nephrology, osteoporosis, and diabetes. The names, expertise, and affiliations of the peer reviewers are listed in Table A.6.1, Appendix A. Additionally, the report was sent to the members of the TEP for review. We entered all comments that we received into a database and collated those pertaining to similar sections of the report. For each comment or group of related comments, we prepared a response detailing how we changed the report or why we did not believe a change was justified. The complete list of peer reviewed comments and our responses are included in Appendix D. Service as a peer reviewer or as a technical expert panelist does not imply agreement or endorsement of the findings of this report.

Chapter 3. Results

Results of Literature Search

Figure 3.1 displays the flow of the literature review. The University of Ottawa EPC e-mailed us a total of 4,212 citations as a result of their computerized library searches. Our two reviewers considered 1,384 of these article titles to be relevant to our research topics. Of these, a senior researcher rejected 347 titles as not being relevant. We also received 25 citations from the literature searches conducted by New England Medical Center (NEMC) EPC, and we identified 42 articles by hand searching the reference lists of articles that we reviewed. Thus, we identified a total of 1,105 relevant article titles. We were able to retrieve all but 8 of these articles.

Of the 1,097 articles retrieved, 115 were accepted for further review, because they reported on results from randomized clinical trials or controlled clinical trials of omega-3 fatty acids in the treatment of RA, IBD, diabetes, renal disease, and SLE or reported results from randomized clinical trials, controlled clinical trials, or case series of omega-3 fatty acids on the effects on bone mineral metabolism. Of those articles that were rejected at this stage, 149 reported on a condition other than those of interest, 301 reported on a topic other than omega-3 fatty acids, 22 did not report on a population of interest, and 504 were rejected for study design (i.e., descriptive studies or editorials/commentaries, previous reviews or meta-analyses, and observational studies in all topic areas except bone mineral metabolism). Three articles were duplicates of articles already on file, and four were not reviewed due to language.

Of the 115 articles that went to further review, 10 were rejected because they did not report on outcomes of interest, 15 because they did not report a difference in omega-3 content among study arms, and 7 because they were duplicate reports of the same trial. Thus, a total of 83 articles were accepted for supplementary analysis. Of these, 21 articles reported on RA, 13 articles reported on IBD, 34 articles reported on diabetes, 9 articles reported on renal, 3 articles reported on lupus, and 4 articles reported on bone mineral metabolism. One article reported outcomes for both SLE and renal disease.

Due to the limited number of articles found for renal failure, SLE, and bone mineral metabolism, these outcomes are discussed qualitatively.

Ten trials[16-25] were included in the meta-analysis of RA outcomes (not all trials were included for each outcome). Eleven trials were not included in meta-analysis for the following reasons: insufficient statistics[26-35] and no outcome of interest.[38]

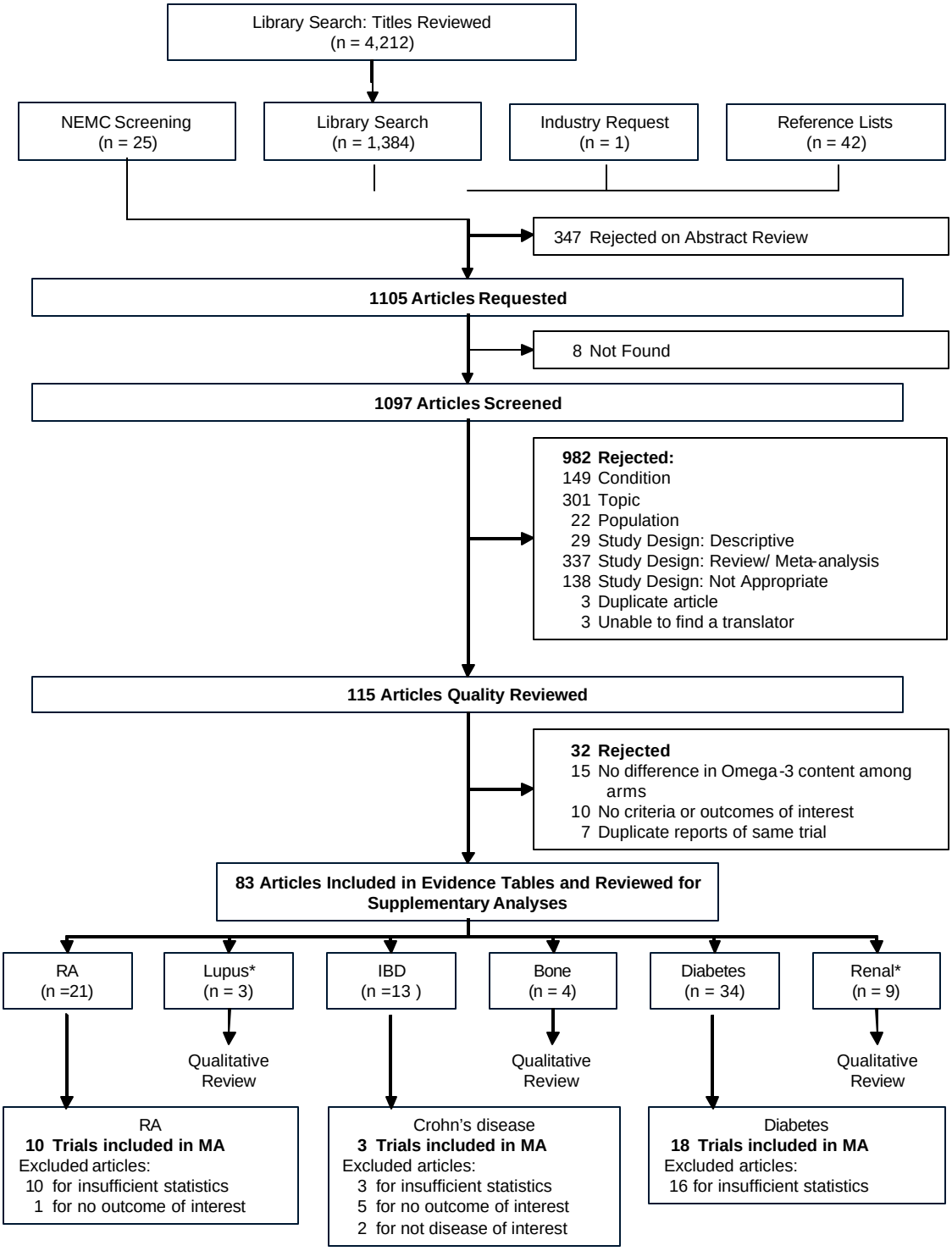
Three trials[39-41] were included in the meta-analysis of remission/relapse in ulcerative colitis. Ten trials were not included in meta-analysis for the following reasons: insufficient statistics,[42, 43,95] no outcome of interest,[44,46,52,53,94] and wrong disease (Crohn's disease, not ulcerative colitis).[54, 55]

Eighteen trials[56-73] were included in the meta-analysis of diabetes outcomes (not all trials were included for each outcome). Sixteen articles were not included in meta-analysis for insufficient statistics.[74-83,86-91]

In addition, as a result of our request to industry experts for unpublished data, Herbert Woolf, Technical Marketing Manager for BASF Corporation, sent us the following document: "Food Labeling: Health Claims and Label Statement – Omega-3 Fatty Acids and Coronary Heart Disease," prepared by members of the Joint Task Group (CHPA, CRN, NFI), FDA Docket No: 91N-0103.[15]

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

Figure 3.1. Literature flow.



* One article reported both lupus and renal outcomes.

DIABETES

Summaries of all evaluated diabetes studies can be found in appendix C.1.

Diabetes: Total Cholesterol

Overall effect. We identified 32 studies[56-72, 75-83, 86-91] that evaluated the effect to of omega-3 fatty acids on total cholesterol in type II diabetics. Among these, 14 contained sufficient data to be included in a meta-analysis. (Table 3.1) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for total cholesterol is 0.72 mg/dl (95% CI, -5.90, 7.33) (Table 3.1 and Figure 3.2). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone, and combined fish oil and atorvastatin. Both atorvastatin alone and combined fish oil and atorvastatin reduced total cholesterol significantly, relative to placebo; there was an insignificant reduction with fish oil alone. The reduction for atorvastatin alone was greater than that for the other groups, although statistical testing was not reported.

Effects of dose, source and exposure duration. None of the studies specifically assessed the effects of dose, source, or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect. On stratified analysis of source, the pooled random effects estimates of the mean difference between omega-3 fatty acids and placebo, for studies using a fish-oil and studies using a plant source, respectively, were 1.21 mg/dl (95% CI, -6.51, 8.49) and –1.82 (95% CI, -5.87, 12.20).

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with type II diabetes), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.2). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

Table 3.1. Diabetes: mean difference for total cholesterol.

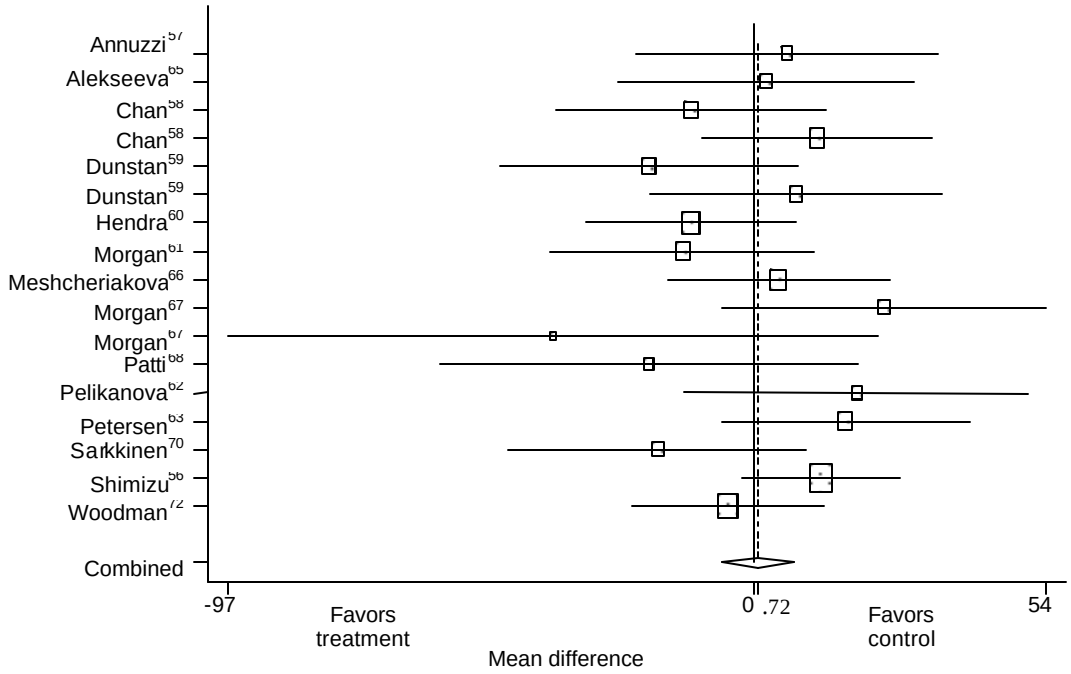
	Intervention		Control		Mean Difference (mg/dl) (95% CI)
Trial	**Source**	**n**	**Source**	**n**	
Alekseeva[65]	Linseed oil	30	Placebo	30	2.32 (-24.97, 29.60)
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	6.80 (-21.65, 34.00)
Chan[58]	Omacor	12	Placebo	13	-11.58 (-36.35, 13.19)
	Omacor/Atorvastatin	11	Atorvastatin	13	11.58 (-9.59, 32.76)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	-19.31 (-46.67, 8.06)
	Fish/moderate exercise	14	Placebo	11	7.72 (-19.28, 34.73)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-11.58 (-30.89, 7.72)
Meshcheriakova[66]	Linseed oil/Eiconol	60	Low-fat/Low sodium diet	60	4.63 (-15.75, 25.01)
Morgan[61]	Fish oil	10	Placebo	10	-13.13 (-37.43, 11.18)
	Fish oil	10	Placebo	10	
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-37.00 (-96.98, 22.98)
	High dosage Fish oil	6	Placebo	6	24.00 (-5.75, 53.75)
Patti[68]	Fish oil	8	Placebo	8	-19.31 (-57.98, 19.37)
Pelikanova[62]	Fish oil	10	Placebo	10	18.92 (-12.96, 50.80)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	16.99 (-5.97, 39.95)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-17.76 (-45.21, 9.69)
Shimizu[56]	EPA-E	29	Placebo	16	12.40 (-2.30, 27.10)
Woodman[72]	EPA	17	Placebo	16	-4.75 (-22.48, 12.97)
	DHA	18			
Pooled Random Effects Estimate*					0.72 (-5.90, 7.33)

*Chi-squared test of heterogeneity p-value = 0.22

Table 3.2. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on total cholesterol among people with type II diabetes.

Methodological Quality										
		A	B				C			
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	-11.58	(-30.89, 7.72)	Shimizu[56]	45	12.40	(-2.30, 27.10)
			Morgan[67]	13	-37.00	(-96.98, 22.98)	Morgan[61]	40	-13.13	(-37.43, 11.18)
				12	24.00	(-5.75, 53.75)				
			Petersen[63]	42	16.99	(-5.97, 39.95)	Patti[68]	16	-19.31	(-57.98, 19.37)
							Sarkkinen[70]	31	-17.76	(-45.21, 9.69)
	II		Chan[58]	25	-11.58	(-36.35, 13.19)	Annuzzi[57]	8	6.18	(-21.65, 34.00)
				24	11.58	(-9.59, 32.76)				
			Woodman[72]	51	-4.75	(-22.48, 12.97)	Dunstan[59]	24	-19.31	(-46.67, 8.06)
								25	7.72	(-19.28, 34.73)
							Pelikanova[62]	20	18.92	(-12.96, 50.80)
	III									

Figure 3.2. Diabetes: total cholesterol.



Diabetes: HDL Cholesterol

Overall effect. We identified 30 studies[56-61, 63,64,67-73, 75-83, 86-91] that evaluated the effect to of omega-3 fatty acids on HDL cholesterol in type II diabetics. Among these studies, 12 contained sufficient data to be included in a meta-analysis. (Table 3.4) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for HDL cholesterol is 1.17 mg/dl (95% CI, -1.08, 3.42) (Table 3.3 and Figure 3.3). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis[116] studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study assessed the effects of fish oil alone, atorvastatin alone, and combined fish oil and atorvastatin.[58] There was an insignificant increase and decrease in HDL with atorvastatin alone and fish oil alone, respectively, and a significant increase with a combination of fish oil and atorvastatin.

Effects of dose, source, and exposure duration. None of the studies specifically assessed the effects of dose, source or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect. In one study, plants were the source of omega-3 fatty acids. In this study,[70] the mean difference between omega-3 fatty acids and placebo for HDL cholesterol was –3.09 mg/dl (95% CI, -9.84, 3.67). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for HDL cholesterol was 1.53 mg/dl (95% CI, -0.82, 3.87).

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with type II diabetes), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.4). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

Table 3.3. Diabetes: mean difference for high-density lipoprotein (HDL).

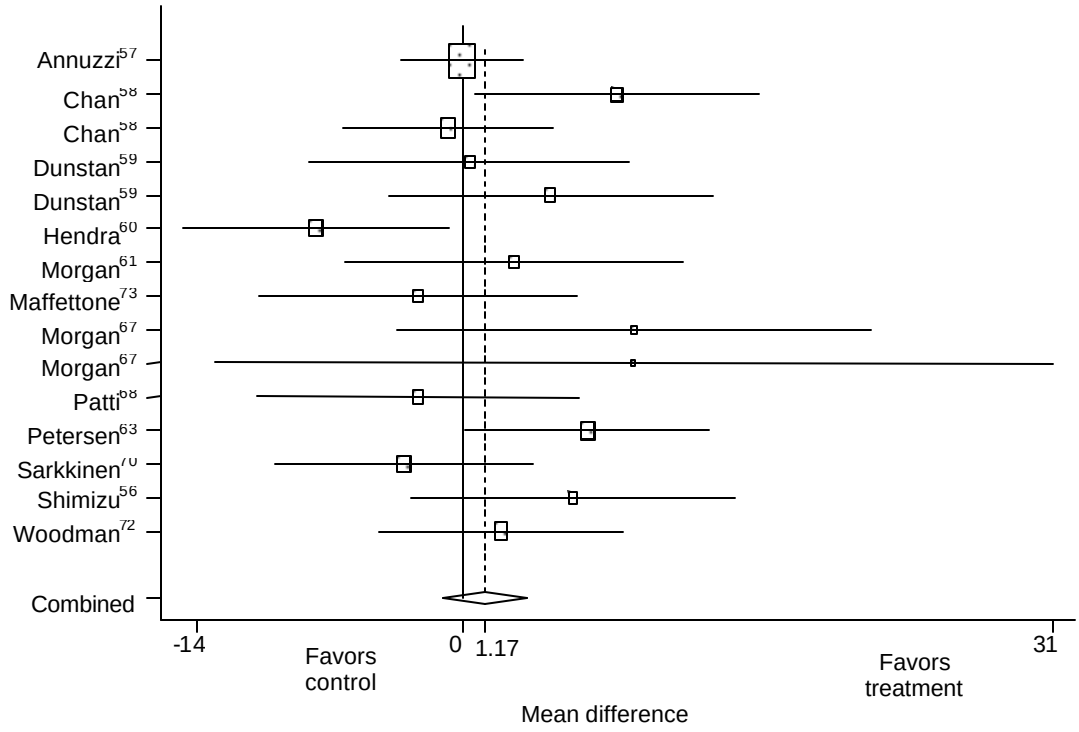
	Intervention		Control		Mean Difference
Trial	**Source**	**n**	**Source**	**n**	**(mg/dl) (95% CI)**
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	0.00 (-3.21, 3.21)
Chan[58]	Omacor	12	Placebo	13	-0.77 (-6.33, 4.78)
	Omacor/Atorvastatin	11	Atorvastatin	13	8.11 (0.63, 15.59)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	4.63 (-3.90, 13.16)
	Fish oil/mod. exercise	14	Placebo	11	0.39 (-8.03, 8.80)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-7.72 (-14.68, -0.76)
Morgan[61]	Fish oil	10	Placebo	10	2.70 (-6.18, 11.58)
	Fish oil	10	Placebo	10	
Maffettone[73]	Fish oil	8	Placebo	8	-2.32 (-10.69, 6.06)
Morgan[67]	Low dosage Fish oil	7	Placebo	6	9.00 (-3.49, 21.49)
	High dosage Fish oil	6	Placebo	6	9.00 (-13.03, 31.03)
Patti[68]	Fish oil	8	Placebo	8	-2.32 (-10.78, 6.14)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	6.56 (0.13, 13.00)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-3.09 (-9.84, 3.67)
Shimizu[56]	EPA-E	29	Placebo	16	5.80 (-2.70, 14.30)
Woodman[72]	EPA	17	Placebo	16	2.02 (-4.44, 8.48)
	DHA	18			
Pooled Random Effects Estimate*					1.17 (-1.08, 3.42)

*Chi-squared test of heterogeneity p-value = 0.13

Table 3.4. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on HDL among people with type II diabetes.

		Methodological Quality							
		A	B				C		
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**
			Hendra[60]	80	-7.72	(-14.68, -0.76)	Shimizu[56]	45	5.80 (-2.70, 14.30)
			Morgan[67]	13	9.00	(-3.49, 21.49)	Morgan[61]	40	2.70 (-6.18, 11.58)
				12	9.00	(-13.03, 31.03)			
			Petersen[63]	42	6.56	(0.13, 13.00)	Patti[68]	14	-2.32 (-10.78, 6.14)
							Sarkkinen[70]	31	-3.09 (-9.84, 3.67)
	II		Chan[58]	25	-0.77	(-6.33, 4.78)	Annuzzi[57]	8	0.00 (-3.21, 3.21)
				24	8.11	(0.63, 15.59)			
			Woodman[72]	51	2.02	(-4.44, 8.48)	Dunstan[59]	24	4.63 (-3.90, 13.16)
								25	0.39 (-8.03, 8.80)
	III								

Figure 3.3. Diabetes: high density lipoprotein (HDL).



Diabetes: LDL Cholesterol

Overall effect. We identified 28 studies that evaluated the effect of omega-3 fatty acids on LDL cholesterol in type II diabetics[57-61, 63,64,67, 69-73, 75-83, 86-91]. Among these, 11 contained sufficient data to be included in a meta-analysis. (Table 3.5) The pooled random effects estimate of the effect of omega-3 fatty acids on LDL cholesterol is 5.12 mg/dl (95% CI, -1.02, 11.25) (Table 3.5 and Figure 3.4). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here, although the results in the other meta-analysis were statistically significant.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone, and a combination of fish oil and atorvastatin. Atorvastatin alone and combined fish oil and atorvastatin reduced LDL cholesterol with significantly relative to placebo; fish oil alone reduced LDL cholesterol relative to placebo, though not significantly. The reduction was greatest for atorvastatin alone, although statistical testing between atorvastatin and fish oil groups was not reported.

Effects of dose, source and exposure duration. None of the studies specifically assessed the effects of dose, source or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect. In one study, plants were the source of omega-3 fatty acids. In this study,[70] the mean difference between omega-3 fatty acids and placebo for LDL cholesterol was –10.04 mg/dl (95% CI, -37.38, 17.30). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for LDL cholesterol was 5.92 mg/dl (95% CI, -0.38, 12.22).

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with type II diabetes) and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.6). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies were identified that assessed the effect of omega-3 fatty acids among children with type II diabetes.

Table 3.5. Diabetes: mean difference for low-density lipoprotein (LDL).

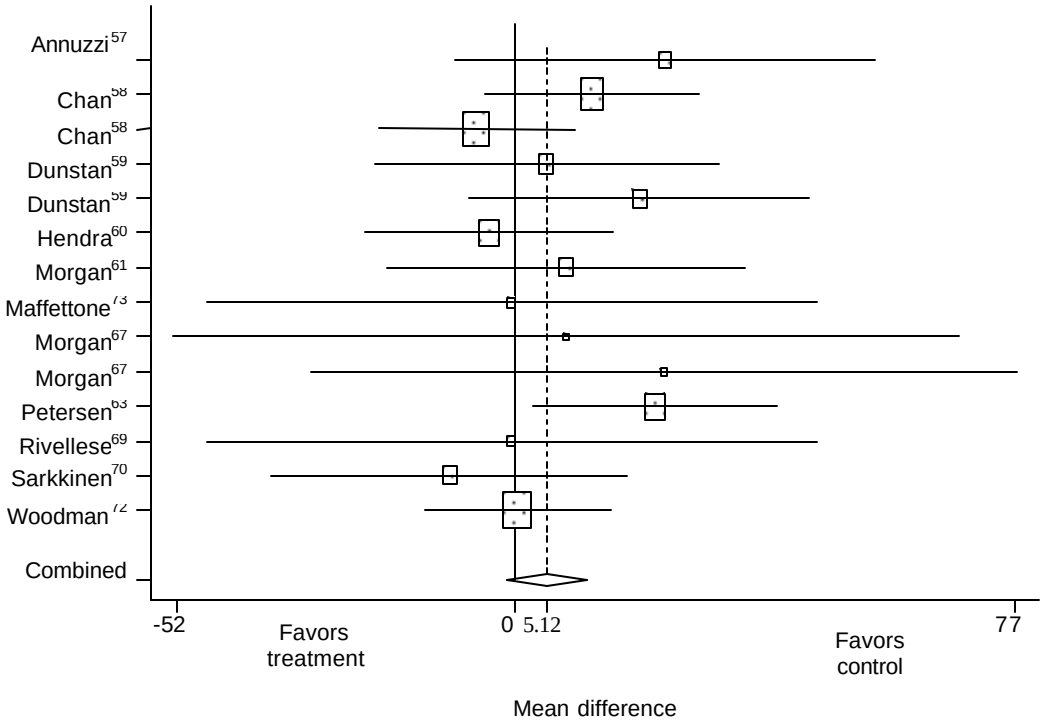
	Intervention		Control		Mean Difference
Trial	**Source**	**n**	**Source**	**n**	**(mg/dl) (95% CI)**
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	23.17 (-9.22, 55.56)
Chan[58]	Omacor	12	Placebo	13	-5.79 (-20.88, 9.29)
	Omacor/Atorvastatin	11	Atorvastatin	13	11.97 (-4.51, 28.45)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	5.02 (-21.44, 31.48)
	Fish oil/mod. exercise	14	Placebo	11	19.31 (-6.81, 45.42)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-3.86 (-22.97, 15.25)
Morgan[61]	Fish oil	10	Placebo	10	8.11 (-19.46, 35.67)
	Fish oil	10	Placebo	10	
Maffettone[73]	Fish oil	8	Placebo	8	-0.39 (-47.32, 46.55)
Morgan[67]	Low dosage Fish oil	7	Placebo	6	8.00 (-52.53, 68.53)
	High dosage Fish oil	6	Placebo	6	23.00 (-31.39, 77.39)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	21.62 (2.79, 40.45)
Rivellese[69]	Fish oil	8	Placebo	8	-0.39 (-47.31, 46.54)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-10.04 (-37.38, 17.30)
Woodman[72]	EPA	17	Placebo	16	0.50 (-13.80, 14.79)
	DHA	18			
Pooled Random Effects Estimate*					5.12 (-1.02, 11.25)

*Chi-squared test of heterogeneity p-value = 0.62

Table 3.6. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on LDL among people with type II diabetes.

		Methodological Quality							
		A	B			C			
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**	**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	-3.86 (-22.97, 15.25)	Morgan[61]	40	8.11	(-19.46, 35.67)
			Morgan[67]	13	8.00 (-52.53, 68.53)	Rivallese[69]	16	-0.39	(-47.31, 46.54)
				12	23.00 (-31.39, 77.39)				
			Petersen[63]	42	21.62 (2.79, 40.45)	Sarkkinen[70]	31	-10.04	(-37.38, 17.30)
	II		Chan[58]	25	-5.79 (-20.88, 9.29)	Annuzzi[57]	8	23.17	(-9.22, 55.56)
				24	11.97 (-4.51, 28.45)				
			Woodman[72]	51	0.50 (-13.80, 14.79)	Dunstan[59]	24	5.02	(-21.44, 31.48)
							25	19.31	(-6.81, 45.42)
	III								

Figure 3.4. Diabetes: low density lipoprotein (LDL).



Diabetes: Triglycerides

Overall effect. We identified 33 studies that evaluated the effect to of omega-3 fatty acids on triglycerides in type II diabetics.[56-72, 74-83, 86-91] Among these, 14 contained sufficient data to be included in a meta-analysis. (Table 3.7) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for triglycerides is -31.61 mg/dl (95% CI, -49.58, -13.64) (Table 3.7 and Figure 3.5). Although a large number of the studies identified were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. None of the studies evaluated the differential effects of omega-3 fatty acids on distinct subpopulations. There were insufficient data to perform pooled analyses on subpopulations across studies.

Covariates. One study[58] assessed the effects of fish oil alone, atorvastatin alone and combined fish oil and atorvastatin. Fish oil alone, atorvastatin alone and combined fish oil and atorvastatin reduced triglycerides significantly relative to placebo. The reduction for combined atorvastatin and fish oil was greater that for either drug alone, although statistical testing was not reported.

One study assessed the independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control.[93] There was a significant reduction in triglycerides and an increase in glycosylated hemoglobin with a diet high in fish. With combined moderate exercise and the fish diet, reduction in triglycerides was maintained and glycosylated hemoglobin did not increase.

Effects of dose, source, and exposure duration. None of the studies specifically assessed the effects of dose, source, or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect. On stratified analysis of source, the pooled random effects estimates of the mean difference between omega-3 fatty acids and placebo, for studies using a fish-oil and studies using a plant source, respectively, were –35.93 mg/dl (95% CI, -56.02, -15.83) and –12.08 (95% CI, -56.90, 32.73).

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that were included in the meta-analysis, none had both an applicability rating of I (representative of general adult population with type II diabetes), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.8). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies that assessed the effect of omega-3 fatty acids among children with type II diabetes were identified.

Table 3.7. Diabetes: mean difference for triglycerides.

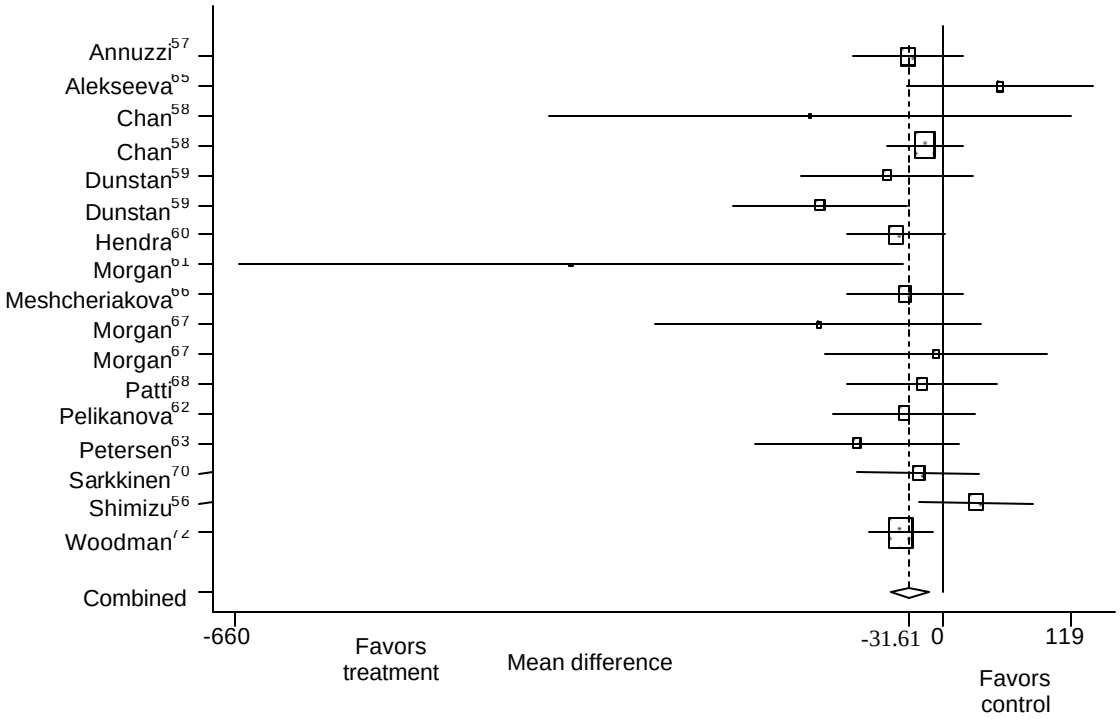
	Intervention		Control		Mean Difference (mg/dl) (95% CI)	
Trial	**Source**	**n**	**Source**	**n**		
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	-32.74	(-84.25, 18.77)
Alekseeva[65]	Linseed oil	30	Placebo	30	53.10	(-33.54, 139.74)
Chan[58]	Omacor	12	Placebo	13	-123.89	(-366.93, 119.14)
	Omacor/Atorvastatin	11	Atorvastatin	13	-17.70	(-52.99, 17.59)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	-115.04	(-195.84, -34.24)
	Fish oil/moderate exercise	14	Placebo	11	-53.10	(-132.84, 26.65)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	-44.25	(-89.80, 1.31)
Meshcheriakova[66]	Linseed oil/Eiconol	60	Low-fat/Low sodium diet	60	-35.40	(-88.83, 18.03)
Morgan[61]	Fish oil	10	Placebo	10	-346.90	(-656.00, -37.81)
	Fish oil	10	Placebo	10		
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-116.00	(-267.44, 35.44)
	High dosage Fish oil	6	Placebo	6	-7.00	(-110.19, 96.19)
Patti[68]	Fish oil	8	Placebo	8	-19.47	(-89.24, 50.30)
Pelikanova[62]	Fish oil	10	Placebo	10	-36.28	(-101.90, 29.33)
Petersen[63]	Futura 1000 (fish oil)	20	Placebo	22	-80.53	(-175.69, 14.63)
Sarkkinen[70]	Rapeseed (LEAR) oil	17	Sunflower oil	14	-23.01	(-80.05, 34.03)
Shimizu[56]	EPA-E	29	Placebo	16	30.40	(-23.37, 84.17)
Woodman[72]	EPA	17	Placebo	16	-39.52	(-68.98, -10.06)
	DHA	18				
Pooled Random Effects Estimate*					-31.61	(-49.58, -13.64)

*Chi-squared test of heterogeneity p-value = 0.16

Table 3.8. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on triglycerides among people with type II diabetes.

Methodological Quality										
		A	B				C			
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	-44.25	(-89.80, 1.31)	Shimizu[56]	45	30.40	(-23.37, 84.17)
			Morgan[67]	13	-116.00	(-267.44, 35.44)	Morgan[61]	40	-346.90	(-656.00, -37.81)
				12	-7.00	(-110.19, 96.19)				
			Petersen[63]	42	-80.53	(-175.69, 14.63)	Patti[68]	14	-19.47	(-89.24, 50.30)
							Sarkkinen[70]	31	-23.01	(-80.05, 34.03)
	II		Chan[58]	25	-123.89	(-366.93, 119.14)	Annuzzi[57]	8	-32.74	(-84.25, 18.77)
				24	-17.70	(-42.99, 17.59)				
			Woodman[72]	51	-39.52	(-68.98, -10.06)	Dunstan[59]	24	-115.04	(-195.84, -34.24)
								25	-53.10	(-132.84, 26.65)
							Pelikanova[62]	20	-36.28	(-101.90, 29.33)
	III									

Figure 3.5. Diabetes: triglycerides.



Diabetes: Insulin Sensitivity/Glycemic Control

Overall effect. We identified 3 studies that evaluated the effect to of omega-3 fatty acids on plasma insulin in type II diabetics,[57, 82, 93] and 1 that evaluated this effect in the metabolic syndrome.[92] We did not perform meta-analysis because the outcomes used for measuring plasma insulin in these studies were sufficiently different to preclude pooling across studies.

In one study among type II diabetics, glucose-stimulated plasma insulin response during a hyperglycemic clamp was not influenced by fish oil.[57] In the second study, there was no effect on fasting serum insulin or insulin as measured by area under the curve during a fasting glucose tolerance test.[93] In the third study, there was no difference in insulin suppression of hepatic glucose production or in insulin stimulation of whole-body glucose disposal measured by the euglycemic-hyperinsulinemic clamp.[82]

In the study of metabolic syndrome, fish oil had no effect on insulin resistance estimated by Homeostatic Model Assessment.[92]

We identified 26 studies that evaluated the effect of omega-3 fatty acids on fasting blood sugar in type II diabetics.[57, 59-61, 63-65,67-72, 75-83,86,87, 89-91] Among these, 9 contained sufficient data to be included in a meta-analysis. (Table 3.9) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for fasting blood sugar is 5.87 mg/dl (95% CI, -0.15, 11.88) (Table 3.9 and Figure 3.6). Although a large number of the studies identified with this outcome were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

We identified 23 studies that evaluated the effect of omega-3 fatty acids on glycosylated hemoglobin in type II diabetics.[56,57, 61-64, 67-69, 71,72,74-76, 78,79, 80-83, 86,87,90,91] Among these 8 contained sufficient data to be included in a meta-analysis. (Table 3.11) The pooled random effects estimate of the mean difference between omega-3 fatty acids and placebo for glycosylated hemoglobin is 0.21 (%) (95% CI, -0.01, 0.44) (Table 3.11 and Figure 3.12). Although a large number of the studies identified with this outcome were not included in this meta-analysis, the results presented here are consistent with the results of another meta-analysis,[116] that included a number of the studies that were excluded here.

Sub-populations. The effects of omega-3 fatty acids on insulin were assessed in type II diabetes and metabolic syndrome.

Covariates. One study assessed the effects of fish oil alone, atorvastatin alone and combined fish oil and atorvastatin.[92] There were increases in HOMA scores with fish oil alone, atorvastatin alone and combined fish oil and atorvastatin relative to placebo, though none were significant. Statistical testing was not reported, except the comparisons with placebo.

One study assessed the independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control.[93] There was a significant reduction in triglycerides and an increase in glycosylated hemoglobin with fish diet. With a combination of moderate exercise and fish diet, reduction in triglycerides was maintained and glycosylated hemoglobin did not increase.

Effects of dose, source, and exposure duration. None of the studies specifically assessed the effects of dose, source, or exposure duration. A pooled analysis of dose effect using meta-regression revealed no significant dose effect on fasting blood glucose or glycosylated hemoglobin. No studies were identified that assessed the effects of omega-3 fatty acids from a plant source on insulin sensitivity or glycemic control.

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Among studies that were included in the meta-analysis for fasting blood glucose and glycosylated hemoglobin, none had both an applicability rating of I (representative of general adult population with type II diabetes), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Tables 3.10 and 3.12). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with type II diabetes. Of note, no studies that assessed the effect of omega-3 fatty acids among children with type II diabetes were identified.

Table 3.9. Diabetes: mean difference of fasting blood glucose.

	Intervention		Control		Mean Difference
Trial	**Source**	**n**	**Source**	**n**	**(mg/dl) (95% CI)**
Annuzzi[57]	Max EPA (Fish oil)	4	Placebo	4	-7.93 (-66.18, 50.32)
Alekseeva[65]	Linseed oil	30	Placebo	30	9.01 (-24.30, 42.32)
Dunstan[59]	Fish oil/light exercise	12	Placebo	12	9.01 (-33.00, 51.02)
	Fish oil/mod. exercise	14	Placebo	11	3.60 (-37.85, 45.06)
Hendra[60]	Max EPA (fish oil)	40	Placebo	40	21.62 (-18.06, 61.3)
Morgan[61]	Fish oil	10	Placebo	10	-14.41 (-52.95, 24.12)
	Fish oil	10	Placebo	10	
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-41.00 (-114.16, 32.16)
	High dosage Fish oil	6	Placebo	6	-17.00 (-89.43, 55.43)
Patti[68]	Fish oil	8	Placebo	8	10.81 (-28.67, 50.29)
Sirtori[64]	Esepent (fish oil)	203	Placebo	211	4.30 (-2.82, 11.42)
Woodman[72]	EPA	17	Placebo	16	19.81 (2.25, 37.37)
	DHA	18			
Pooled Random Effects Estimate*					5.87 (-0.15, 11.88)

*Chi-squared test of heterogeneity p-value = 0.76

Table 3.10. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on fasting blood sugar among people with type II diabetes.

Methodological Quality										
		A	B				C			
Applicability	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Hendra[60]	80	21.62	(-18.06, 61.30)	Morgan[61]	40	-14.41	(-52.95, 24.12)
			Morgan[67]	13	-41.00	(-114.16, 32.16)	Patti[68]	16	10.81	(-28.67, 50.29)
				12	-17.00	(-89.43, 55.43)				
			Sirtori[64]	414	4.30	(-2.82, 11.42)				
	II		Woodman[72]	51	19.81	(2.25, 37.37)	Annuzzi[57]	8	-7.93	(-66.18, 50.32)
							Dunstan[59]	24	9.01	(-33.00, 51.02)
								25	3.60	(-37.85, 45.06)
	III									

Figure 3.6. Diabetes: fasting blood glucose.

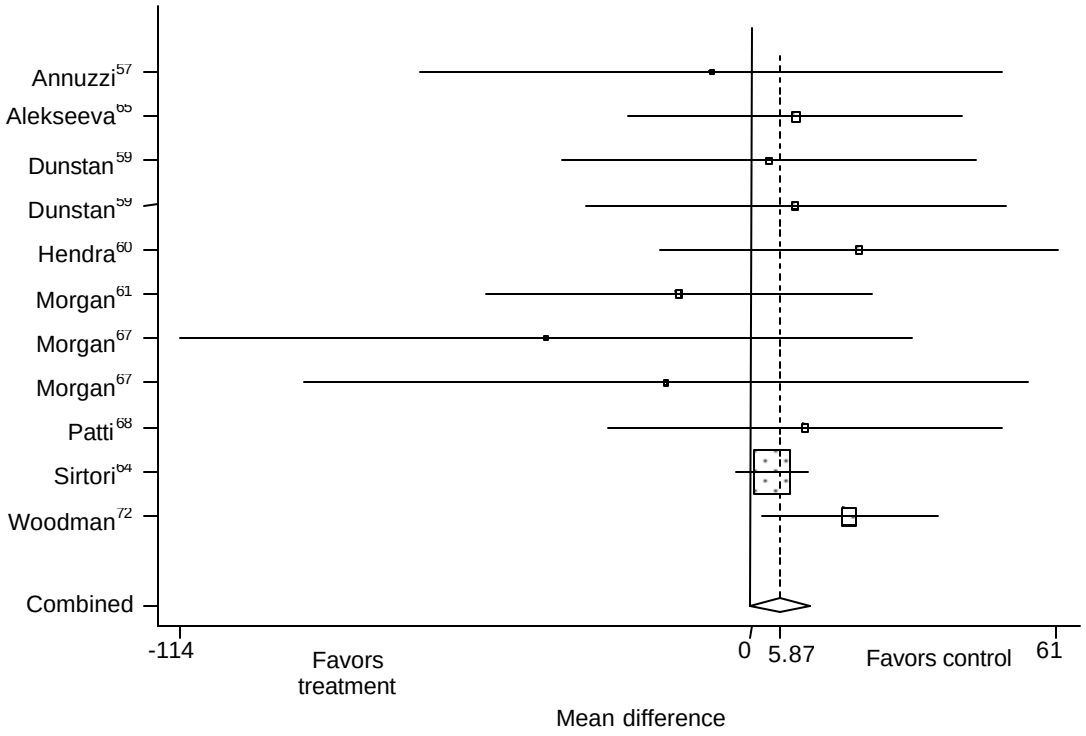


Table 3.11. Diabetes: effect size of hemoglobin A1c (HbA1c).

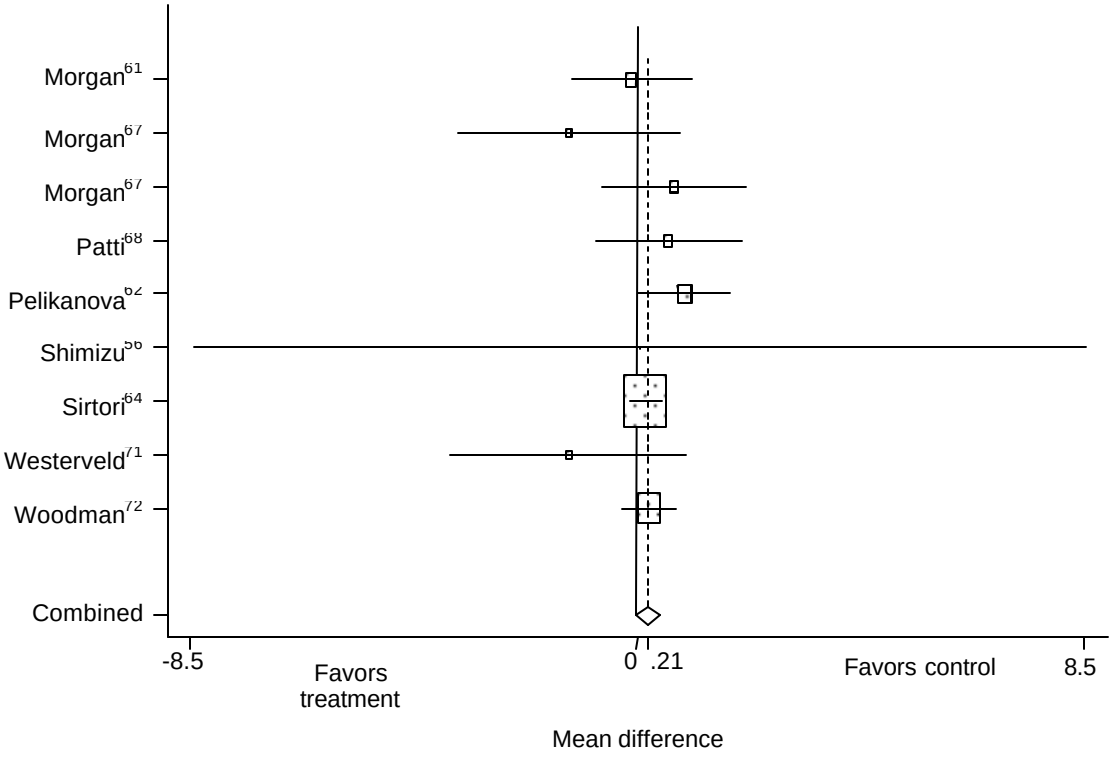
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**(%) (95% CI)**
Morgan[61]	Fish oil	10	Placebo	10	-0.10 (-1.25, 1.05)
	Fish oil	10	Placebo	10	
Morgan[67]	Low dosage Fish oil	7	Placebo	6	-1.30 (-3.42, 0.82)
	High dosage Fish oil	6	Placebo	6	0.70 (-0.68, 2.08)
Patti[68]	Fish oil	8	Placebo	8	0.60 (-0.79, 1.99)
Pelikanova[62]	Fish oil	10	Placebo	10	0.90 (0.02, 1.78)
Shimizu[56]	EPA-E	29	Placebo	16	0.06 (-8.44, 8.56)
Sirtori[64]	Esepent (fish oil)	203	Placebo	211	0.17 (-0.12, 0.46)
Westerveld[71]	EPA-E	8	Placebo	8	-1.30 (-3.55, 0.95)
	EPA-E	8			
Woodman[72]	EPA	17	Placebo	16	0.23 (-0.28, 0.75)
	DHA	18			
Pooled Random Effects Estimate*					0.21 (-0.01, 0.44)

*Chi-squared test of heterogeneity p-value = 0.52

Table 3.12. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on glycosylated hemoglobin among people with type II diabetes.

Methodological Quality										
Applicability		A	B				C			
	I		**Study**	**n**	**Mean difference (95% CI)**		**Study**	**n**	**Mean difference (95% CI)**	
			Morgan[67]	13	-1.30	(-3.42, 0.82)	Morgan[61]	40	-0.10	(-1.25, 1.05)
				12	0.70	(-0.68, 2.08)				
			Sirtori[64]	414	0.17	(-0.12, 0.46)	Patti[68]	16	0.60	(-0.79, 1.99)
			Westerveld [71]	24	1.30	(-3.55, 0.95)				
	II		Woodman[72]	51	0.23	(-0.28, 0.75)	Pelikanova[62]	20	0.90	(0.02, 1.78)
	III									

Figure 3.7. Diabetes: hemoglobin A1$_c$ (HgA1$_c$).



INFLAMMATORY BOWEL DISEASE

Summaries of all inflammatory bowel disease studies that were evaluated can be found in appendix C.2.

Inflammatory Bowel Disease: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following outcomes was assessed: clinical score, sigmoidoscopic score, histologic score, induced remission and relapse. In total, 13 studies described in 14 reports were identified that reported these outcomes. All outcomes were assessed separately for ulcerative colitis and Crohn's disease. There were sufficient data to perform meta-analysis only for relapse and only for ulcerative colitis. Clinical score was described for ulcerative colitis in 5 studies; two reported no effect[39, 52] and three reported statistically significant improvement with omega-3 fatty acids.[44, 46, 94] Clinical score was described for Crohn's disease in only 1 study, which reported no effect.[52]

Sigmoidoscopic score was reported for ulcerative colitis in 3 studies,[44, 52, 94] each of which reported a statistically significant improvement with omega-3 fatty acids. Sigmoidoscopic score was reported for Crohn's disease in 1 study,[52] which showed a statistically significant improvement with omega-3 fatty acids. Histologic score was reported for ulcerative colitis in 3 studies; 2 reported no effect[42, 46] and 1 statistically significant improvement.[44] Histologic score was not reported in any of the studies of Crohn's disease.

Induction of remission was reported for ulcerative colitis in 2 studies,[44, 95] both of which showed improvement with omega-3 fatty acids. However, neither was statistically significant, and in one study,[44] comparable data for the placebo group was not reported. Induction of remission was not reported in the studies of Crohn's disease.

Relapse was described for ulcerative colitis in 5 studies, 3 of which could be used for meta-analysis. Among these studies, 1 reported a lower relapse rate with omega-3 fatty acids than with placebo,[42] 2 found no difference and 2 reported an increased rate of relapse.[39, 43] However, the results were not statistically significant in any of these studies. The pooled random effect estimate of the risk of relapse for omega-3 fatty acids relative to placebo for ulcerative colitis was 1.13 (95% CI: 0.81, 1.57) (Table 3.13, Figure 3.7). The data yield an average control group risk of 38% (all studies weighted equally). Combining these yields a NNH of 21. So the number of patients needed to treat on average to result in one relapse is 21. Among the studies not included in the meta-analysis, one reported a lower relapse rate and one reported a higher relapse rate with omega-3 fatty acids.

Relapse was described for Crohn's disease in two studies; one reported a significantly lower relapse rate with omega-3 fatty acids than with placebo.[54]

Sub-populations. Among the 13 studies identified, the study sample was restricted to patients with ulcerative colitis in 10[39-44, 46, 53, 94, 95] and to Crohn's disease in two;[54, 55] one study included both patients with ulcerative colitis and those with Crohn's disease and reported data separately for each disease.[52] In this study, the effect of omega-3 fatty acids on clinical score was the same for subjects with ulcerative colitis and Crohn's disease (no effect). The effect on histologic score was also the same; however the improvement reached statistical significance only when diseases were pooled.

Covariates. Reported covariates included use of other drugs, previous surgery and presence of fistulae. However, no comparisons of the effects of covariates on outcomes were identified.

Effects of dose, source, and exposure duration. All studies identified used fish oil as the source of omega-3 fatty acids. No studies compared the effect of different doses of omega-3 fatty acids. There were too few studies that assessed the effects of any single outcome to perform a pooled analysis of dose effect.

Of note, one study administered the fish oil via an enteric-coated capsule, which was designed to deliver the omega-3 fatty acids to the small bowel. [54] This study, which included only patients with Crohn's disease, demonstrated a reduced relapse rate relative to placebo.

Duration of exposure varied from 2 to 24 months across the studies. Too few studies assessed any single outcome across similar time periods to analyze the effect of duration of exposure.

Sustainment of effect. Sustainment of the assessed effects was not evaluated in any of the studies.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general population with IBD) and a summary quality score of A (Jadad score = 5 with concealment of allocation). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with IBD. Of note, no studies that assessed the effect of omega-3 fatty acids among children with IBD were identified.

Table 3.13. Ulcerative colitis disease: relative risk of relapse.

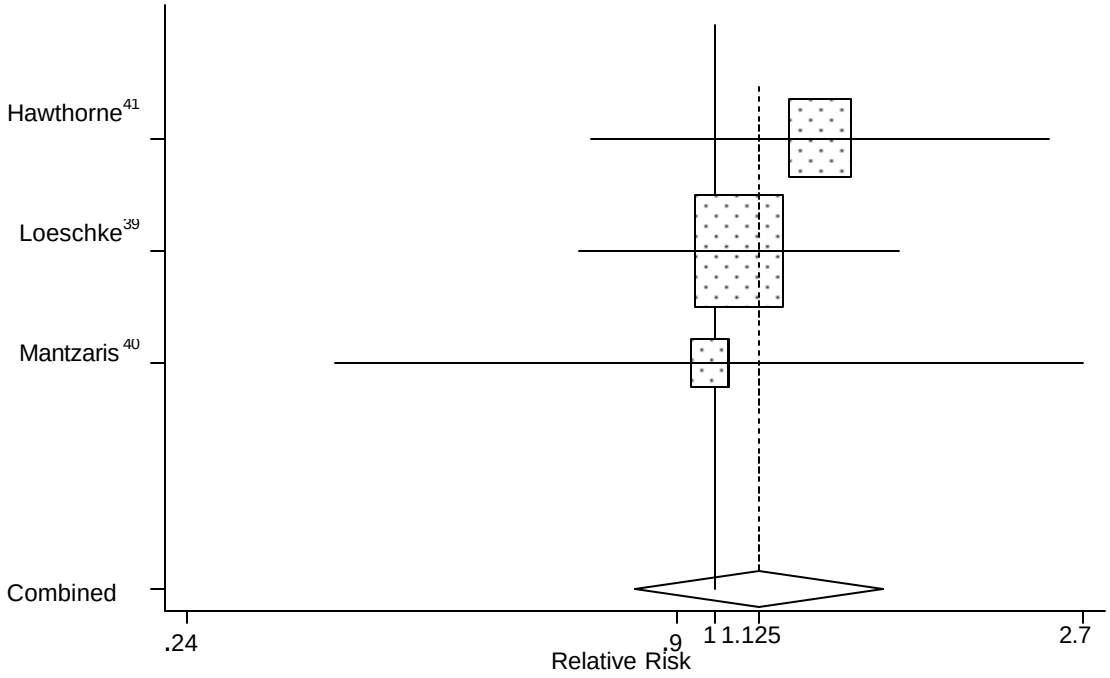
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Relative Risk (95% CI)**
Hawthorne[41]	Hi EPA	35	Placebo	34	1.32 (0.71, 2.46)
Loeschke[39]	Fish oil	31	Placebo	33	1.06 (0.69, 1.64)
Mantzaris[40]	Max EPA (fish oil)	22	Placebo	18	0.98 (0.36, 2.70)
Pooled Random Effects Estimate*					1.13 (0.81, 1.57)

*Chi-squared test of heterogeneity p-value = 0.82

Table 3.14. Relationship between methodological quality and applicability for estimates of effect of omega-3 fatty acid consumption with ulcerative colitis disease for relapse/remission.

Methodological Quality					
		A	B		C
Applicability	I		**Study** **n** **Relative Risk (95%, CI)**		
			Loeschke[39] 64 1.06 (0.69, 1.64)		
			Mantzaris[40] 40 0.98 (0.36, 2.70)		
	II				
	III		Hawthorne[96] 69 1.32 (0.71, 2.46)		

Figure 3.8. Ulcerative colitis disease: relative risk of relapse.



Inflammatory Bowel Disease: Effect on Requirement for Steroids/Other Immunosuppressive Drugs

Overall effect. We identified only 2 studies that assessed the effect of omega-3 fatty acids on requirements for corticosteroids or other immunosuppressive agents, both of which assessed the effect on corticosteroid requirement.[44, 53] Both of these studies found a reduced requirement for corticosteroids with omega-3 fatty acid treatment relative to placebo, but the differences were not statistically significant. Sustainment of effect after discontinuation of the omega-3 fatty acids was not assessed.

We found no data on the effect of omega-3 fatty acids on requirements for steroids and other immunosuppressive drugs for different subpopulations, doses, exposures and sources.

RHEUMATOID ARTHRITIS

Summaries of all rheumatoid arthritis studies we evaluated can be found in Appendix C.3.

Rheumatoid Arthritis: Pain

Overall effect. The effect of omega-3 fatty acids on patient-assessed pain in rheumatoid arthritis was described in 19 studies, 9 of which could be used for meta-analysis. Among these studies, 3 reported significant improvement relative to placebo,[17, 29, 34] and 4 reported significant improvement from baseline.[16, 21, 26, 30] There were no significant effects in twelve studies.[18, 19, 22-25, 28, 31-33, 35, 38] The pooled random estimate of effect size for the effect of omega-3 fatty acids on pain relative to placebo is -0.19 (95% CI, -0.43, 0.06) (Table 3.15, Figure 3.8). An effect size of 1.0 is equivalent to 2.72 cm units on the Visual Analogue Scale. Hence, an effect size of -0.19 translates to a 0.52 cm decrease on the visual analog scale. Of note, among the 10 studies that were not included in the meta-analysis, 8 did not demonstrate a significant effect from omega-3 fatty acids, and 2 did demonstrate such an effect.[29, 34]

Sub-populations. None of the studies assessed the effects of omega-3 fatty acids on different subpopulations of patients with RA.

Covariates. One study assessed the effect of different diets (Western versus modified lacto-vegetarian) combined with omega-3 fatty acids on pain in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in pain among patients on a modified lacto-vegetarian diet relative to a Western diet ($P<0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, the effect of fish oil on pain did not differ among doses. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

In 1 study, plants were the source of omega-3 fatty acids. In this study[23] the effect size for omega-3 fatty acids for pain was -0.21 (95% CI, -1.04, 0.63). Restricting the pooled analysis to

the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for pain is unchanged at –0.19 (95% CI, -0.46, 0.09).

Only 1 study assessed the effects of different durations of exposure on outcomes in RA.[19] In this study, there was no effect on pain at 24 and 36 weeks, although statistical testing of the effect between these time points was not performed. There were insufficient data across studies to perform a pooled analysis of exposure duration effect.

Sustainment of effect. Two studies assessed the sustainment of effects of omega-3 fatty acids on outcomes in RA.[18, 28] In 1 study, pain worsened in a fish oil-treated arm 3 months after discontinuation of the fish oil ($p<0.05$). In the other study, 100% of the control arm (evening primrose oil) and 80% of the fish oil group "returned to baseline or became worse." Although pain, joint swelling, and acute phase reactants were assessed in this study, the parameters on which this assessment was made were not specified. There were insufficient data across studies to perform a pooled analysis of sustainment of effect.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.16). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on pain among children with Juvenile RA (JRA) were identified.

Table 3.15. RA: effect size for patient assessment of pain.

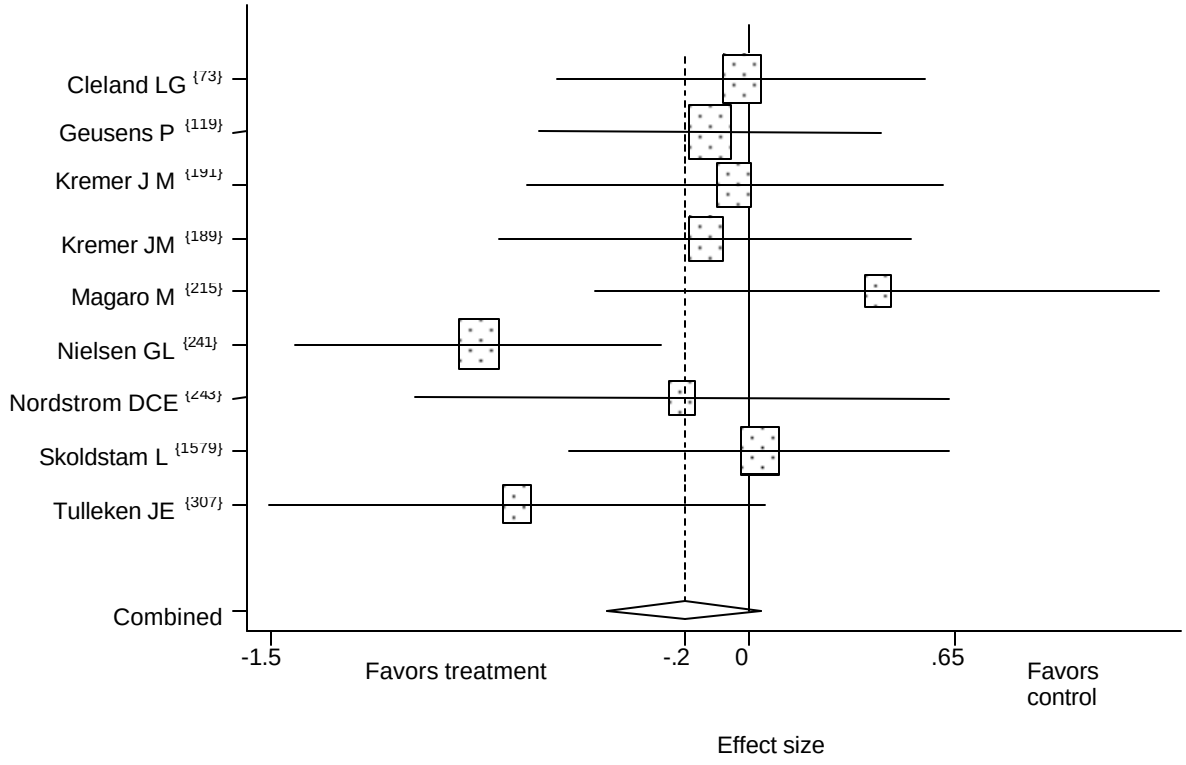
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	-0.02 (-0.60, 0.56)
Geusens[17]	Fish oil	21	Placebo	20	-0.04 (-0.57, 0.50)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.04 (-0.69, 0.61)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.13 (-0.78, 0.51)
Magaro[21]	Max EPA (fish oil)	10	Placebo	10	0.41 (-0.48, 1.29)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	-0.85 (-1.42, -0.27)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	-0.21 (-1.04, 0.63)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.04 (-0.56, 0.63)
Tulleken[24]	Fish oil	13	Placebo	14	-0.72 (-1.5, 0.06)
Pooled Random Effects Estimate*					-0.19 (-0.43, 0.06)

*Chi-squared test of heterogeneity p-value = 0.23

Table 3.16. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on pain among people with rheumatoid arthritis.

Methodological Quality										
		A	B				C			
Applicability	I		**Study**	**n**	**Effect Size(95% CI)**		**Study**	**n**	**Effect Size(95% CI)**	
			Cleland[16]	46	-0.02	(-0.60, 0.56)	Kremer[19]	49	-0.04	(-0.69, 0.61)
			Geusens[17]	60	-0.04	(-0.57, 0.50)				
			Kremer[18]	37	-0.13	(-0.78, 0.51)				
			Skoldstam[25]	43	0.04	(-0.56, 0.63)				
	II		Tulleken[24]	27	-0.72	(-1.5, 0.06)	Magaro[21]	20	0.41	(-0.48, 1.29)
	III									

Figure 3.9. RA: patient assessment of pain.



Rheumatoid Arthritis: Swollen Joints

Overall effect. The effect of omega-3 fatty acids on swollen joint count in RA was described in 15 studies, 6 of which could be included in meta-analysis. Among these studies, 2 reported significant improvement relative to placebo[29, 33] and 4 reported significant improvement from baseline.[19, 25, 26, 30] There were no significant effects in 9 studies.[18, 22-24, 28, 31, 35, 38] In one study, swollen joint count was significantly worse with omega-3 treatment relative to placebo.[16] The pooled random effect estimate for the effect of omega-3 fatty acids on swollen joint count relative to placebo is -0.13 (95% CI, -0.35, 0.08 (Table 3.17, Figure 3.9). In this analysis, an effect size of 1.0 is equivalent to 3.21 swollen joints. So an effect size of –0.13 is equivalent to a reduction in the swollen joint count by 0.42 joints. Among the 9 studies that were excluded from meta-analysis, 2 reported statistically significant improvements with omega-3 fatty acids and 7 did not. Among the 2 that reported significant improvements, one[29] was of poor methodologic quality (Jadad score =1, concealment of allocation not reported) and the other, [33] although of good methodologic quality (Jadad score = 4, concealment of allocation not reported) was a cross-over study and did not include a wash-out period.

The effect of omega-3 fatty acids on swollen joints in rheumatoid arthritis has also been assessed in a previously published meta-analysis. [97] This meta-analysis reported improvement favoring fish oil over placebo that was not statistically significant (estimate not reported).

Sub-populations. No studies assessed the effect on specific subpopulations.

Covariates. One study assessed the effect of two different diets (Western versus modified lacto-vegetarian) combined with omega-3 fatty acids on joint swelling in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in the number of swollen joints among patients on a modified lacto-vegetarian diet relative to a Western diet ($p < 0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of two different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, there was a significant improvement in the number of swollen joints at 24 and 36 weeks relative to baseline for subjects treated with a lower dose of fish oil. Among patients treated with a higher dose of fish oil, the improvement relative to baseline was significant only at 24 weeks. There were insufficient data across studies to perform a pooled analysis of dose effect.

In one study, plants were the source of omega-3 fatty acids. In this study[23] the effect size of omega-3 fatty acids for swollen joints was -0.06 (95% CI, -0.90, 0.77). Restricting the pooled analysis to the remaining studies, which a fish source, the pooled random effects estimate of the effect size for swollen joints unchanged at –0.14 (95% CI, -0.36, 0.09).

Sustainment of effect. Two studies assessed the sustainment of effects of omega-3 fatty acids on outcomes in RA.[18, 28] In one study, there was no change in swollen joint count in a fish oil-treated arm 1-2 months after discontinuation of the fish oil ($p<0.05$). In the other study, 100% of the control arm (evening primrose oil) and 80% of the fish oil group "returned to baseline or became worse." Although pain, joint swelling, and acute phase reactants were assessed in this study, the parameters on which this assessment was made were not specified. There were insufficient data across studies to perform a pooled analysis of sustainment of effect.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.18). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on swollen joints among children with JRA were identified.

Table 3.17. RA: effect size for swollen joint count.

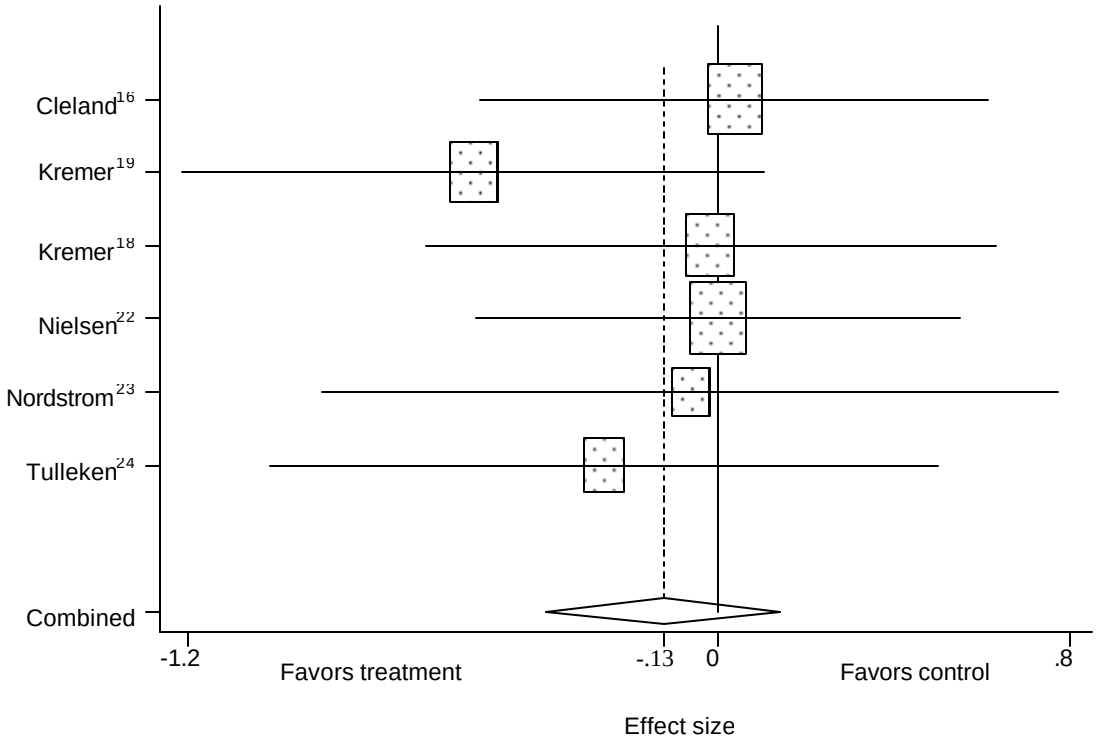
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Cleland[16]	Max EPA (fish oil)	23	Placebo	23	0.04 (-0.54, 0.62)
Kremer[19]	Fish oil	20	Placebo	12	-0.63 (-1.30, 0.03)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.02 (-0.66, 0.63)
Magalish[20]	Omega-3 fatty acid (source not specified)	65	Placebo	47	-0.13 (-0.51, 0.25)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	0.00 (-0.55, 0.55)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	-0.06 (-0.90, 0.77)
Tulleken[24]	Fish oil	13	Placebo	14	-0.26 (-1.02, 0.50)
Pooled Random Effects Estimate					-0.13 (-0.35, 0.08)

*Chi-squared test of heterogeneity p-value = 0.81

Table 3.18. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on swollen joints among people with rheumatoid arthritis.

		Methodological Quality								
		A	B				C			
Applicability	I		**Study**	**n**	**Effect Size (95% CI)**		**Study**	**n**	**Effect Size (95% CI)**	
			Cleland[16]	46	0.04	(-0.54, 0.62)	Kremer[19]	49	-0.63	(-1.30, 0.03)
			Kremer[18]	37	-0.02	(-0.66, 0.63)				
	II		Tulleken[24]	27	-0.26	(-1.02, 0.50)				
	III									

Figure 3.10. RA: swollen joint count.



Rheumatoid Arthritis: Disease Activity (Erythrocyte Sedimentation Rate)

Overall effect. The effect of omega-3 fatty acids on disease activity (Erythrocyte Sedimentation Rate [ESR]) in rheumatoid arthritis was described in 16 studies, 6 of which could be used for meta-analysis. Among these studies, 1 (in which the population had JRA) reported significant improvement relative to placebo[27] and 1 reported significant improvement from baseline.[21] There were no significant effects in 13 studies. [16, 18, 19, 22-24, 25, 28, 29, 32-35, 38] The pooled random effect estimate for the effect of omega-3 fatty acids on ESR relative to placebo is -0.32 (95% CI, -0.83, 0.19) (Table 3.19, Figure 3.10). In this analysis and effect size of 1.0 is equivalent to 23.79 mm/hr. So, an effect size of –0.32 is equivalent to a reduction in ESR by 7.6 mm/hr. Among the studies excluded from the meta-analysis, one reported a benefit for omega-3 relative to placebo, but in a special population, JRA; none of the remaining studies reported a significant benefit relative to placebo.

Of note, there was significant heterogeneity among these studies (chi-squared test of heterogeneity =0.01). Visual inspection of the Forest plot identified one outlier study.[24] With this study removed from the pooled analysis, the pooled random effects estimate for the effect of omega-3 fatty acids on ESR relative to placebo is -0.07 (95% CI, -0.37, 0.23), and the chi-squared test for heterogeneity is not significant ($p = .77$). The outlier study is similar to the other studies in the pooled analysis in terms of study design, source, dose, and duration of omega-3 fatty acid treatment. The characteristics of the study population in the outlier study are also similar to those of the other studies in the pooled analysis in terms of age, disease duration, number of swollen joints, and number of tender joints. However, the baseline ESR and C-Reactive Protein (CRP) values for the control group in the outlier study were significantly higher than for the experimental group ($p<0.05$). This observation suggests that the disease activity may have been higher in the control group than in the experimental group, which could bias toward a more favorable estimate of the effect of omega-3 fatty acids.

The effect of omega-3 fatty acids on ESR in rheumatoid arthritis has also been assessed in a previously published meta-analysis. [97] This meta-analysis reported improvement with fish oil relative to placebo; however, this improvement was not statistically significant (estimate not reported).

Sub-populations. One study assessed the effect of cod liver oil on ESR among children with JRA. This study demonstrated a significant reduction in ESR for cod liver oil relative to placebo.[27]

Covariates. The effect of covariates on the efficacy of omega-3 fatty acids was not specifically assessed in any of the studies identified.

Effects of dose, source, and exposure duration. One study assessed the effect of two different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, there was a significant improvement in ESR at 24 and 36 weeks relative to baseline for subjects treated with a lower dose of fish oil. Among patients treated with a higher dose of fish oil, the improvement relative to baseline was significant only at 24 weeks. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

In one study, plants were the source of omega-3 fatty acids. In this study,[23] the effect size of omega-3 fatty acids for ESR was 0.13 (95% CI, -0.71, 0.96). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for ESR was –0.41 (95% CI, -0.99, 0.18).

Sustainment of effect. The sustainment of effects of omega-3 fatty acids on ESR or CRP in RA was not clearly described in any studies. In one study,[28] 100% of the control arm (evening primrose oil) and 80% of the fish oil group "returned to baseline or became worse." Although pain, joint swelling, and ESR were assessed in this study, the parameters on which this assessment was made were not specified.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.20). Similarly, there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, one study that assessed the effect of omega-3 fatty acids on ESR among children with JRA was identified.

Table 3.19. RA: effect size for ESR.

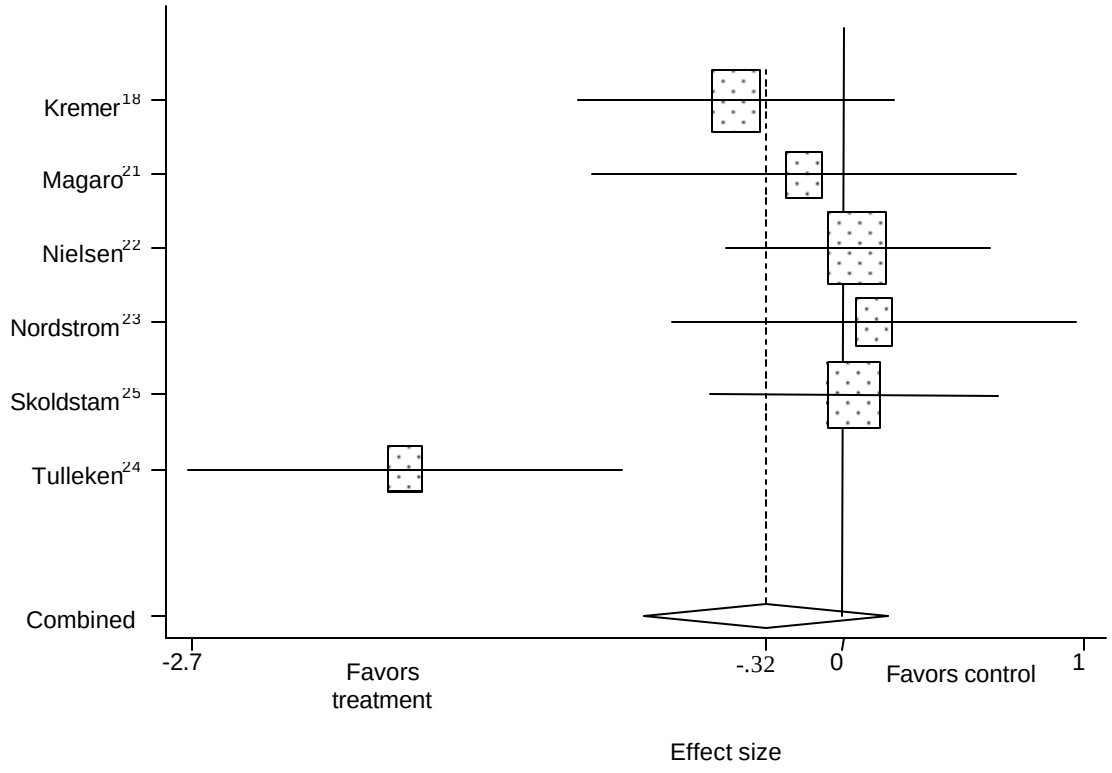
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.44 (-1.1, 0.21)
Magaro[21]	Max EPA (fish oil)	10	Placebo	10	-0.16 (-1.04, 0.72)
Nielsen[22]	Pikasol (fish oil)	27	Placebo	24	0.06 (-0.49, 0.61)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	0.13 (-0.71, 0.96)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.04 (-0.55, 0.64)
Tulleken[24]	Fish oil	13	Placebo	14	-1.82 (-2.71, -0.92)
Pooled Random Effects Estimate					-0.32 (-0.83, 0.19)

*Chi-squared test of heterogeneity p-value = 0.01

Table 3.20. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on ESR among people with rheumatoid arthritis.

Methodological Quality									
		A	B				C		
Applicability	I		**Study**	**n**	**Effect Size(95% CI)**		**Study**	**n**	**Effect Size(95% CI)**
			Kremer[18]	37	-0.44	(-1.10, 0.21)			
			Skoldstam[25]	43	0.04	(-0.55, 0.64)			
	II		Tulleken[24]	27	-1.82	(-2.71, -0.92)	Magaro[21]	20	-0.16 (-1.04, 0.72)
	III								

Figure 3.11. RA: ESR.



Rheumatoid Arthritis: Patient's Global Assessment

Overall effect. The effect of omega-3 fatty acids on patient's global assessment in RA was described in 8 studies, 5 of which could be used for meta-analysis. Among these studies, 1 reported significant improvement relative to placebo,[17] and 3 reported significant improvement from baseline.[25, 26, 30] There were no significant effects in 4 studies.[16, 18, 19, 31] The pooled random effect estimate for the effect of omega-3 fatty acids on patient's global assessment relative to placebo is -0.30 (95% CI, -0.90, 0.30) (Table 3.21, Figure 3.11). In this analysis, an effect size of 1.0 is equivalent to 0.7 units on the patient global assessment scale. So, an effect size of –0.30 is equivalent to a decrease on the scale by 0.21 units. None of the studies that were excluded from the meta-analysis demonstrated a significant of omega-3 fatty acids on patient's global assessment.

Of note, there was significant heterogeneity among these studies (chi-squared test of heterogeneity =0.002). Visual inspection of the Forest plot identified one outlier study.[17] With this study removed from the pooled analysis, the pooled random effect estimate for the effect of omega-3 fatty acids on patient global assessment relative to placebo is -0.02 (95% CI, -0.36, 0.31) and the chi-squared test for heterogeneity is not significant (p = .76). On qualitative review of the outlier study, we could find no characteristics that differed from the other studies. The outlier study is similar to the other studies in the pooled analysis in terms of study design, source, and dose of omega-3 fatty acid. The characteristics of the study population in the outlier study are similar to those of the other studies in the pooled analysis in terms of age, disease duration, number of swollen joints, and number of tender joints. Although the study duration is longer (12 months) in the outlier study than in the other studies (3-9 months), a common time point for assessment (3 months) was used in the pooled analysis.

The effect of omega-3 fatty acids on patient's global assessments in RA has also been assessed in a previously published meta-analysis.[97] This meta-analysis reported improvement with fish oil relative to placebo; however, this improvement was not statistically significant (estimate not reported).

Sub-populations. No studies assessed the effects across sub-populations.

Covariates. One study assessed the effect of combining different diets (Western versus modified lacto-vegetarian) with omega-3 fatty acids on patient's global assessment in RA.[26] In this study, among subjects treated with fish oil, there was a reduction in patient's global assessment among patients on a modified lacto-vegetarian diet relative to a Western diet ($p<0.01$)

Effects of dose, source, and exposure duration. One study assessed the effect of different doses of omega-3 fatty acids on outcomes in RA.[19] In this study, the effect of fish oil on patient's global assessment did not differ between doses. There were insufficient data across studies to perform a pooled analysis of dose or source effect.

In one study plants were the source of omega-3 fatty acids. In this study,[23] the effect size of omega-3 fatty acids for patient global assessment was 0.26 (95% CI, -0.58, 1.10). Restricting the pooled analysis to the remaining studies, which used a fish source, the pooled random effects estimate of the effect size for patient global assessment was –0.42 (95% CI, -1.09, 0.26).

One study assessed the effects of omega-3 fatty acids on outcomes in RA for different durations of exposure.[19] In this study, there was no effect on patient's global assessment at 24 and 36 weeks, although statistical testing of the effect between these time points was not performed.

Sustainment of effect. One study assessed the sustainment of effects of omega-3 fatty acids on patient's global assessment in RA.[18] In this study, patient's global assessment worsened in a group that had been in a fish oil-treated arm, 3 months after discontinuation of the fish oil ($p<0.05$).

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with rheumatoid arthritis), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.22). Similarly there were no studies with the lowest rating of both applicability (III) and quality (C). Most studies were applicable to the general population of adult patients with RA. Of note, no studies that assessed the effect of omega-3 fatty acids on patient's global assessment among children with JRA were identified.

Table 3.21. RA: effect size for patient global assessment.

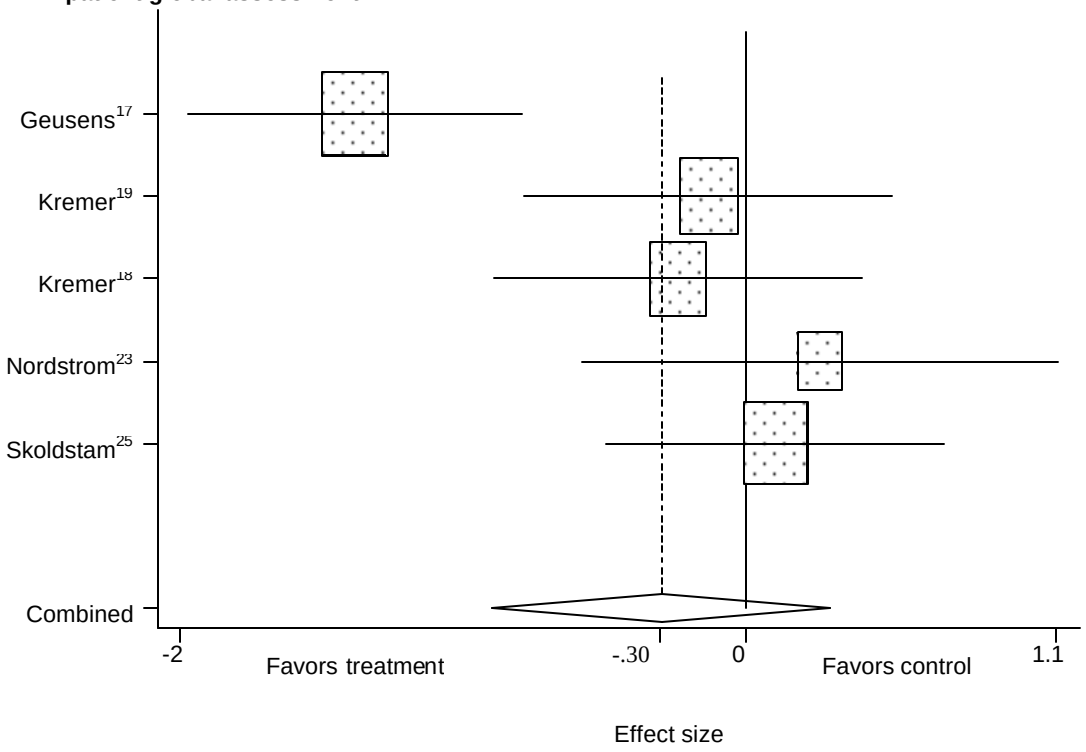
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Effect Size (95% CI)**
Geusens[17]	Fish oil	21	Placebo	20	-1.38 (-1.97, -0.79)
	Fish oil	19			
Kremer[19]	Fish oil	20	Placebo	12	-0.13 (-0.78, 0.52)
	Fish oil	17			
Kremer[18]	Max EPA (fish oil)	17	Placebo	20	-0.24 (-0.89, 0.41)
Nordstrom[23]	Flaxseed oil	11	Placebo	11	0.26 (-0.58, 1.10)
Skoldstam[25]	Max EPA (fish oil)	22	Placebo	21	0.11 (-0.49, 0.71)
Pooled Random Effects Estimate					-0.30 (-0.90, 0.30)

*Chi-squared test of heterogeneity p-value = 0.002

Table 3.22. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on global assessment among people with rheumatoid arthritis.

		Methodological Quality								
		A	B				C			
Applicability	I		**Study**	**n**	**Effect Size (95% CI)**		**Study**	**n**	**Effect Size(95% Ci)**	
			Geusens[17]	60	-1.38	(-1.97, -0.79)	Kremer[19]	49	-0.13	(-0.78, 0.52)
			Kremer[18]	37	-0.24	(-0.89, 0.41)				
			Skoldstam[25]	43	0.11	(-0.49, 0.71)				
	II									
	III									

Figure 3.12. RA: patient global assessment.



Rheumatoid Arthritis: Joint Damage

Overall effect. We identified one study that assessed the effect of omega-3 fatty acids on joint damage in RA.[29] In this study, the Larsen score of radiographic damage was not affected by administering the omega-3 fatty acids in the form of a diet high in fish.

Rheumatoid Arthritis: Tender Joint Count

Overall effect. The effect of omega-3 fatty acids on tender joint count in RA has been assessed in a previously published meta-analysis. [97] Inclusion criteria for this meta-analysis were 1) double blind, placebo controlled trial, 2) use of at least one of seven predetermined outcome measures, including tender joint count, 3) results reported for both placebo and treatment groups at baseline and follow-up, 4) randomization, and 5) parallel or cross-over design. A Medline search through 1991 identified 10 trials that met the inclusion criteria, 6 of which were analyzed for tender joint count. The rate difference between fish oil and placebo for tender joint count was –2.9 (95% CI, -3.8, -2.1).

Analysis of subpopulations and covariates, effects of dose, source, and exposure duration, and sustainment of effect were not addressed in this meta-analysis.

Rheumatoid Arthritis: Effect on Anti-inflammatory/ Immunosuppressive Drug Requirement

Overall effect. We identified 7 studies that assessed the effect of omega-3 fatty acids on anti-inflammatory and/or immunosuppressive drug requirements among patients with RA. All 7 studies assessed the effect on requirement for anti-inflammatory drugs. Among these studies, there was significant improvement relative to placebo for omega-3 treated subjects in 3,[30-32] significant improvement relative to baseline requirements in 3,[25, 26, 28] and no difference in NSAID requirement in 1.[29] One study, which assessed the effect of omega-3 fatty acids on steroid requirements, demonstrated significant improvement relative to placebo.[30] We did not identify any studies that assessed the effect of omega-3 fatty acids on disease modifying antirheumatic drug (DMARD) requirement.

Sub-populations. Not assessed in any identified studies.

Covariates. Not assessed in any identified studies.

Effects of dose, source, and exposure duration. The effects of dose, source, and exposure duration were not specifically assessed in any of the studies.

Sustainment of effect. Two studies demonstrated that the effect of omega-3 fatty acids on the requirement for NSAIDs in RA was not sustained.[30, 31]

RENAL DISEASE

Summaries of all renal disease studies we evaluated can be found in Appendix C.4.

Renal Disease: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following was assessed in patients with renal disease: serum creatinine, creatinine clearance, progression to end stage renal disease (ESRD), hemodialysis graft thrombosis/patency, and mortality. A total of studies were identified that reported these outcomes. There were insufficient data to perform meta-analysis on any of the outcomes.

Effects on serum creatinine were described in 4 studies: 1 reported a statistically significant improvement with fish oil relative to placebo,[98] 1 reported no effect,[99] and 2 reported worsening.[100, 101] Among the studies that reported worsening, neither reported testing of statistical significance between the omega-3 and control arms, and in one, there was worsening for both the omega-3 and control group.

Creatinine clearance was reported in 3 studies: 1 reported a statistically significant improvement with fish oil relative to placebo,[98] and 2 reported worsening.[100, 101] Among the studies that reported worsening, neither reported testing of statistical significance between the omega-3 and control arms, and in one, there was worsening for both the omega-3 and control groups.

Progression to ESRD was reported in 2 studies:[98, 100] one demonstrated a favorable effect for fish oil relative to placebo,[98] and the other demonstrated no effect.

Hemodialysis graft thrombosis/patency was described in 2 studies.[102, 103] In one, graft patency was significantly better for fish oil than for placebo.[102] There were no graft thromboses in either the omega-3 fatty acid or the control groups.[103]

Mortality was reported in two studies.[98, 104] Statistical testing for between group mortality rates was not reported in either. In one, mortality over 5 years was 2.0% in the placebo group and 1.8% in the omega-3 group;[98] in the other, the mortality over 5 years was zero in a low-dose fish oil group and 6% in a high-dose fish oil group.[104]

Meta-Analysis. Across the studies identified, only three were sufficiently homogeneous in terms of the population studies and the outcomes reported to consider for meta-analysis. These studies evaluated the effects of omega-3 fatty acids on Immunoglobulin A(IgA) nephropathy.[98, 100, 101] These studies, along with two other studies[117,118] that were identified but not included in this report because they did not meet our inclusion criteria, have been evaluated in a previously published meta-analysis.[105] This meta-analysis calculated effect sizes for treatment effect based on either serum creatinine concentration or creatinine clearance. Although the pooled effect size for the five studies was positive (i.e. favoring treatment over control), it was small (0.25) and not statistically significant (p=0.27).

Sub-populations. No studies that assessed the differential effect of omega-3 fatty acids across distinct subpopulations of renal disease were identified. Among the studies identified, the renal disease in the study sample was IgA nephropathy in four,[98, 100, 101, 104] lupus nephritis in one,[99] glomerular disease in one,[106] and ESRD requiring dialysis in two.[102, 103]

Covariates. The effect of omega-3 fatty acids on covariates was not assessed in any of the identified studies.

Dose and source effect. Dose and source effects of omega-3 fatty acids were not assessed in any of the identified studies.

Exposure duration. Effect of exposure duration of omega-3 fatty acids was not assessed in any of the identified studies.

Sustainment of effect. Sustainment of effect after discontinuation of omega-3 fatty acids was not assessed in any of the identified studies.

Renal Disease: Effect on Corticosteroid/Other Immunosuppressive Drug Requirement

We did not identify any studies that assessed the effects of omega-3 fatty acids on requirements for corticosteroids or other immunosuppressive drugs.

SYSTEMIC LUPUS ERYTHEMATOSUS

Summaries of all systemic lupus erythematosus studies we evaluated can be found in Appendix C.5.

Systemic Lupus Erythematosus: Clinical Effect

Overall effect. The effect of omega-3 fatty acids on each of the following was assessed in patients with SLE: disease activity, damage, and patient perception of disease. A total of 3 studies was identified that reported disease activity;[99, 107, 108] no studies that assessed the other outcomes were identified. There were insufficient data to perform meta-analysis on disease activity.

Disease activity was described using clinical and laboratory scores. Improvement in disease activity was reported in one study, which used a clinical score developed for that study (validity of score not described).[107] The other studies reported no effect on the SLE Disease Activity Index (SLEDAI)[99] or on another clinical score developed for the study (validity of instrument not described).[108] Levels of anti-DNA antibodies and complement levels were assessed in two of the studies;[99, 108] neither demonstrated an omega-3 fatty acid effect. No studies were identified that assessed effect on damage or patient perception of disease.

Sub-populations. No studies that assessed the differential effect of omega-3 fatty acids across distinct subpopulations of SLE were identified.

Covariates. The effect of omega-3 fatty acids on covariates were not assessed in any of the identified studies.

Dose and source effect. Dose and source effects of omega-3 fatty acids were not assessed in any of the identified studies.

Exposure duration. Effect of exposure duration of omega-3 fatty acids was not assessed in any of the identified studies.

Sustainment of effect. One study was designed to evaluate for sustainment of effect after discontinuation of omega-3 fatty acids.[108] However, in this study, no main effect was demonstrated before discontinuation of the omega-3 fatty acid.

Systemic Lupus Erythematosus: Effect on Steroid/Other Immunosuppressive Drug Requirement

We identified one study that assessed the effects of omega-3 fatty acids on requirements for corticosteroids.[99] In this study, omega-3 fatty acids had no effect on steroid requirements. We identified no studies that assessed the effects of omega-3 fatty acids on requirements for other immunosuppressive drugs.

BONE DENSITY/OSTEOPOROSIS

Summaries of all bone density/osteoporosis studies evaluated can be found in Appendix C.6.

Bone Density/Osteoporosis: Clinical Effect

Overall effect. The effects of omega-3 fatty acids on bone mineral density and fracture rate were assessed. In total, 5 studies described in 4 reports were identified that reported bone mineral density;[109-112] no studies of fracture rate were identified. There were insufficient data to perform meta-analysis on bone mineral density.

Improvement in bone mineral density for omega-3 fatty acids relative to placebo was described in one study;[111] improvement relative to baseline was described in one study.[110] In two studies, omega-3 fatty acids had no effect on bone mineral density.[109, 112]

Sub-populations. One report described separate studies performed in pre-menopausal and post-menopausal women. No effect was seen in either population.

Covariates. The effect of omega-3 fatty acids on covariates was not assessed in any of the identified studies.

Dose and source effect. Dose and source effects of omega-3 fatty acids were not assessed in any of the identified studies.

Exposure duration. Effect of exposure duration of omega-3 fatty acids was not assessed in any of the identified studies.

Sustainment of effect. Sustainment of effect after discontinuation of omega-3 fatty acids was not assessed in any of the identified studies.

Publication Bias

There was no evidence of publication bias on the funnel plots and adjusted rank correlation testing (not shown) performed for studies that entered meta-analysis.

Adverse Events

Among 83 articles across the six topic areas of this report that were reviewed for adverse events, 28 reported adverse events, which are summarized in Table 3.22.

Table 3.23. Summary of reported adverse events.*

Adverse Event	Total # of studies	Sample size		Adverse event count		Adverse event rate Omega 3	Adverse event rate Placebo
		N for Omega 3	N for Placebo/ Control	N for Omega 3	N for Placebo/ Control		
Clinical bleeding	1	73	NR**	2	0	2.74%	----
GI complaint or nausea	13	885	685	72	34	8.14%	4.96%
Diarrhea	3	159	104	11	5	6.92%	4.81%
Headaches	2	31	26	2	0	6.45%	0.00%
Withdrawal due to adverse event	10	353	228	13	9	3.68%	3.95%
Dermatological	4	190	159	5	10	2.63%	6.29%

- N = number of individuals with an adverse event. **Not reported. No placebo arm reported on clinical bleeding.

Chapter 4. Discussion

Overview

We screened 4,212 titles, from which we reviewed 1,097 full text articles. Among these, 83 articles met our inclusion criteria; 34 for diabetes/ metabolic syndrome, 13 for inflammatory bowel disease, 21 for rheumatoid arthritis, 9 for renal disease, 3 for systemic lupus erythematosus and 4 for bone density and fractures. All articles except one were randomized controlled trials; one was an observational study of bone density.

Most of the studies assessed the effect of omega-3 fatty acids in the form of fish oil; however, some assessed the effect of diets rich in fish. Across all conditions and studies, only 4 studies evaluated omega-3 fatty acids derived from plant oils; three for diabetes [65,66,70] and 1 for RA.[23] Few studies assessed dose or source effect, effect of treatment duration, or the sustainment of effect after discontinuation of omega-3 fatty acid consumption.

Main Findings

Diabetes/metabolic syndrome. Among 13 studies of type II diabetes or the metabolic syndrome, that were assessed by meta-analysis, omega-3 fatty acids had a favorable effect on triglyceride levels relative to placebo (pooled random effects estimate: -31.61; 95% CI, -49.58, -13.64) but had no effect on total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood sugar, or glycosylated hemoglobin, by meta-analysis. Omega-3 fatty acids had no effect on plasma insulin or insulin resistance in type II diabetics or patients with the metabolic syndrome, by qualitative analysis of four studies.

These results are consistent with the results of another meta-analysis for fish oil,[116] which found significant triglyceride-lowering and LDL-raising effects and no significant effect on fasting blood glucose, glycosylated hemoglobin, total cholesterol, or HDL cholesterol among diabetics. Although the analysis presented here did not find a significant effect on LDL, the point estimate is consistent with a LDL raising effect and the confidence interval barely crosses null (95% CI, -1.02, 11.25).

The effects of omega-3 fatty acids on triglycerides in diabetics presented here and elsewhere are consistent with the triglyceride-lowering effects of omega-3 fatty acids that have been demonstrated for the general population and are being detailed in a separate evidence report "Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors" (in preparation at the New England Medical Center Evidence Based Practice Center). Regarding the lack of effect that omega-3 fatty acids have on insulin sensitivity, it is possible that any beneficial effects of omega-3 fatty acids on insulin sensitivity could be attenuated by their high calorie content.

Inflammatory bowel disease. Among 13 studies reporting outcomes in patients with inflammatory bowel disease, variable effects of omega-3 fatty acids on clinical score, sigmoidoscopic score, histologic score, induced remission, and relapse were reported. In ulcerative colitis, omega-3 fatty acids had no effect on the relative risk of relapse in a meta-analysis of 3 studies. There was a statistically non-significant reduction in requirement for

corticosteroids for omega-3 fatty acids relative to placebo in 2 studies. No studies evaluated the effect of omega-3 fatty acids on requirement for other immunosuppressive agents.

Rheumatoid arthritis. Among 9 studies reporting outcomes in patients with rheumatoid arthritis, omega-3 fatty acids had no effect on patient report of pain, swollen joint count, ESR, and patient's global assessment by meta-analysis. The one study that assessed the effect on joint damage found no effect. In a qualitative analysis of 7 studies that assessed the effect of omega-3 fatty acids on anti-inflammatory drug or corticosteroid requirement, 6 demonstrated reduced requirement for these drugs. No studies assessed the effect on requirements for disease modifying anti-rheumatic drugs. None of the studies used a composite score that incorporates both subjective and objective measures of disease activity, such as the American College of Rheumatology response criteria.

A previously performed meta-analysis[97] reached the same conclusions for swollen joint count, ESR, and patient's global assessment. That meta-analysis found a statistically significant improvement in tender joint count compared to placebo (rate difference= -2.9, 95% CI –3.8, -2.1).

Renal disease. In a qualitative analysis of nine studies that assessed the effect of omega-3 fatty acids in renal disease, there were varying effects on serum creatinine and creatinine clearance; one study demonstrated less progression to end stage renal disease with omega-3 fatty acids relative to control. In a single study that assessed the effect on hemodialysis graft patency, graft patency was significantly better with fish oil than with placebo. No studies that assessed the effects of omega-3 fatty acids on requirements for corticosteroids or other immunosuppressive drugs for the treatment of renal disease were identified.

Systemic lupus erythematosus. Among 3 studies that assessed the effects of omega-3 fatty acids in SLE, variable effects on clinical activity were reported. No studies were identified that assessed effect on damage or patient perception of disease. Omega-3 fatty acids had no effect on corticosteroid requirements in 1 study. No studies were identified that assessed the effects of omega-3 fatty acids on requirements for other immunosuppressive drugs for SLE. None of the studies used a measure of disease activity that incorporates both subjective and objective measures of disease activity.

Bone mineral density/fracture. Among five studies described in 4 reports the effect of omega-3 fatty acids on bone mineral density was variable. No studies that assessed the effect of omega-3 fatty acids on fracture were identified.

Dose, source, duration effects and sustainment of effect. Among studies that assessed the effects of omega-3 fatty acids in diabetes, there was no dose effect for any outcome by meta-regression. There are insufficient data to draw conclusions about source or duration effects, or about sustainment of effect.

Adverse events. Across all conditions, the incidence of gastrointestinal complaints or nausea, diarrhea, and headaches appears to be higher among patients receiving omega-3 fatty acids than among those in control groups. Strong conclusions cannot be drawn from this

observation because adverse events were not reported in a standard manner in clinical trials, either in terms of the events defined or the frequency with which they were recorded. Additionally, the underlying conditions being studied will affect the rates of specific adverse events.

Conclusions

The quantity and strength of evidence for effects of omega-3 fatty acids on outcomes in the conditions assessed varies greatly. The findings of many studies among type II diabetics provide strong evidence that omega-3 fatty acids reduce serum triglycerides but have no effect on total cholesterol, HDL cholesterol and LDL cholesterol. For rheumatoid arthritis, the available evidence suggests that omega-3 fatty acids reduce tender joint counts and may reduce requirements for corticosteroids, but does not support an effect of omega-3 fatty acids on other clinical outcomes. There are insufficient data available to draw conclusions about the effects of omega-3 fatty acids on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics.

Future Research

We offer the following observations and recommendations regarding future research on the effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis.

1. Additional research on the effects of omega-3 fatty acids need to be performed on inflammatory bowel disease, renal disease, SLE, bone density, or fractures or the effects of omega-3 fatty acids on insulin resistance among type II diabetics before recommendations regarding the use of omega-3 fatty acids for these conditions can be made.

2. Studies of inflammatory bowel disease that include patients with both Crohn's disease and ulcerative colitis should report data separately for these groups.

3. Studies that assess the effects of omega-3 fatty acids should use standard validated instruments to assess clinical outcomes.

4. Trials that assess the effects of omega-3 fatty acids should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 fatty acid consumption.

5. Studies of omega-3 fatty acids should explicitly define both the quantity of the omega-3 fatty acid source and of the specific omega-3 fatty acids present in a study dose of that source.

6. Trials of omega-3 fatty acids should include a baseline assessment of dietary omega-3 and omega-6 fatty acid intake.

7. In controlled trials that assess the effects of omega-3 fatty acids, analysis should include and report explicit testing of the effects of the omega-3 fatty acid relative to the control substance.

8. In studies that use a crossover design, outcome data for all study arms should be reported at the end of each treatment period.

References and Included Studies

1. Innis S. Essential dietary lipids. In: Present knowledge in nutrition. Washington, DC: International Life Sciences Institute; 1996.

2. James M, Gibson R, Cleland L. Dietary polyunsaturated fatty acids and inflammatory mediator production. *American Journal of Clinical Nutrition* 2000;71(1):343S-348S.

3. Fallon S, Enig MG. The Price-Pottenger Nutrition Foundation. Tripping Lightly Down the Prostaglandin Pathways. *http://www.price-pottenger.org/Articles/Prostaglandin.htm* 2001.

4. Simopoulos A. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedicine & Pharmacotherapy* 2002;56(8):365-379.

5. Institute of Medicine. . Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrition). The National Academies Press. 2002 (Abstract)

6. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273(5):408-12.

7. Ioannidis JP, Cappelleri JC, Lau J et al. Early or deferred zidovudine therapy in HIV-infected patients without an AIDS-defining illness. *Ann Intern Med* 1995;122(11):856-866.

8. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for Meta-Analysis in Medical Research. In: Wiley Series in Probability and Statistics. Chichester, UK: John Wiley & Sons; 2000.

9. Hedges LV, Olkin L. Statistical Methods for Meta-Analysis. San Diego, CA: Academic Press, Inc; 1985.

10. Rosenthal R. Meta-Analytic Procedures for Social Research. In: Applied Social Research Methods Series. Newbury Park: Sage Publications; 1991.

11. DerSimonian R., Laird N. Meta-analysis in clinical trials. *Control Clin rials* 1986;7(3):177-188.

12. Egger M, Davey Smith G, Schneider M/ Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315(7109):629-634.

13. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publiction bias. *Biometrics* 1994;50(4):1088-1101.

14. .Stata Statistical Software: Release 7.0 [computer program]. Version 7.0. 2001.

15. Joint Task Group (CHPA, CRN, NFI). Food Labeling: Health Claims and Label Statement - Omega-3 Fatty Acids and Coronary Heart Disease . *Docket No: 91N-0103* .

16. Cleland L, French J, Betts W, Murphy G, Elliott M. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. *Journal of Rheumatology* 1988;15(10):1471-1475.

17. Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis: A 12-month, double-blind, controlled study. *Arthritis & Rheumatism* 1994 ;37(6):824-829.

18. Kremer J, Bigauoette J, Michaler A. Effects of manipulations of dietary fatty acids on clinical manifestations of rheumatoid arthritis. *Lancet* 1985;1(8422):184-187.

19. Kremer J, Lawrence D, Jubiz W, DiGiacomo R, Rynes R, Bartholomew L, et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunologic effects. *Arthritis & Rheumatism* 1990;33(6):810-820.

20. Magalish T, Ivanov E, Iubitskaia N. Ultraphonophoresis of omega-3 polyunsaturated fatty acids in the complex therapy of rheumatoid arthritis. *Voprosy.Kurortologii., Fizioterapii.i.Lechebnoi.Fizicheskoi.Kultury* 2002 ;(2):43-44.

21. Magaro M, Altomonte L, Zoli A, Mirone L, De Sole P, Di Mario G, et al. Influence of diet with different lipid composition on neutrophil chemiluminescence and disease activity in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1988;47(10):793-796.

22. Nielsen G, Faarvang K, Thomsen B, Teglbjaerg K, Jensen L, Hansen T, et al. The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. *European Journal of Clinical Investigation* 1992;22(10):687-691.

23. Nordstrom D, Honkanen V, Nasu Y, Antila E, Friman C, Konttinen Y. Alpha-linolenic acid in the treatment of rheumatoid arthritis: A double blind, placebo-controlled and randomized study: Flaxseed vs safflower seed. *Rheumatology International* 1995;14(6):231-234.

24. Tulleken J, Limburg P, Muskiet F, van Rijswijk M. Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis & Rheumatism* 1990;33(9):1416-1419.

25. Skoldstam L, Borjesson O, Kjallman A, Seiving B, Akesson B. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double blind, controlled study. *Scand J Rheumatol* 1992;21:178-85.

26. Adam O, Beringer C, Kless T, Lemmen C, Adam A, Wiseman M, et al. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatology International* 2003;23(1):27-36.

27. Alpigiani M, Ravera G, Buzzanca C, Devescovi R, Fiore P, Iester A. Use of n-3 fatty acids in Juvenile Chronic Arthritis (JCA). *Pediatria Medica e Chirurgica* 1996;18(4):387-390.

28. Belch J, Ansell D, Madhok R, O'Dowd A, Sturrock R. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: A double blind placebo controlled study. *Annals of the Rheumatic Diseases* 1988;47(2):96-104.

29. Hansen G, Nielsen L, Kluger E, Thysen M, Emmertsen H, Stengaard-Pedersen K, et al. Nutritional status of Danish rheumatoid arthritis patients and effects of a diet adjusted in energy intake, fish-meal, and antioxidants. *Scandinavian Journal of Rheumatology* 1996;25(5):325-330.

30. Kjeldsen-Kragh J, Lund J, Riise T, Finnanger B, Haaland K, Finstad R, et al. Dietary omega-3 fatty acid supplementation and naproxen treatment in patients with rheumatoid arthritis. *Journal of Rheumatology* 1992;19(10):1531-1536.

31. Kremer J, Lawrence D, Petrillo G, Litts L, Mullaly P, Rynes R, et al. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs: Clinical and immune correlates. *Arthritis & Rheumatism* 1995;38(8):1107-1114.

32. Lau C, Morley K, Belch J. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis--a double-blind placebo controlled study. *British Journal of Rheumatology* 1993;32(11):982-989.

33. van der Tempel H, Tulleken J, Limburg P, Muskiet F, van Rijswijk M. Effects of fish oil supplementation in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1990;49(2):76-80.

34. Tulleken J, Limburg P, van Rijswijk M. Fish oil and plasma fibrinogen. *BMJ* 1988;297:615-616.

35. Volker D, Fitzgerald P, Major G, Garg M. Efficacy of Fish Oil Concentrate in the Treatment of Rheumatoid Arthritis. *J Rheumatol* 2000;27:2343-6.

36. Astorga G. Active rheumatoid arthritis: effect of dietary supplementation with omega-3 oils. A controlled double-blind trial. *Revista Medica de Chile* 1991;119(3):267-272.

37. Espersen G, Grunnet N, Lervang H, Nielsen G, Thomsen B, Faarvang K, et al. Decreased interleukin-1 beta levels in plasma from rheumatoid arthritis patients after dietary supplementation with n-3 polyunsaturated fatty acids. *Clinical Rheumatology* 1992;11(3):393-395.

38. Lau C, McLaren M, Belch J. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. *Clinical & Experimental Rheumatology* 1995;13(1):87-90.

39. Loeschke K, Ueberschaer B, Pietsch A, Gruber E, Ewe K, Wiebecke B, et al. n-3 fatty acids only delay early relapse of ulcerative colitis in remission. *Digestive Diseases & Sciences* 1996;41(10):2087-2094.

40. Mantzaris G, Archavlis E, Zografos C, Petraki K, Spiliades C, Triantafyllou G. A prospective, randomized, placebo-controlled study of fish oil in ulcerative colitis. *Hellenic Journal of Gastroenterology* 1996;9(2):138-141.

41. Hawthorne A, Daneshmend T, Hawkey C, Shaheen M, Edwards T, Filipowicz B, et al. Fish oil in ulcerative colitis: Final results of a controlled cliinical trial. *Gastroenterology* 98:A174.

42. Greenfield S , Green A, Teare J, Jenkins A, Punchard N, Ainley C, et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Alimentary Pharmacology & Therapeutics* 1993;7(2):159-166.

43. Middleton S, Naylor S, Woolner J, Hunter J. A double-blind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Alimentary Pharmacology & Therapeutics* 2002;16(6):1131-1135.

44. Almallah Y, Richardson S, O'Hanrahan T, Mowat N, Brunt P, Sinclair T, et al. Distal procto-colitis, natural cytotoxicity, and essential fatty acids. *American Journal of Gastroenterology* 1998;93(5):804-809.

45. Almallah Y, Ewen S, El Tahir A, Mowat N, Brunt P, Sinclair T , et al. Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. *Journal of Clinical Immunology* 2000;20(1):68-76.

46. Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *American Journal of Gastroenterology* 1992;87(4):432-437.

47. Belluzzi A, Brignola C, Campieri M, Camporesi E, Gionchetti P, Rizzaello F, et al. Effects of a new fish oil derivative on fatty acid phospholipid-membrane pattern in a group of Crohn's disease patients. *Dig Dis Sci* 1994;39:2589-2594.

48. Dichi I, Frenhane P, Dichi J, Correa C, Angeleli A, Bicudo M, et al. Comparison of omega-3 fatty acids and sulfasalazine in ulcerative colitis. *Nutrition* 2000;16(2):87-90.

49. Hillier K. Human colon mucosa: effect of marine oils on lipid fatty acid composition and eicosanoid synthesis in inflammatory bowel disease. *British Journal of Clinical Pharmacology* 1988;25(1):129P-30P.

50. Hillier K, Jewell R, Dorrell L, Smith C. Incorporation of fatty acids from fish oil and olive oil into colonic mucosal lipids and effects upon eicosanoid synthesis in inflammatory bowel disease. *Gut* 1991;32(10):1151-1155.

51. Ikehata A, Hiwatashi N, Kinouchi Y, Yamazaki H, Kumagai Y, Ito K, et al. Effect of intravenously infused eicosapentaenoic acid on the leukotriene generation in patients with active Crohn's disease. *American Journal of Clinical Nutrition* 1992;56(5):938-942.

52. Lorenz R, Weber P, Szimnau P, Heldwein W, Strasser T, Loeschke K. Supplementation with n-3 fatty acids from fish oil in chronic inflammatory bowel disease--a randomized, placebo-controlled, double-blind cross-over trial. *Journal of Internal Medicine Supplement* 1989;225(731):225-232.

53. Stenson W, Cort D, Rodgers J, Burakoff R, DeSchryver-Kecskemeti K, Gramlich T, et al. Dietary supplementation with fish oil in ulcerative colitis. *Annals of Internal Medicine* 1992;116(8):609-614.

54. Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *New England Journal of Medicine* 1996;334(24):1557-1560.

55. Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purrmann J, Fleig W, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). *Scandinavian Journal of Gastroenterology* 1996;31(8):778-785.

56. Shimizu H, Ohtani K, Tanaka Y, Sato N, Mori M, Shimomura Y. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes Research & Clinical Practice* 1995;28(1):35-40.

57. Annuzzi G, Rivellese A, Capaldo B, Di Marino L, Iovine C, Marotta G, et al. A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients. *Atherosclerosis* 1991;87(1):65-73.

58. Chan D, Watts G, Mori T, Barrett P, Beilin L, Redgrave T. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. *European Journal of Clinical Investigation* 2002;32(6):429-436.

59. Dunstan D, Mori T, Puddey I, Beilin L, Burke V, Morton A, et al. Exercise and fish intake: Effects on serum lipids and glycemic control for type 2 diabetics. *Cardiology Review* 1998;15(8):34-37.

60. Hendra T, Britton M, Roper D, Wagaine-Twabwe D, Jeremy J, Dandona P, et al. Effects of fish oil supplements in NIDDM subjects. Controlled study. *Diabetes Care* 1990;13(8):821-829.

61. Morgan W, Raskin P, Rosenstock J. A comparison of fish oil or corn oil supplements in hyperlipidemic subjects with NIDDM. *Diabetes Care* 1995;18(1):83-86.

62. Pelikanova T , Kohout M, Valek J, Kazdova L, Base J. Metabolic effects of omega-3 fatty acids in type 2 (non-insulin-dependent) diabetic patients. *Annals of the New York Academy of Sciences* 1993;683:272-278.

63. Petersen M, Pedersen H, Major-Pedersen A, Jensen T, Marckmann P. Effect of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients. *Diabetes Care* 2002;25(10): 1704-1708.

64. Sirtori C, Crepaldi G, Manzato E, Mancini M, Rivellese A, Paoletti R, et al. One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance: reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations. *Atherosclerosis* 1998;137(2):419-427.

65. Alekseeva R, Sharafetdinov K, Kh Plotnikova OA, Meshcheriakova V, Mal'tsev G, Kulakova S. Effects of a diet including linseed oil on clinical and metabolic parameters in patients with type 2 diabetes mellitus. *Voprosy Pitaniia* 2000;69(6):32-35.

66. Meshcheriakova V, Plotnikova O, Sharafetdinov K, Kh AR, Mal'tsev G, Kulakova S. Comparative study of effects of diet therapy including eiconol or linseed oil on several parameters of lipid metabolism in patients with type 2 diabetes mellitus . *Voprosy Pitaniia* 2001;70(2):28-31.

67. Morgan WA. The effects of fish oil versus corn oil on subjects with hyperlipidemia and type ii, noninsulin-dependent diabetes mellitus (Fatty acids). *Dissertation Abstracts International* 51-06, Section: B:2825-.

68. Patti L, Maffettone A, Iovine C, Marino L, Annuzzi G, Riccardi G, et al. Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyceridemia. *Atherosclerosis* 1999;146(2):361-367.

69. Rivellese A, Maffettone A, Iovine C, Di Marino L, Annuzzi G, Mancini M, et al. Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. *Diabetes Care* 1996 ;19(11):1207-1213.

70. Sarkkinen E, Schwab U, Niskanen L, Hannuksela M, Savolainen M, Kervinen K, et al. The effects of monounsaturated-fat enriched diet and polyunsaturated-fat enriched diet on lipid and glucose metabolism in subjects with impaired glucose tolerance. *European Journal of Clinical Nutrition* 1996;50(9):592-598.

71. Westerveld H , de Graaf J, van Breugel H, Akkerman J, Sixma J, Erkelens D, et al. Effects of low-dose EPA-E on glycemic control, lipid profile, lipoprotein(a), platelet aggregation, viscosity, and platelet and vessel wall interaction in NIDDM. *Diabetes Care* 1993;16(5):683-688.

72. Woodman R, Mori T, Burke V, Puddey I, Watts G, Beilin L. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *American Journal of Clinical Nutrition* 2002;76(5):1007-1015.

73. Maffettone A. Long-term effects (six months) of omega-3 polyunsaturated fatty acids on insulin sensitivity and lipid metabolism in patients with type 2 diabetes and hypertriglycaeridemia. *Giornale Italiano di Diabetologia* 1996;16(4):185-193.

74. Hermans M, Sauvegarde A, Ketelslegers J, Lambert A. Effects of omega-3 fatty acids on insulin-dependent diabetic patients with microalbuminuria. *European Journal of Clinical Investigation* 23(Suppl 1).

75. 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.

76. Boberg M, Pollare T, Siegbahn A, Vessby B. Supplementation with n-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin-dependent diabetes mellitus. *European Journal of Clinical Investigation* 1992;22(10):645-650.

77. Borkman M, Chisholm D, Furler S, Storlien L, Kraegen E, Simons L, et al. Effects of fish oil supplementation on glucose and lipid metabolism in NIDDM. *Diabetes* 1989;38(10):1314-1319.

78. Connor W, Prince M, Ullmann D, Riddle M, Hatcher L, Smith F, et al. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. *Annals of the New York Academy of Sciences* 1993;683:337-340.

79. Fasching P, Rohac M, Liener K, Schneider B, Nowotny P, Waldhausl W. Fish oil supplementation versus gemfibrozil treatment in hyperlipidemic NIDDM. A randomized crossover study. *Hormone & Metabolic Research* 1996;28(5):230-236.

80. Goh Y, Jumpsen J, Ryan E, Clandinin M. Effect of omega 3 fatty acid on plasma lipids, cholesterol and lipoprotein fatty acid content in NIDDM patients. *Diabetologia* 1997;40(1):45-52.

81. Jensen T, Stender S, Goldstein K, Holmer G, Deckert T. Partial normalization by dietary cod-liver oil of increased microvascular albumin leakage in patients with insulin-dependent diabetes and albuminuria. *New England Journal of Medicine* 1989;321(23):1572-1577.

82. Luo J, Rizkalla S, Vidal H, Oppert J, Colas C, Boussairi A, et al. Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type 2 diabetic men. Results of a controlled study. *Diabetes Care* 1998;21(5):717-724.

83. McGrath L, Brennan G, Donnelly J, Johnston G, Hayes J, McVeigh G. Effect of dietary fish oil supplementation on peroxidation of serum lipids in patients with non-insulin dependent diabetes mellitus. *Atherosclerosis* 1996;121(2):275-283.

84. McVeigh G, Brennan G, Johnston G, McDermott B, McGrath L, Henry W, et al. Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1993;36(1):33-38.

85. McVeigh G, Brennan G, Cohn J, Finkelstein S, Hayes R, Johnston G. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. *Arteriosclerosis & Thrombosis* 1994;14(9):1425-1429.

86. Puhakainen I , Ahola I, Yki-Jarvinen H. Dietary supplementation with n-3 fatty acids increases gluconeogenesis from glycerol but not hepatic glucose production in patients with non-insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1995;61(1):121-126.

87. Schectman G, Kaul S, Kissebah A. Effect of fish oil concentrate on lipoprotein composition in NIDDM. *Diabetes* 1988;37(11):1567-1573.

88. Schwab U, Sarkkinen E, Lichtenstein A, Li Z, Ordovas J, Schaefer E, et al. The effect of quality and amount of dietary fat on the susceptibility of low density lipoprotein to oxidation in subjects with impaired glucose tolerance. *European Journal of Clinical Nutrition* 1998;52(6):452-458.

89. Sirtori C, Paoletti R, Mancini M, Crepaldi G, Manzato E, Rivellese A, et al. N-3 fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance. Italian Fish Oil Multicenter Study. *American Journal of Clinical Nutrition* 1997;65(6):1874-1881.

90. Vandongen R, Mori T, Codde J, Stanton K, Masarei J. Hypercholesterolaemic effect of fish oil in insulin-dependent diabetic patients. *Medical Journal of Australia* 1988;148(3):141-143.

91. Vessby B, Boberg M. Dietary supplementation with n-3 fatty acids may impair glucose homeostasis in patients with non-insulin-dependent diabetes mellitus. *Journal of Internal Medicine* 1990;228(2):165-171.

92. Chan D, Watts G, Barrett P, Beilin L, Redgrave T, Mori T. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes* 2002;51(8):2377-2386.

93. Dunstan D, Mori T, Puddey I, Beilin L, Burke V, Morton A, et al. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care* 1997;20(6):913-921.

94. Varghese T, Coomansingh D. Clinical response of ulcerative colitis with dietary omega-3 fatty acids: a double-blind randomized study. *British Journal of Surgery* 2000;87(1):73.

95. Hawthorne A, Daneshmend T, Hawkey C, Belluzzi A, Everitt S, Holmes G, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut* 1992;33(7):922-928.

96. Sperling R, Weinblatt M, Robiin J, Ravalese J, Hoover R, House Fea. Effects of dietary supplementation with marine fish oil on leukoeyte lipid mediators and function in rheumatoid rthritis. *Arthritis Rheum* 1987;30:988-997.

97. Fortin P, Lew R, Liang M, Wright E, Beckett L, Chalmers T, et al. Validation of a meta-analysis: The effects of fish oil in rheumatoid arthritis. *Journal of Clinical Epidemiology* 1995;48(11):1379-1390.

98. Donadio J, Jr, Bergstralh E, Offord K, Spencer D, Holley K. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *New England Journal of Medicine* 1994;331(18):1194-1199.

99. Clark W, Parbtani A, Naylor C, Levinton C, Muirhead N, Spanner E, et al. Fish oil in lupus nephritis: clinical findings and methodological implications. *Kidney International.* 1993;44(1):75-86.

100. Bennett W, Walker R, Kincaid-Smith P. Treatment of IgA nephropathy with eicosapentanoic acid (EPA): a two-year prospective trial. *Clinical Nephrology* 1989;31(3):128-131.

101. Pettersson E, Rekola S, Berglund L, Sundqvist K, Angelin B, Diczfalusy U, et al. Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: a prospective, double-blind, randomized study. *Clinical Nephrology* 1994;41(4):183-190.

102. Schmitz P, McCloud L, Reikes S, Leonard C, Gellens M. Prophylaxis of hemodialysis graft thrombosis with fish oil: double-blind, randomized, prospective trial. *Journal of the American Society of Nephrology* 2002 ;13(1):184-190.

103. de Fijter C , Popp-Snijders C, Oe L, Tran D, van der M, Donker A. Does additional treatment with fish oil mitigate the side effects of recombinant human erythropoietin in dialysis patients? *Haematologica* 1995;80(4):332-334.

104. Donadio J, Jr, Larson T, Bergstralh E, Grande J. A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *Journal of the American Society of Nephrology* 2001;12(4):791-799.

105. Dillon JJ. Fish oil therapy for IgA nephropathy: efficacy and interstudy variability. *Journal of the American Society of Nephrology* 1997;8(11):1739-1744.

106. Gentile M, Fellin G, Cofano F, Delle Fave A, Manna G, Ciceri R, et al. Treatment of proteinuric patients with a vegetarian soy diet and fish oil. *Clinical Nephrology* 1993;40(6):315-320.

107. Walton A, Snaith M, Locniskar M, Cumberland A, Morrow W, Isenberg D. Dietary fish oil and the severity of symptoms in patients with systemic lupus erythematosus. *Annals of the Rheumatic Diseases.* 1991;50(7):463-466.

108. Westberg G, Tarkowski A. Effect of MaxEPA in patients with SLE. A double-blind, crossover study. *Scandinavian Journal of Rheumatology.* 1990;19(2):137-143.

109. Bassey E, Littlewood J, Rothwell M, Pye D. Lack of effect of supplementation with essential fatty acids on bone mineral density in healthy pre- and postmenopausal women: two randomized controlled trials of Efacal v. calcium alone. *British Journal of Nutrition* 2000;83(6):629-635.

110. Kruger M, Coetzer H, de Winter R, Gericke G, van Papendorp D. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. *Aging (Milano).* 1998;10(5):385-394.

111. Terano T. Effect of omega 3 polyunsaturated fatty acid ingestion on bone metabolism and osteoporosis. *World Review of Nutrition & Dietetics* 2001;88:141-147.

112. Tsuchida K, Mizushima S, Toba M, Soda K. Dietary soybeans intake and bone mineral density among 995 middle-aged women in Yokohama. *Journal of Epidemiology.* 1999;9(1):14-19.

113. Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17:1-12.

114. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? LANCET. 1998;352: 609-613.

115. Khan KS, Daya S, Jadad AR. The importance of quality of primary studies in producing unbiased systematic reviews. Arch Intern Med. 1996;156:661-666.

116. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care.* 2000;23(9): 1407-1415.

117. Cheng IK, Chan PC, Chan MK. The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. *Nephrology Dialysis Transplantation.* 1990;5(4):241-246.

118. Hamazaki T, Tateno S, Shishido H. Eicosapentaenoic acid and IgA nephropathy. *Lancet*. 1984;1(8384): 1017-1018

Acronyms

AA	Arachidonic acid	Mo	Month
Ab	Antibody	n	Number
AHRQ	Agency for Healthcare Research and Quality	n-3	Omega-3
AI	Adequate intake	n-6	Omega-6
ALA	Alpha-linolenic acid	NA	Not applicable
AMDR	Acceptable macronutrient distribution ranges	NHANES III	The Third National Health and Nutrition Examination
ANCOVA	Analysis of covariance	NCI	National Cancer Institute
ANOVA	Analysis of variance	NEI	National Eye Institute
Ca	Calcium	NEMC	New England Medical Center
CCT	Controlled clinical trial	NHANES	National Health and Nutrition Examination
CI	Confidence interval	NHLBI	National Heart, Lung and Blood Institute
CRP	C-reactive protein	NIAAA	National Institute of Alcohol Abuse and Alcoholism
CSFII	Continuing Food Survey of Intakes by Individuals	NIAID	National Institute of Allergy and Infectious Diseases
d	day	NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
D6D	Delta-6 Desaturase	NICHD	National Institute of Child Health and Human Development
DGLA	Dihomo-gamma-linolenic acid	NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
DHA	Docosahexaenoic acid	NIH	National Institutes of Health
DPA	Docosapentaenoic acid	NNH	Number needed to harm
DRI	Dietary Reference Intake	NR	Not reported
Ds-DNA	Double-stranded DNA	NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
EF	Effect size	ODS	Office of Dietary Supplements
EFA	Essential fatty acid	PG	Prostaglandin
EPA	Eicosapentaenoic acid	PGD	Prostaglandin-D
EPC	Evidence-Based Practice Center	PGE	Prostaglandin-E
ESR	Erythrocyte sedimentation rate	PGF	Prostaglandin-F
FNB	Food and Nutrition Board	PGL	Prostaglandin-L
g	grams	PGH	Prostaglandin-H
GI	Gastrointestinal	PUFA	Polyunsaturated fatty acid
GLA	Gamma-linolenic acid	QRF	Quality review form
HDL	High density lipoprotein	RA	Rheumatoid arthritis
IBD	Inflammatory bowel disease	RCT	Randomized controlled trial
IL-1ß	Interleukin 1ß	RDA	Recommended daily allowances
JRA	Juvenile rheumatoid arthritis	RXT	Randomized crossover trial
IOM	Institute of Medicine	Sd	Standard deviation
LA	Linoleic acid	SCEPC	Southern California Evidence-Based Practice Center
LC PUFA	Long-chain polyunsaturated fatty acid	SLE	Systemic lupus erythematosus
LDL	Low density lipoprotein	SEM	Standard errors of the means
MA	Metaanalysis	TEP	Technical expert panel
MANOVA	Multivariate analysis of variance	TNF-*a*	Tumor necrosis factor-*a*
MeSH Term	Medical Subject Headings Term	TX	Treatment
mg/dl	Milligrams per deciliter	TXA	Thromboxane-A
min	Minutes	UCLA	University of California, Los Angeles
		VLCFA	Very long chain fatty acid
		VLN-3FA	Very long chain n-3 fatty acids
		wk	Week

Listing of Excluded Studies

Rejected on Abstract Review

AnonymousDietary fats and oils in human nutrition; report of an expert consultation held in Rome. *FAO Food and Nutrition Paper* 1977;

AnonymousThe effect of omega-3 fatty acids. *Therapiewoche* 1990;40:12-18.

AnonymousFish, diabetes, and the arterial wall. *Lancet* 1989;2:1332-

AnonymousFish oil for type 2 diabetes. *Health News* 2000;6:7-

AnonymousFish oils and diabetic microvascular disease. *Lancet* 1990;335:508-509.

AnonymousIncreasing fish oil intake - Any net benefits? *Drug & Therapeutics Bulletin* 1996;34:60-62.

AnonymousItalian Society of Dietetics and Clinical Nutrition. XII national conference - lipids in dietetics and clinical nutrition, Torino, Italy, 16-November, 1995. *Minerva Gastroenterologica e Dietologica* 1997;169-219.

AnonymousLectures given at the 9th Aachen Dietetics Further Education Meeting, 21-23 September, 2001. *Ernahrung and Medizin* 2002;

AnonymousManagement of hyperlipidaemia. *Drug & Therapeutics Bulletin* 1996;34:89-93.

AnonymousNutrition and chronic inflammatory bowel disease. *Medizinische Welt* 2001;52:74-75.

AnonymousUpdate on inflammatory bowel disease. *Pharmaceutical Journal* 2001;267:574-575.

Abrahamsson H, Gustafson A, Ohlson R: Polyunsaturated fatty acids in hyperlipoproteinemia. 1. Influences of a sucrose-rich diet on fatty acid composition of serum lipoprotein lipids. *Nutrition and Metabolism* 1974;

Adam O: Nutritional influences on eicosanoid biosynthesis - clinical consequences. *Fett Wissenschaft Technologie* 1994;95:

Aldhous MC, Meister D, Subrata Ghosh, Ghosh S: Modification of enteral diets in inflammatory bowel disease. *Symposium on Dietary influences on mucosal immunity, Harrogate, UK* 2000;457-461.

Alekseeva RI, Sharafetdinov Kh, Plotnikova OA, Meshcheriakova VA, Mal'tsev GI, Kulakova SN: Effects of diet therapy including eiconol on clinical and metabolic parameters in patients with type 2 diabetes mellitus. *Voprosy Pitaniia* 2000;69:36-39.

Alfin-Slater RB, Aftergood L: Essential fatty acids reinvestigated. *Physiological Reviews* 1968;48:758-784.

Anadere I, Schmitt Y, Schneider H, Walitza E: The effect of omega-3 polyunsaturated fatty acids on hemorheological parameters of patients under chronic hemodialysis treatment. *Clinical Hemorheology* 1992;12:243-254.

Andersson Agneta: Fatty acid composition in skeletal muscle. Influence of physical activity and dietary fat quality. *Dissertation Abstracts International* 67-

Astrup A: Healthy lifestyles in Europe: prevention of obesity and type II diabetes by diet and physical activity. *Public Health Nutrition* 2001;56:

Aued Pimentel S, Caruso MSF: Gamma-linolenic acid: sources, and perspectives on its therapeutic application. *Boletim da Sociedade Brasileira de Ciencia e Tecnologia de Alimentos* 1999;54:

Avula C, Lawrence R, Jolly C, Fernandes G: Role of n-3 polyunsaturated fatty acids (PUFA) in autoimmunity, inflammation, carcinogenesis, and apoptosis. *Recent.Research.Developments.in.Lipids* 2000;

Ayling RM, Preedy VR, Grimble G, Watson R: Nutritional management of diabetes mellitus. *Nutrition in the infant: problems and practical procedures* 2001;36:-

Ba Jaber AS, Al Faris NA: Effects of high carbohydrate, high insoluble fiber and low fatty acids diets on patients with non-insulin-dependent diabetes mellitus. *Bulletin of Faculty of Agriculture, University of Cairo* 1997;22:

Ba Jaber AS, Al Faris NA, Al Robean K: Short-term effect of soluble fiber in fat diets on plasma glucose and lipids in patients with non-insulin dependent diabetes mellitus. *Bulletin of Faculty of Agriculture, University of Cairo* 1997;25:

Baggio B: Fatty acids, calcium and bone metabolism. *Journal of Nephrology* 2002;15:601-4.

Bamba T: Lifestyle guidance and diet for inflammatory bowel disease (IBD) patients. *JMAJ Japan Medical Association Journal* 2002;4:

Bang HO, Dyerberg J, Nielsen AB: Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. *Lancet* 1971;1:1143-1145.

Barsottelli E, Berra B: Omega-3 Fatty acids and prevention of thrombosis and atherosclerosis. Critical evaluation of data from the literature. *Rivista Italiana delle Sostanza Grasse* 1994;42:

Bartels M, Nagel E, Pichlmayr R: What is the role of nutrition in ulcerative colitis? A contribution to the current status of diet therapy in treatment of inflammatory bowel diseases. *Langenbecks Archiv fur Chirurgie* 1995;380:37722

Bassaganya Riera J, Hontecillas R, Wannemuehler MJ: Nutritional impact of conjugated linoleic acid: a model functional food ingredient. *In Vitro Cellular and Developmental Biology Plant* 2002;50:

Beare Rogers J, Nera EA, Levin OL, et al: 20th International Conference on the Biochemistry of Lipids, Aberdeen, Scotland, September 6-8, 1977. *1977, xi + 44pp* mimeographed.:-

Beitz J, Schimke E, Liebaug U, et al: Influence of a cod liver oil diet in healthy and insulin-dependent diabetic volunteers on fatty acid pattern, inhibition of prostacyclin formation by low density lipoprotein (LDL) and platelet thromboxane. *Klinische Wochenschrift* 1986;64:793-799.

Belch J, Muir A: n-6 and n-3 essential fatty acids in rheumatoid arthritis and other rheumatic conditions. *Proceedings of the Nutrition Society* 1998;563-569.

Belluzzi A: Lipid treatment in inflammatory bowel disease. *Nestle Nutrition Workshop Series Clinical & Performance Program* 1999;2:199-211.

Belluzzi A: N-3 and n-6 fatty acids for the treatment of autoimmune diseases. *European Journal of Lipid Science and Technology* 2001;6:

Belluzzi A, Campieri M, Brignola C, Gionchetti P, Miglioli M, Barbara L: Polyunsaturated fatty acid pattern and fish oil treatment in inflammatory bowel disease. *Gut* 1993;34:1289-1290.

Berdanier CD, Bodwell CE, Erdman JW: Interacting effects of carbohydrate and lipid on metabolism. *Nutrient interactions* 1988;

Berry EM, Valagussa F, Marchioli R: Are diets high in omega-6 polyunsaturated fatty acids unhealthy? Evidence and perspectives on n 3 polyunsaturated fatty acids in cardiovascular disease. *European-Heart-Journal-Supplements* 2001;

Betteridge DJ: Lipids, diabetes, and vascular disease: The time to act. *Diabetic Medicine* 1989;6:195-218.

Bhathena SJ: Relationship between fatty acids and the endocrine system. *Biofactors* 2000;13:35-39.

Bhathena SJ, Chow CK: Dietary fatty acids and fatty acid metabolism in diabetes. *Fatty acids in foods and their health implications* 2000;488:-

Bisson LF, Watkins TR: Metabolic Syndrome X and the French paradox. *Wine: nutritional and therapeutic benefits* 1997;66:-

Bitton A: Medical management of ulcerative proctitis, proctosigmoiditis, and left-sided colitis. *Seminars in Gastrointestinal Disease* 2001;12:263-274.

Bodem SH: Is fish oil effective against IgA-nephropathy? *Pharmazeutische Zeitung* 1995;140:67-68.

Boissonneault G, Chow C: Dietary fat, immunity and inflammatory disease. *Fatty.acids.in.foods.and.their.health.implications* 2000;-

Brennan GM , McVeigh GE , Johnston GD , Hayes JR: Dietary fish oil augments EDRF production or release in patients with non-insulin dependent diabetes mellitus. *British Journal of Clinical Pharmacology* 1992;33:531

Brown A: Lupus erythematosus and nutrition: a review of the literature. *Journal of Renal Nutrition.* 2000;10:170-183.

Brunner EJ, Wunsch H, Marmot MG: What is an optimal diet? Relationship of macronutrient intake to obesity, glucose tolerance, lipoprotein cholesterol levels and the metabolic syndrome in the Whitehall II study. *International Journal of Obesity* 2001;30:

Burakoff R: Inflammatory bowel disease workshop. Vail, Colorado, March 22 and 23, 1998. Less commonly used therapies for IBD or treatments on the fringe. *Inflammatory Bowel Diseases* 1998;4:308-313.

Burden ML, Samanta A, Spalding D, Burden AC: A comparison of the glycaemic and insulinaemic effects of an Asian and a European meal. *Practical Diabetes* 1994;11:208-211.

Campbell Joy Marlene: Influence of oligosaccharides and fish oil on gastrointestinal tract characteristics and metabolic profiles of humans, pigs, and rats. *Dissertation Abstracts International* 4798-

Caprilli R, Taddei C, Viscido A: In favour of prophylactic treatment for post-operative recurrence in Crohn's disease. *Italian Journal of Gastroenterology & Hepatology* 1998;30:219-225.

Carpentier YA: Dietary intake and hyperlipoproteinemias. *Revue Medicale de Bruxelles* 1997;18:32-36.

Castiglioni A, Savazzi GM: Clinical significance of consumption of polyunsaturated n-3 fatty acids of marine origin. *Recenti Progressi in Medicina* 1991;82:59-60.

Caterina R, de BG, De Caterina R, Valagussa F, Marchioli R: n-3 Fatty acids and the inflammatory response -biological background. Evidence and perspectives on n.3 polyunsaturated fatty acids in cardiovascular disease. *European-Heart-Journal* 2001;

Caterina Rde Caprioli R, Giannessi D, Sicari R, et al: The use of fish oil in human chronic glomerular disease. *n 3 fatty acids and vascular disease: background and pathophysiology, hyperlipidaemia, renal diseases, ischaemic heart disease* 1993;51:

Cerrato PL: Omega-3 fatty acids: nothing fishy here! *RN* 1999;62:59-60.

Chambers Kathleen Mailie: Assessment of the nutritional properties of regular and low linolenic acid canola oil in non-insulin-dependent (Type ii) Diabetes mellitus subjects. *Masters Abstracts International* 519-

Chandrasekaran A, Radhakrishna B, Uma B, Gopalan C, Krishnaswamy K: Rheumatic diseases. *Nutrition.in.major.metabolic.diseases* 2000;11:-

Chaumerliac P, Pehuet-Figoni M, Escourolle H, Giauque JP, Luton JP: Lipid disorders in diabetes mellitus. Pathophysiology and therapeutic implications. I.- Physiologic review of the metabolism of VLDLs, HDLs and LDLs. *Semaine des Hopitaux* 1991;67:1528-1540.

Chen SSC: Soybeans and health. *Journal of the Chinese Nutrition Society* 1994;19:335-345.

Cheng IKP: Non-immune therapy of IgA glomerulonephritis. *Nephrology* 1997;3:109-111.

Chowienczyk PJ, Watts GF: Endothelial dysfunction, insulin resistance and non-insulin-dependent diabetes. *Endocrinology & Metabolism, Supplement* 1997;4:225-232.

Chutkan RK: Inflammatory bowel disease. *Primary Care; Clinics in Office Practice* 2001;28:539-556.

Cimmino M: Regional differences in the occurrence and severity of rheumatoid arthritis in Europe. *Cpd Rheumatology* 1999;1:28-32.

Clamp A: Investigations into the mechanisms by which fats modulate the inflammatory response to cytokines. *Dissertation.Abstracts.International* 56-

Cleland LG, James MJ: Adulthood - prevention: Rheumatoid arthritis. *Medical Journal of Australia* 2002;176:S119-S120

Comas Maria: Patron plasmatico de los acidos grasos poliinsaturados en las diferentes fases evolutivas de la enfermedad inflamatori intestinal: Su relacion con factores clinicos, biologicos y nutricionales. *Dissertation Abstracts International* 694-

Connor SL, Connor WE, Rivlin RS: Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Fats and oil consumption in health and disease: current concepts and controversies* 53:

Connor WE, Connor SL, Bendich A, Deckelbaum RJ: n-3 fatty acids from fish and plants: primary and secondary prevention of cardiovascular disease. *Preventive nutrition: the comprehensive guide for health professionals* 2001; 73:-

Coppo R, Amore A, Emancipator SN, et al: Idiopathic IgA nephropathy. Clinic pathological conference. *Giornale Italiano di Nefrologia* 1999;16:79-93.

Costain L: Mediterranean diet. *Family Medicine London* 2001;10:

Crapo P, Vin ik AI: Nutrition controversies in diabetes management. *Journal of the American Dietetic Association* 1987;

Crotty Band Jewell DP: Drug therapy of ulcerative colitis. *British Journal of Clinical Pharmacology* 1992; 34:189-198.

Danao-Camara T, Shintani T: The dietary treatment of inflammatory arthritis: case reports and review of the literature. *Hawaii Medical Journal*. 1999;58:126-131.

Das U: Oxidants, anti-oxidants, essential fatty acids, eicosanoids, cytokines, gene/oncogene expression and apoptosis in systemic lupus erythematosus. *Journal of the Association of Physicians of India* 1998;46:630-634.

Das UN, Kumar KV, Mohan IK: Lipid peroxides and essential fatty acids in patients with diabetes mellitus and diabetic nephropathy. *Journal of Nutritional Medicine* 1994;4:149-155.

Das UN, Suresh Y, Huang YS, Ziboh VA: Prevention of alloxan-induced cytotoxicity and diabetes mellitus by gamma-linolenic acid and other polyunsaturated fatty acids both in vitro and in vivo. *gamma Linolenic acid: recent advances in biotechnology and clinical applications* 2001;31 :-

Davids Rebecca Susanne: Identifying food constituents that may improve cardiovascular disease risk factors in persons with or at risk for type 2 diabetes mellitus. *Masters Abstracts International* 39-04:1135-

De Deckere E, Korver O, Verschuren P, Katan M: Health aspects of fish and n-3 polyunsaturated fatty acids from plant and marine origin. *European Journal of Clinical Nutrition* 1998;52:749-753.

De Vita S, Bombardieri S: The diet therapy of rheumatic diseases. *Recenti Progressi.in Medicina* 1992:707-718.

Donadio JV: The emerging role of omega-3 polyunsaturated fatty acids in the management of patients with IgA nephropathy. *Journal of Renal Nutrition* 2001;11:122-128.

Donadio JV, Jr, De Caterina R, Endres S (ed, Kristensen SD, Schmidt EB: An overview of n-3 fatty acids in clinical renal diseases. *n 3 fatty acids and vascular disease: background and pathophysiology, hyperlipidaemia, renal diseases, ischaemic heart disease* 1993;31:-

Dreval AV, Pokrovski, VB: [Essential fatty acids in the prevention and treatment of vascular complications of diabetes mellitus. *Voprosy Pitaniia* 1992;6-14.

Egan LJ, Sandborn WJ: Drug therapy of inflammatory bowel disease. *Drugs of Today* 1998;34:431-446.

Engelmann GJ: Het effect van polyonverzadigde vetzuren in het dieet van insuline dependente diabetespatienten (Type i) Op de lipidensamenstelling en de deformeerbaarheid van erythrocyten met behulp van h.P.L.C. *Dissertation Abstracts International* 2459-

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA: Long-term effects of n-3 fatty acids on serum lipids and glycaemic control. *Scandinavian Journal of Clinical & Laboratory Investigation* 1994;54:273-280.

Erlangen CB: Long term feeding with a chemically defined diet. *Infusionstherapie und Klinische Ernahrung - Sonderheft* 1975;3:4-6.

Ernst E: Fish oil for ulcerative colitis. *Fortschritte der Medizin* 1992;110:14-

Esteve Comas M, Nunez MC, Fernandez Banares F, et al: Abnormal plasma polyunsaturated fatty acid pattern in non-active inflammatory bowel disease. *Gut* 1993;

Esteves EA, Monteiro JBR: Beneficial effects of soy isoflavones on chronic diseases. *Revista de Nutricao* 2001;14:43-52.

Evans MF: Can we prevent high-risk patients from getting type 2 diabetes? *Canadian Family Physician* 2002;48:279-281.

Ezaki O, Takahashi M, Shigematsu T, et al: Long-term effects of dietary alpha-linolenic acid from perilla oil on serum fatty acids composition and on the risk factors of coronary heart disease in Japanese elderly subjects. *Journal of Nutritional Science & Vitaminology* 1999;45:759-772.

Fasching P, Ratheiser K, Waldhausl W, Rohac M, Vierhapper H: Fish oil as lipostatic factor . *Vasa - Supplementum* 1990;30:62-63.

Fatati G, Croccolino D, Puxeddu A: Omega-3 fatty acids in the treatment of dyslipidemia. *Rivista Italiana di Biologia e Medicina* 1996;16:59-62.

Fineberg SE: The treatment of hypertension and dyslipidemia in diabetes mellitus. *Primary Care; Clinics in Office Practice* 1999;26:951-964.

Fitzgerald TK, Manderson L: Dietary change among Cook Islanders in New Zealand. *Shared wealth and symbol* 1986;-

Foerste A: Fish-oil preparations. Composition, general evaluation, and application possibilities. *Fortschritte der Medizin* 1988;106:

Folwaczny C, Endres S: Fish oil to prevent recurrence of Crohn disease? *Zeitschrift fur Gastroenterologie* 1997;35:651-653.

Fontaine F, Brassinne A, Delforge M, et al: Review on inflammatory bowel disease: Crohn disease and ulcero-hemorrhagic recto-colitis. *Revue Medicale de Liege* 1993;48:593-618.

Frayn KN: Effects of fat on carbohydrate absorption: More is not necessarily better. *British Journal of Nutrition* 2001;86:1-2.

Gaby A: Alternative treatments for rheumatoid arthritis. *Alternative Medicine Review* 1999;4:392-402.

Gans ROB, Bilo HJG, Schouten JA, Rauwerda JA: Fish oil and plasma fibrinogen. *[Letter]*
Gassull Duro MA: Have long-chain PUFA any therapeutic action in IBD? *Pediatrika* 1998;18:25-28.

Gassull MA: Dietary fat intake and inflammatory bowel disease. *Current Gastroenterology Reports* 2001;3:358-61.

Gassull MA, Green CJ, Elia M, Russell CA, Wilson JHP: New insights in nutritional therapy in inflammatory bowel disease. *Proceedings of the 11th Nutricia Symposium* 136:

Gatti A, Bonavita M, De Matteo A, et al: Use of the association between statins and EPA-DHA in the treatment of diabetes mellitus. *Quaderni di Medicina e Chirurgia* 1997;13:61-64.

Geerling BJ: Improved antioxidant status after supplementation with n-3 fatty acids and or antioxidants in addition to a regular diet in patients with Crohn`s disease in a double blind placebo controlled study. *European Journal of Gastroenterology & Hepatology* 1998;10:23-24.

Geerling BJ, Badart-Smook A, van Deursen C, et al: Nutritional supplementation with N-3 fatty acids and antioxidants in patients with Crohn's disease in remission: effects on antioxidant status and fatty acid profile. *Inflammatory Bowel Diseases* 2000;6:77-84.

Geerling BJ, Stockbrugger RW, Brummer RJ: Nutrition and inflammatory bowel disease: an update. *Scandinavian Journal of Gastroenterology* 1999;230:95-105.

Gerster H: The use of n-3 PUFAs (fish oil) in enteral nutrition. *International Journal for Vitamin & Nutrition Research* 1995;65:3-20.

Giese LA: A study of alternative health care use for gastrointestinal disorders. *Gastroenterology Nursing* 2000;23:19-27.

Grand RJ, Ramakrishna J, Calenda KA: Therapeutic strategies for pediatric Crohn disease. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 1996;19:373-380.

Green K: Type 1 diabetes and bone mass: Interrelationships with nutrient intake and physical activity in children and with dietary fish oil in weanling rats. *Masters Abstracts International* 39:1136-

Griffiths A: Nutrition in inflammatory bowel disease. *Current.Opinion.in.Clinical.Nutrition.and.Metabolic. Care* 2000;33:

Grimminger F, Walmrath D, Seeger W, Lasch HG: Antiinflammatory effects of omega-3-lipidinfusion in clinical and experimental studies. *Medizinische Welt* 1993;44:207-216.

Guesnet P, Alessandri JM, Durand G: Metabolism, biological functions and nutritonal importance of polyenoic fatty acids. Summary of Third ICEFAP Congress (Adelaide, Australia, 1-5 March 1992). *Cahiers de Nutrition et de Dietetique* 1993;20:

Gulati PD, Rao MB, Vaishnava H: Letter: Diet for diabetics. *Lancet* 1974;2:297-298.

Gwynn CK, O'Neil KM: The effects of fish-oil supplementation in a diabetic CAPD patient using intraperitoneal insulin. *Dialysis & Transplantation* 1989;18:614-616.

Haban P, Simoncic R, Klvanova I, Ozdin L, Zidekova E: The effect of n-3 fatty acid administration on selected indicators of cardiovascular disease risk in patients with type 2 diabetes mellitus. *Bratislavske Lekarske Listy* 1998;99:37-42.

Hahnefeld M: Diabetes-associated dyslipoproteinemia. *Therapiewoche Schweiz* 1992;8:575-581.

Hamazaki T: Intravenous infusion of n-3 polyunsaturated fatty acids. *Proceedings of the Society for Experimental Biology and Medicine* 1992;200:171-173.

Hamazaki T, Tateno S, Shishido H: Eicosapentaenoic acid and IgA nephropathy. *Lancet* 1984;1:1017-1018.

Hanck C, Singer MV: What is the role of nutrition in ulcerative colitis? *Langenbecks Archiv fur Chirurgie* 1995;380:1-3.

Hanefeld M: Dyslipoproteinemia in diabetes. *Therapiewoche* 1992;42:1550-1559.

Harting JW: New developments in the pharmacotherapy of inflammatory bowel disease. *Pharmaceutisch Weekblad - Scientific Edition* 1992;14:275-286.

Hasegawa S, Kano K, Motoki T: Mechanism of elevation in plasma glucagon/insulin ratio by soybean protein intake. *Soy Protein Research, Japan* 1998;7:86-907.

Hauben M: Comment: evening primrose oil in the treatment of rheumatoid arthritis--proper application of statistical analysis. *Annals of Pharmacotherapy* 1994;28:973

Hazra A, Tripathi SK, Ghosh A: Pharmacology and therapeutic potential of the n-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oils. *Indian Journal of Pharmacology* 1999;31:247-264.

Henderson C, Panush R: Diets, dietary supplements, and nutritional therapies in rheumatic diseases. *Rheumatic Disease Clinics of North America* 1999;25:937-968.

Hess E: Are there environmental forms of systemic autoimmune diseases? *Environmental Health Perspectives.* 1999;107:S11

Hirai K, Higuchi H, Inatsugi N, Yosikawa S: Therapeutic potential of n-3 poly unsaturated fatty acid for three cases of Crohn's disease. *Japanese Journal of Nutrition* 1998;10:

Hjermann I: The influence of dietary change on hemostatic risk variables. *Annals of Epidemiology* 1992;2:525-527.

Ho KKL: IgA nephropathy: In Hong Kong. *Hong Kong Practitioner* 2001;23:453-456.

Holler C, Auinger M, Ulberth F, Irsigler K: Eicosanoid precursors: potential factors for atherogenesis in diabetic CAPD patients? *Peritoneal Dialysis International* 1996;16:S3

Horn HR: Case reports in type 2 diabetes. *Cardiology Review* 1998;15:38-39.

Horrobin DF: The use of gamma-linolenic acid in diabetic neuropathy. *Agents & Actions - Supplements* 1992;37:120-144.

Horrobin DF, Huang YS, Ziboh VA: gamma-Linolenic acid in diabetes. *gamma Linolenic acid: recent advances in biotechnology and clinical applications* 2001;36:-

Huang YS, Ziboh VA, Huang YS, Ziboh VA: *gamma Linolenic acid: recent advances in biotechnology and clinical applications* 2001;-

Hunter JO: Nutritional factors in inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology* 1998;10:235-237.

Huve J: Administration of omega-3 fatty acids and/or zinc for diabetics. *9* 7:

Ilowite N: Premature atherosclerosis in systemic lupus erythematosus. *Journal of Rheumatology.* 2000;27:S9

Ireland PD, Niall M, Sadler S, Deluise M, Traianedes K, O' Dea K: Dietary composition and its role in the treatment of type 2 diabetes. *Proceedings of the Nutrition Society of Australia* 1985;200-

Jacobs J, Rasker J, Bijlsma J: Alternative medicine in rheumatology: Threat or challenge? *Clinical & Experimental Rheumatology* 2001;19:117-119.

Jacotot B: Nutritional interest in the consumption of olive oil. *OCL Oleagineux, Corps Gras, Lipides* 1997;14:

Jacotot B: Olive oil and disease prevention. *Nutrition Clinique et Metabolisme* 1996;9:

Jain S, Gaiha M, Bhattacharjee J, Anuradha S: Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress--a prospective preliminary study. *Journal of the Association of Physicians of India* 2002;50:1028-1033.

Jamal GA: Pathogenesis of diabetic neuropathy: The role of the n-6 essential fatty acids and their eicosanoid derivatives. *Diabetic Medicine* 1990;7:574-579.

Jamal GA: The use of gamma linolenic acid in the prevention and treatment of diabetic neuropathy. *Diabetic Medicine* 1994;11:145-149.

Jamal GA, Carmichael H: The effect of gamma-linolenic acid on human diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *Diabetic Medicine* 1990;7:319-323.

Jamal GA, Carmichael H, Weir AI: Gamma-linolenic acid in diabetic neuropathy. *Lancet* 1986;1:1098-

Jayson M: Dietary therapy for rheumatoid arthritis. *British Journal of Rheumatology* 1993 Nov;32:1030-

Jones DB, Haitas B, Bown EG, et al: Platelet aggregation in non-insulin-dependent diabetes is associated with platelet fatty acids. *Diabetic Medicine* 1986;3:52-55.

Julius U, Hanefeld M: Integrated drug therapy in metabolic syndrome. *Internist* 1996;37:722-730.

Kalden J: Diet in rheumatology. *Internist* 1996;37:1068-1068.

Kaminskas A, Levaciov M, Lupinovic V, Kuchinskene Z: The effect of linseed oil on the fatty acid composition of blood plasma low- and very low-density lipoproteins and cholesterol in diabetics. *Voprosy Pitaniia* 1992;13-14.

Katan MB: Fats for diabetics. *Lancet* 1994;343:1518-

Katsilambros N, Phipippides P, Boletis J, Mavroudis K, Frangaki D, Chaniotis D: Blood sugar changes in diabetics after a test meal containing vegetables and olive oil. *Acta Diabetologica Latina* 1982;2:

Kaur K, Mittal P, Singh H, Chhatwal S: Newer drugs in the treatment of idiopathic ulcerative colitis (IUC). *Journal International Medical Sciences Academy* 1998;11:112-115.

Keelan Monika Maria: Dietary omega(3) Fatty acids and cholesterol modify intestinal transport, enterocyte membrane lipid composition and enterocyte lipid synthesis (Ω3 fatty acids). *Dissertation Abstracts International* 2361-

Klahr S, Harris K: Role of dietary lipids and renal eicosanoids on the progression of renal disease. *Kidney International* 1989;27:S27-S31

Klimes I, Sebokova E: The importance of diet therapy in the prevention and treatment of manifestations of metabolic syndrome X. *Vnitrni Lekarstvi* 1995;41:136-140.

Knapp HR, Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson G: Conjugated linoleic acid as a nutraceutical: observations in the context of 15 years on n-3 polyunsaturated fatty acid research. *Advances in conjugated linoleic acid research, volume 1* 1999;28:-

Kolasinski S: Complementary and alternative therapies for rheumatic disease. *Hospital Practice* 2001;36:31-39.

Korber J, Karaus M, Hampel KE: Drug therapy of chronic inflammatory bowel disease. *Medizinische Welt* 1996;47:51-54.

Kremer J, Robinson D: Studies of dietary supplementation with omega 3 fatty acids in patients with rheumatoid arthritis. *World Review of Nutrition & Dietetics* 1991;66:367-382.

Kromhout D, Valagussa F, Marchioli R: 'Protective nutrients' and up-to-date dietary recommendations. Evidence and perspectives on n 3 polyunsaturated fatty acids in cardiovascular disease. *European-Heart-Journal-Supplements* 2001;3:clinical-

Kruger MC, Potgieter HC et al: Calcium, gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) supplementation in osteoporosis. *Osteoporosis International* 1996;6:250

Kulakova SN, Gapparova KM, Pogozheva AV, Levachev MM: Evaluation of the influence of omega-3 polyunsaturated fatty acids of fish and vegetable origin on the the fatty acid composition of erythrocyte lipids in patients with ischaemic heart disease complicated by impaired glucose tolerance. *Voprosy Pitaniya* 1999;15:5-6, 26.

Ladodo KS, Levachev MM, Naumova VI, et al: Experiment on the use of fish oil Polyenin pediatric practice. *Voprosy Pitaniya* 1996;13:-

Lazebnik LB, Vertkin AL, Malichenko SB, Li ED, Konev IuV Romanovskaia TV, Goncharov LF: Experience in the use of eiconol (a complex of unsaturated fatty acids) in non-insulin-dependent diabetes mellitus. *Klinicheskaia Meditsina* 1996;74:29-33.

Lecerf JM: Treatments of hyperlipoproteinemia. *Gazette Medicale* 1993;100:16-18.

Lee T, Arm J, Horton C, Crea A, Mencia-Huerta J, Spur B: Effects of dietary fish oil lipids on allergic and inflammatory diseases. *Allergy Proceedings* 1991:299-303.

Leeuw IH de Gaal L, V Rillaerts E, Dalemans C: Short-term effects of PUFA-enrichment in the diet of insulin-dependent diabetic patients. *Diabete et Metabolisme* 1986;13:

Lefkowith J, Klahr S: Polyunsaturated fatty acids and renal disease. *Proceedings of the Society for Experimental Biology & Medicine.* 1996;213:13-23.

Lemann M: Novel therapeutic approaches to inflammatory bowel disease. *Semaine des Hopitaux* 1998;74:759-760.

Linn T, Klor HU: Clinical therapy with fish oil. *Aktuelle Ernahrungsmedizin* 1989;21:

Lissner L, Heitmann BL, Bengtsson C, Asp NG, Frayn K, Vessby B: Population studies of diet and obesity. *Diet and the metabolic syndrome* 13:

Liu S: Dietary fat and exercise influence regulation of glucose metabolism in skeletal muscle. *Dissertation Abstracts International* 6601-

Locker F: The effect of diet and vitamin d on mineral metabolism in primary hyperparathyroidism. *Dissertation Abstracts International* 57:4134-

Lorenz-Meyer H: Fish oil for prevention of Crohn disease recurrence. *Zeitschrift fur Gastroenterologie* 1997;35:XX-XXI

Lovejoy JC: Dietary fatty acids and insulin resistance. *Current Atherosclerosis Reports* 1999;1:215-220.

Maes B: IgA nephropathy. *Tijdschrift voor Geneeskunde* 2000;56:1496-1508.

Magaro M, Zoli A, Altomonte L, et al: Effect of fish oil on neutrophil chemiluminescence induced by different stimuli in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1992;51:877-880.

Malaguarnera M, Giugno I, Ruello P, Vinci E, Panebianco MP, Motta M: Current treatment of hypertriglyceridemia. [Italian]. *Recenti Progressi in Medicina* 2000;91:379-387.

Malichenko SB, Lazebnik LB, Vertkin AL, Konev IuV Romanovskaia TV, Smirnova OI: The effects of eiconol in elderly patients with non-insulin-dependent diabetes mellitus. *Terapevticheskii Arkhiv* 1996;68:15-18.

Mann JI, Hockaday TD, Hockaday JM, Turner RC: A prospective study of modified-fat and low-carbohydrate dietary advice in the treatment of maturity-onset diabetes. *Proceedings of the Nutrition Society* 1976;35:72A-73A.

March L, Stenmark J: Non-pharmacological approaches to managing arthritis. *Medical Journal of Australia* 2001;175:S102-S107

Marsch-Ziegler U: Chronic inflammatory intestine disease. Aspects for current therapy. *Zeitschrift fur Allgemeinmedizin* 1994;70:53-56.

Mathus-Vliegen EMH: The role of diets in the treatment of inflammatory bowel diseases. *Pharmaceutisch Weekblad* 2000;135:1314-1318.

Matzkies F: Essential fatty acids. *Fortschritte der Medizin* 1980;98:940-944.

McGill EJ: Lipid-lowering dietary advice in diabetes. *Practical Diabetes International* 1995;12:157-158.

Messina M, Messina V: Soyfoods, soybean isoflavones, and bone health: a brief overview. *Journal of Renal Nutrition.* 2000;10:63-68.

Metzner C, Ulrich Merzenich G: Nutrition therapy of the metabolic syndrome and diabetes mellitus with natural substances (dietary fibre, fatty acids). *VitaMinSpur* 2001;13:

Miller B: A pathogenetically substantiated treatment for chronic inflammatory bowel disease - Does it come into view? *Zeitschrift fur Gastroenterologie* 1993;31:30-34.

Misra A: Insulin resistance syndrome: Current perspective and its relevance in Indians . *Indian Heart Journal* 1998;50:385-395.

Miura S, Tsuzuki Y, Hokari R, Ishii H: Modulation of intestinal immune system by dietary fat intake: relevance to Crohn's disease . *Journal of Gastroenterology & Hepatology* 1998;13:1183-1190.

Miyares Gomez AI: Nutritional factors involved in the treatment of inflammatory bowel disease. *Revista Espanola de Pediatria* 1993;51:241-291.

Mizushima S, Moriguchi EH, Ishikawa P, et al: Fish intake and cardiovascular risk among middle-aged Japanese in Japan and Brazil. *Journal of Cardiovascular Risk* 1997;4:191-199.

Moretti G, Mancarella P, Marin V: Diet and cardiovascular diseases in fishermen and farmers in an Italian northern sea town. *Igiene Moderna* 1999;12:

Mori TA: Fish oils, dyslipidaemia and glycaemic control in diabetes. *Practical Diabetes International* 1999;16:223-226.

Mori TA, Puddey IB, Burke V, et al: Effect of omega 3 fatty acids on oxidative stress in humans: GC-MS measurement of urinary F2-isoprostane excretion. *Redox Report* 2000;5:45-46.

Morris MC, Sacks F, Rosner B: Fish oil to reduce blood pressure: A meta-analysis. *Annals of Internal Medicine* 1994;120:10-

Muller SD: Actual aspects about nutritionmedical therapy of hyperlipoproteinaemia. *Ernahrungsforschung* 2001;57:

Muller S, Pfeuffer C: Dietetic treatment of inflammatory rheumatic and rheuma-like diseases. *VitaMinSpur* 2000;1:

Muls E, Furst P: Nutrition recommendations for the person with diabetes. *Consensus roundtable on nutrition support of tube fed patients with diabetes*
Murthy R, Murthy M: Omega-3 fatty acids as anti-inflammatory agents: A classical group of nutraceuticals. *Journal of Nutraceuticals, Functional & Medical Foods* 1999;2:53-72.

Myrup B, Rossing P, Jensen T, et al: Lack of effect of fish oil supplementation on coagulation and transcapillary escape rate of albumin in insulin-dependent diabetic patients with diabetic nephropathy. *Scandinavian Journal of Clinical & Laboratory Investigation* 2001;61:349-356.

Nachman PH, Martin J: Developments in the immunotherapy of glomerular disease. *Journal of Pharmacy Practice* 2002;15:472-489.

Nagel E, Bartels M, Pichlmayr R: Influence of nutrition in ulcerative colitis - The significance of nutritional care in inflammatory bowel disease. *Langenbecks Archiv fur Chirurgie* 1995;380:4-11.

Nakazawa A, Hibi T: Is fish oil (n-3 fatty acids) effective for the maintenance of remission in Crohn's disease? *Journal of Gastroenterology* 2000;35:173-175.

Nettleton JA: Omega-3 fatty acids and health. 1995;xiii + 359

Nordoy A: Statins and omega-3 fatty acids in the treatment of dyslipidemia and coronary heart disease. *Minerva Medica* 2002;93:357-363.

O'Dea K: Westernization and non-insulin-dependent diabetes in Australian Aborigines. *Ethnicity & Disease* 1991;1:171-187.

O'Keefe SJ: Nutrition and gastrointestinal disease. *Scandinavian Journal of Gastroenterology - Supplement* 1996;220:52-59.

O'Morain CA: Does nutritional therapy in inflammatory bowel disease have a primary or an adjunctive role? *Scandinavian Journal of Gastroenterology - Supplement* 1990;172:29-34.

O'Sullivan MA, O'Morain CA: Nutritional therapy in Crohn's disease. *Inflammatory Bowel Diseases* 1998;4:45-53.

Odugbesan O, Barnett AH: Use of a seaweed-based dressing in management of leg ulcers in diabetics: A case report. *Practical Diabetes* 1987;4:46-47.

Okuda Y, Mizutani M, Tanaka K, Isaka M, Yamashita K: Is eicosapentaenoic acid beneficial to diabetic patients with arteriosclerosis obliterans. *Diabetologia Croatica* 1992;21:13-17.

Opara EC, Hubbard VS: Essential fatty acids (EFA): role in pancreatic hormone release and concomitant metabolic effect. *Journal of Nutritional Biochemistry* 1993;102:

Otsuji S, Kamada T, Yamashita T, et al: The influence of dietary sardine oil (eicosapentaenoic acid) on the erythrocyte membrane fluidity in diabetic patients. *Rinsho Byori - Japanese Journal of Clinical Pathology* 1984;32:764-771.

Ozdemir I, Bolu E: Clinical applications of fish oil. *Bulletin of Gulhane Military Medical Academy* 1990;32:681-692.

Panchenko VM, Karabasova MA, Liutova LV, et al: Influence polyunsaturated fatty acids omega-3 on coagulation and fibrinolysis systems in patients with NIDDM. *Klinicheskaia Meditsina* 2002;80:40-43.

Pav J, Rames I, Formanek M: Parameters of fat matabolism and their relation to the compensation of diabetes mellitus. *Vnitrni Lekarstvi* 1972;18:246-252.

Pedersen JI: More on trans fatty acids. *British Journal of Nutrition* 2001;85:249-250.

Pelikanova T, Kohout M, Valek J, et al: The effect of fish oil on the secretion and effect of insulin in patients with type II diabetes. *Casopis Lekaru Ceskych* 1992;131:668-672.

Peppercorn MA: Drug therapy of inflammatory bowel disease, part II: Patient management recommendations. *Drug Therapy* 1992;22:43-48+53.

Peppercorn MA: Medical therapies for ulcerative colitis. Article three in the series. *Practical Gastroenterology* 1992;16:11-19.

Peppercorn MA: Newer agents for the treatment of inflammatory bowel disease. *P & T* 1993;18:583-588.

Pinelli L, Alfonsi L, Mormile R, Piccoli R: Diet for young diabetics: Standard and mediterranean. *Annales de Pediatrie* 1998;45:571-577.

Pinelli L, Mormile R, Alfonsi L, et al: The role of nutrition in prevention of complications in insulin-dependent diabetes mellitus. *Proceedings of the First Workshop on Insulin dependent Diabetes Mellitus in Children and Adolescents,* 1997;25:

Pinelli L, Mormile R, Gonfiantini E, et al: Recommended dietary allowances (RDA) in the dietary management of children and adolescents with IDDM: an unfeasible target or an achievable cornerstone? *Journal of Pediatric Endocrinology & Metabolism* 1998;11:S46

Plessas ST, Athanasiadis N, Papadakis S: omega-3 polyunsaturated fatty acids and eicosanoids: Sources, biochemistry and functions in physiological conditions and in cardiovascular disease current status. *Review of Clinical Pharmacology & Pharmacokinetics, International Edition* 1998;16:5-29.

Podell R: Nutritional treatment of rheumatoid arthritis. Can alterations in fat intake affect disease course? *Postgraduate Medicine* 1972;1985:65-69.

Pogozheva AV, Tutelyan VA, Gapparova KM, Trushina EN, Myagkova MA: The influence of antiatherosclerotic diet with inclusion PUFA omega-3 of a vegetative and sea origin on parameters of cellular and humoral immunity in patients with ishemic heart disease complicated by impaired carbohydrates tolerance. *Voprosy Pitaniya* 2000;16:

Present DN, Ginsberg AL, Arora S, Kaplan M: New drugs improve prognosis for patients with IBD. *Internal Medicine* 1993;14:20-30.

Press AG, Ramadori G: Therapy of chronic enteritis. Part II. Indications for therapy. *Therapiewoche* 1994;44:962-970.

Prier A: Effects of dietetic manipulations on the course of rheumatoid arthritis. *Presse Medicale* 1988:1181-1183.

Prindiville TP, Cantrell MC, Gershwin ME, German JB, Keen CL: Autoimmune diseases of the digestive tract. *Nutrition and immunology: principles and practice* 2000;140:-

Prokopiuk M, Wierzbicki P, Kade G: IgA nephropathy--advances of therapy. *Polskie Archiwum Medycyny Wewnetrznej* 2001;106:1079-1086.

Pullman-Mooar S, Laposata M, Lem D, et al: Alteration of the cellular fatty acid profile and the production of eicosanoids in human monocytes by gamma-linolenic acid. *Arthritis & Rheumatism* 1990:1526-1533.

Putz K: Dietary aspects of osteoporosis. *VitaMinSpur* 2001;

Raheja B, Bhakta V, Chandiramani A, et al: Use of fish oil locally in the management of diabetic foot-preliminary observations. *Journal of the Diabetic Association of India* 1989;29:47-48.

Raheja BS: Essential fatty acids, atherosclerosis and diabetes. *Journal of the Diabetic Association of India* 1990;30:20-

Rahman MA, Stork JE, Dunn MJ: The roles of eicosanoids in experimental glomerulonephritis. *Kidney International - Supplement* 1987;22:S40-S48

Rao S, Erasmus RT: Pilot study on plasma fatty acids in poorly controlled non insulin dependent diabetic Melanesians. *East African Medical Journal* 1996;73:816-818.

Rasmussen O, Lauszus FF, Christiansen C, Thomsen C, Hermansen K: Differential effects of saturated and monounsaturated fat on blood glucose and insulin responses in subjects with non-insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1996;63:249-253.

Rasmussen OW, Lauszus FF, Christiansen CS, Thomsen CH, Hermansen K: Saturated and monounsaturated fats in patients with insulin-dependent diabetes. Different effects on blood glucose and insulin response in NIDDM. *Ugeskrift for Laeger* 1998;160:842-846.

Rasmussen OW, Thomsen CH, Hansen KW, Vesterlund M, Winther E, Hermansen K: [Favourable effect of olive oil in patients with non-insulin-dependent diabetes. The effect on blood pressure, blood glucose and lipid levels of a high-fat diet rich in monounsaturated fat compared with a carbohydrate-rich diet. *Ugeskrift for Laeger* 1995;157:1028-1032.

Rastegar S: Identifying and characterizing agents in soy that have a potential role in diabetes development. *Masters Abstracts International* 36-01: 94-

Reseland JE, Anderssen SA, Solvoll K, et al: Effect of long-term changes in diet and exercise on plasma leptin concentrations. *American Journal of Clinical Nutrition* 2001;73:240-245.

Riemersma RA, Armstrong R, Kelly RW, Wilson R: Essential fatty acids and eicosanoids: invited papers from the Fourth International Congress, Edinburgh, Scotland, UK, July 20-24, 1997. 1998;432

Rivellese AA, De Natale C, Lilli S: Type of dietary fat and insulin resistance. *Annals of the New York Academy of Sciences* 2002;967:329-335.

Rivlin RS: Fats and oil consumption in health and disease: current concepts and controversies. Proceedings of a symposium held at the Rockefellar University, New York, USA, 24-25 April, 1995. *American Journal of Clinical Nutrition* 1997;

Roberts J, Davies B, McKeigue P, Davey G: Specific and combined use of exercise training and omega-3 fatty acids as interventions for insulin resistance. *Journal of Sports Sciences* 1998;16:59-

Robinson DR: Alleviation of autoimmune disease by dietary lipids containting Omega-3 fatty acids. *Rheumatic Disease Clinics of North America* 1991;17:213-222+viii.

Robinson DR, Colvin RB, Hirai A, et al: Dietary marine lipids modify autoimmune diseases. *Health effects of polyunsaturated fatty acids in seafoods* 1986;16 ref.:-

Robinson DR, Xu LL, Olesiak W, et al: Suppression of autoimmune disease by purified n-3 fatty acids. *Health effects of dietary fatty acids* 1991;5:-

Roesli Rully: Study on the prevalence of non-insulin-dependent diabetes mellitus and impaired glucose tolerance in a rural area of west java, indonesia. *Dissertation Abstracts International* 656-

Rohrbach J, Reinelt D: Polyunsaturated fatty acids in the serum of patients with various diseases. *Zeitschrift fur die Gesamte Innere Medizin und Ihre Grenzgebiete* 1968;23:656-659.

Rontoyannis GP, Simopoulos AP: Diet and exercise in the prevention of cardiovascular disease. Nutrition and fitness in health and disease. *World Review of Nutrition and Dietetics* 1993;72:

Rossing P, Hansen BV, Nielsen FS, Myrup B, Holmer G, Parving HH: Fish oil in diabetic nephropathy. *Diabetes Care* 1996;19:1214-1219.

Rutgeerts PJ: Postoperative recurrence prophylaxis in Crohn's disease: An update. *Research & Clinical Forums* 1998;20:49-55.

Sailer D: Diet as therapy - Changes in therapeutic concepts? *Fortschritte der Medizin* 1988;106:52-55.

Samsonov MA, Isaev VA: Latest in the prevention and treatment of atherosclerosis, ischaemic heart disease, hypertension and other disorders. *Voprosy Pitaniya* 1995;-

Sathe SR, Raheja BS: Fish oil in the management of diabetic foot. *Journal of the Diabetic Association of India* 1994;34:51-54.

Savage GP, Webster G, Plows E: Nutritional trends for the future. Proceedings of a Continuing Education Seminar, Orakei Basin, Auckland, New Zealand, 15th November 1994 . 1994;-

Schacky Cvon Baumann K, Angerer P, Von Schacky C : The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications. *Prevention and treatment of vascular disease: a nutrition based approach, Aarhus, Denmark, 18 20 May, 2000* 2000;

Schaller J: Aggressive treatment in childhood rheumatic diseases. *Clinical & Experimental Rheumatology* 1994;12:S97-S105

Scheurlen C: Dietary therapy in Crohn disease. *Internist* 1990;31:433-

Scheurlen M, Steinhilber D, Daiss W, Clemens M, Schmidt H, Jaschonek K: Effects of an elemental diet containing fish oil on neutrophil LTB4 synthesis and membrane lipid composition. *Progress in Clinical & Biological Research* 1989;301:505-509.

Schiele J, Nowack R, Julian BA, van der Woude FJ: Treatment of immunoglobulin A nephropathy. *Annales de Medecine Interne* 1999;150:127-136.

Schleiffer T, Brass H: Lipid metabolism of chronic renal failure and diabetic nephropathy - Update. *Nieren- und Hochdruckkrankheiten* 1992;21:58-71.

Schmidt EB, Moller JM, Svaneborg N, Dyerberg J: Safety aspects of fish oils. Experiences with an n-3 concentrate of re-esterified triglycerides (Pikasol(TM)). *Drug Investigation* 1994;7:215-220.

Schmitz PG, O' Donnell MP, Kasiske BL, Keane WF: Glomerular hemodynamic effects of dietary polyunsaturated fatty acid supplementation. *Journal of Laboratory and Clinical Medicine* 1991;43:

Schwab D, Raithel M, Hahn EG: Enteral nutrition in acute Crohn disease. *Zeitschrift fur Gastroenterologie* 1998;36:983-995.

Selby W: Current management of inflammatory bowel disease. *Journal of Gastroenterology & Hepatology* 1993;8:70-83.

Seppanen R, Reunanen A: Diet habits of diabetics and nondiabetics in Finland. *Naringsforskning* 1979;
Sharma RK, Sural S: Current management of glomerular diseases. *Journal of Internal Medicine of India* 1999;2:155-160.

Shen Chwan Li: Effect of dietary polyunsaturated fatty acids on prostaglandin e(2) Aand insulin-like growth factor-i in bone modeling. *Dissertation Abstracts International* 56-09, Section: B:4663-

Siamopoulou A, Challa A, Kapoglou P, Cholevas V, Mavridis A, Lapatsanis P: Effects of intranasal salmon calcitonin in juvenile idiopathic arthritis: An observational study. *Calcified Tissue International* 2001;69:25-30.

Silvis N, Vorster HH, Mollentze WF, Jagar Jde Huisman HW, De Jager J: Metabolic and haemostatic consequences of dietary fibre and N-3 fatty acids in black type 2 (NIDDM) diabetic subjects: a placebo controlled study. *International Clinical Nutrition Review* 1990;

Simonsen N: Nutritional Determinants of Rheumatoid Arthritis. *Dissertation.Abstracts.International*

Simopoulos AP, Pavlou KN, Simopoulos AP, Pavlou KN: *Nutrition and fitness 2: metabolic studies in health and disease* 2001;-

Simpser E, Daum F, Dinari G, et al: Nutrition in pediatric inflammatory bowel disease . *Pediatric nutrition* 1998;40:-

Singer P, Gnauck G, Honigmann G, et al: The fatty acid pattern of adipose tissue and liver triglycerides according to fat droplet size in liver parenchymal cells of diabetic subjects. *Diabetologia* 1974;

Singer P, Honigmann G, Schliack V: Decrease of eicosapentaenoic acid in fatty liver of diabetic subjects. *Prostaglandins & Medicine* 1980;5:183-200.

Singer P, Honigmann G, Schliack V: On the fatty acids of the triglycerides in inflammatory liver diseases of diabetics without and with hyperlipoproteinemia. *Zeitschrift fur die Gesamte Innere Medizin und Ihre Grenzgebiete* 1981;36:513-519.

Singh G: Fish oils in rheumatoid arthritis. *Annals of Internal Medicine* 1988;108:904-905.

Singh RB, Rastogi SS, Rao PV, et al: Diet and lifestyle guidelines and desirable levels of risk factors for the prevention of diabetes and its vascular complications in Indians: a scientific statement of The International College of Nutrition. Indian Consensus Group for the Prevention of Diabetes. *Journal of Cardiovascular Risk* 1997;4:201-208.

Sircar S, Kansra U: Choice of cooking oils--myths and realities. *Journal of the Indian Medical Association* 1998;96:304-307.

Socha P, Ryzko J, Koletzko B, et al: The influence of fish oil therapy in children with inflammatory bowel disease on the fatty acid status. *Pediatria Wspolczesna* 2002;4:413-416.

Song T: Soy isoflavones: Database development, estrogenic activity of glycitein and hypocholesterolemic effect of daidzein. *Dissertation Abstracts International* 59:5638-

Sorokin EL, Smoliakova GP, Bachaldin IL: Clinical efficacy of eiconol in patients with diabetic retinopathy. *Vestnik Oftalmologii* 1997;113:37-39.

Soustre Y, Laurent B, Schrezenmeir J, Pfeuffer M, Miller G, Parodi P: Trans fatty acids. *Bulletin of the International Dairy Federation* 2002;-

Stender S, Jensen T, Deckert T: Experience with fish oil treatment with special emphasis on diabetic nephropathy. *Journal of Diabetic Complications* 1990;4:70-71.

Stone NJ, Van Horn L: - Therapeutic Lifestyle Change and Adult Treatment Panel III: Evidence Then and Now. *Current Atherosclerosis Reports* 2002;4:433-443.

Stotland BR, Lichtenstein GR: Newer treatments for inflammatory bowel disease. *Primary Care; Clinics in Office Practice* 1996;23:577-608.

Stotland BR, Lichtenstein GR: Newer treatments for inflammatory bowel disease. *Drugs of Today* 1998;34:177-192.

Sugano M, Ikeda A: Regulation of soybean protein of alpha-linolenic acid metabolism: effect of diabetes. *Report of the Soy Protein Research Committee Japan* 1995;6 ref.:18-206.

Takazakura E, Ohsawa K, Hamamatsu K, et al: Prevention and treatment of diabetic nephropathy; Decreased microalbuminuria after six months treatment with eicosapentaenoic acid (EPA) ethyl ester. *Conference: The Third International Symposium on treatment of Diabetes Mellitus 13 JUL 1988 to 15 JUL 1988; Nagoya, JAPAN* 1990;562-566.

Tamas D, Gyorgyi C, Katalin T, et al: Polyunsaturated fatty acids in plasma lipids of obese children with and without metabolic cardiovascular syndrome. *Lipids* 2000;

Tjornum TE: Olive oil for patients with diabetes. *Ugeskrift for Laeger* 1995;157:2457-2458.

Tjornum TE: Olive oil to diabetics--again. *Ugeskrift for Laeger* 1995;157:3637-

Tobin A: Fish oil supplementation and ulcerative colitis. *Annals of Internal Medicine* 1992;117:535-536.

Toeller M: Nutritional therapy in diabetes mellitus. *Aktuelle Ernahrungsmedizin* 2002;27 :101-107.

Tonstad S: Drug therapy of hyperlipidemia -- unanswered questions. *Tidsskrift for Den Norske Laegeforening* 1997;117:674-677.

Tonstad S: Indications for lipid-lowering drugs: Unanswered questions. *Tidsskrift for Den Norske Laegeforening* 1997;117:674-677.

Tonstad S, Leren TP, Ose L: Diagnosis and treatment of severe hyperlipidemia. *Tidsskrift for Den Norske Laegeforening* 1997;117:4241-4244.

Turpin G, Bruckert E: Management of atherogenic hyperlipidemia. *Annales de Cardiologie et d Angeiologie* 1998;47:627-632.

Uauy R, Mena P, Valenzuela A: Essential fatty acids as determinants of lipid requirements in infants, children and adults. *European Journal of Clinical Nutrition* 1999;53:S 7

Ueki M, Matsui T, Yamada M, et al: Randomized controlled trial of amino acid based diet versus oligopeptide based diet in enteral nutritional therapy of active Crohn's disease. *Japanese Journal of Gastroenterology* 1994;91:1415-1425.

Uhlig T: Clinical application of omega 3 fatty acids (fish oil). *Deutsche Medizinische Wochenschrift* 1995;120:1262-1263.

Uusitupa M, Louheranta A, Lindstrom J, et al: The Finnish Diabetes Prevention Study. *Diet and the metabolic syndrome*

Valensi P, Attalah M, Behar A, Attali JR: Capillary permeability in diabetes. [French]. *Sang Thrombose Vaisseaux* 1994;6:473-481.

Valtuena S, Sette S, Branca F: Influence of Mediterranean diet and Mediterranean lifestyle on calcium and bone metabolism. *International Journal for Vitamin & Nutrition Research.* 2001;71:189-202.

Vanbeber Anne Duffy: The effect of omega-3, omega-6, and omega-9 fatty acid supplements on the serum fatty acid profile and immune response of renal dialysis patients (Fish oil). *Dissertation Abstracts International* 4133-

Vaupel N: Substitution of Omega-3 fatty acids in type I and type II diabetics. *Fortschritte der Medizin* 1996;114:32-

Venter CS, van Eyssen E: More legumes for better overall health. *SAJCN South African Journal of Clinical Nutrition* 2001;S32-3.

Vergroesen AJ, Crawford M: Role of fats in human nutrition. 2002;Hardback.:-

Vessby B: Dietary fat and insulin action in humans. *British Journal of Nutrition* 2000;83:S6

Voigt J, Hagemeister H: Dietary influence on a desirable fatty acid composition in milk from dairy cattle. *New trends in animal nutrition, 28 29 June, 2001, Jachranka, Poland* 2001;

Volkert R: Omega 3 fatty acids: Fish oil capsules as drugs. *Zeitschrift fur Allgemeinmedizin* 1990;66:776-

Von Ritter C: Inflammatory bowel disease. Pathophysiology and medical treatment. *Radiologe* 1998;38:3-7.

Wahlqvist ML, Lo CS, Myers KA: Fish intake and arterial wall characteristics in healthy people and diabetic patients. *Lancet* 1989;2:944-946.

Wahlqvist ML, Lo CS, Myers KA: Relationships between fish intake and arterial wall characteristics. *Proceedings of the Nutrition Society of Australia* 1988;3 ref.:1013-

Wahrburg U: Mediterranean diet and its role in the prevention and treatment of diet-related diseases. *Internistische Praxis* 2001;41:815-826.

Wardle EN: Alternative therapies for vasculitis and proliferative nephritides: The role of cyclic AMP elevating agents. *Renal Failure* 1998;20:7-13.

Wardle EN: IgA nephropathy. *New England Journal of Medicine Online* 2003;348:79-81.

Wardle EN: Rationales for treating IgA nephropathies. *Renal Failure* 2000;22:1-16.

Watkins B, Seifert M: Conjugated linoleic acid and bone biology. *Journal of the American College of Nutrition* 2000;478S-486S.

Watson J, Madhok R, Wijelath E, et al: Mechanism of action of polyunsaturated fatty acids in rheumatoid arthritis. *Biochemical.Society Transactions.* 1990;284-285.

Weber N: Oleic acid-rich fats in nutrition. *Schriftenreihe des Bundesministeriums fur Ernahrung, Landwirtschaft und Forsten* 1997;-

Wijendran Vasuki: Long chain polyunsaturated fatty acid metabolism in normal pregnancy and pregnancy complicated with gestational diabetes mellitus. *Dissertation Abstracts International* 2617-

Wilhelmi G: Potential effects of nutrition including additives on healthy and arthrotic joints. I. Basic dietary constituents. *Zeitschrift fur Rheumatologie* 1993;52:174-179.

Wolfram G: Diet therapy in metabolic diseases 1996. *20 years of rational dietetics in Germenay 1976-1996* 1996;

Wolfram G: Omega3- and omega6-Fatty acids - biochemical specialities and biological effects. *Fett Wissenschaft Technologie* 1989;

Woo J, Ho SC, Yu AL: Lifestyle factors and health outcomes in elderly Hong Kong chinese aged 70 years and over. *Gerontology* 2002;48:234-240.

Wright J, Furst P: Effect of high-carbohydrate versus high-monounsaturated fatty acid diet on metabolic control in diabetes and hyperglycemic patients. *Consensus roundtable on nutrition support of tube fed patients with diabetes*

Yam D, Friedman J, Bott-Kanner G, Genin I, Shinitzky M, Klainman E: Omega-3 fatty acids reduce hyperlipidaemia, hyperinsulinaemia and hypertension in cardiovascular patients. *Journal of Clinical & Basic Cardiology* 2002;5:229-231.

Yamamoto S: Essential unsaturated fatty acids. *Nippon Rinsho - Japanese Journal of Clinical Medicine* 1999;57:2242-2246.

Yeh Lan Lan Liang: The relationship of serum fatty acid distributions to the risk of coronary heart disease and dietary intake (Fatty acids). *Dissertation Abstracts International* 2793-

Yszko JS, Yszko J, Pawlak K, liwiec M: Effect of treating glomerulonephritis with omega 3 fatty acids for selected parameters of hemostasis, blood platelet function and lipid metabolism. *Przeglad Lekarski* 1996;53:600-603.

Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ: Advances in conjugated linoleic acid research, volume 1. 1999;-

Zaccagna CA, Zullo G: The erectile dysfunction. Alimentary approach by metabolic supplementation with PUFA - 3. *Gazzetta Medica Italiana* 2002;161:53-61.

Zak A, Zeman M, Tvrzicka E, et al: Glucose tolerance, insulin secretion, plasma lipid fatty acids, and the hypolipidemic effects of fish oil. *Dietary lipids and insulin action Second International Smolenice Insulin Symposium* 378-379.

Zeman M, Zak A, Tvrzicka E, Buchtikova M, Stipek S, Pousek L: [Insulinemia, fatty acids in plasma lipids and lipoproteins and oxidation of VLDL and LDL in hyperlipidemia. *Sbornik Lekarsky* 2000;101:77-82.

Zurier R, Rossetti R, Furse R, Huang Y, Ziboh V: Gamma-Linolenic acid, inflammatory arthritis, and immune responses. *Gamma.Linolenic.acid:.recent.advances.in.biotechnology.and.clinical.applications.* 2001;38:-

Rejected RAND's Search Unsuccessful

Adam O: The role of dietary fat] in the prevention and therapy of nutrition-related diseases: the point of view of a rheumatologist. *7th Aachen dietetic continuing education* 6:

Castiglioni A, Savazzi GM: The prevention and treatment of diabetic nephropathy. *European Journal of Internal Medicine* 1993;4:181-192.

Corda Christophe: Contribution a l'etude du role des acides gras polyinsatures de la serie omega-3 dans la prevention de la nephrotoxicite de la ciclosporine a chez des patients ayant beneficie d'une greffe de rein: Etude randomisee en double aveugle contre placebo. *Dissertation Abstracts International* 53: 693-

Donnellan Christopher Edward: The effect of different dietary fatty acids upon the development of obesity and insulin resistance. *Dissertation Abstracts International* 61-04:1023-

Heller A, Koch T: Omega-3 fatty acids as adjuvant therapy in inflammatory diseases. *Anaesth Intensivmedizin* 1996;10:517-28.

Lau C, Morley K, McMahon H, Belch J: Maxepa reduced non-steroidal anti-inflamatory drug requirement in patients with mild rheumatoid arthritis. *Hung Rheumatol* 1991;32:126a

Lee T, Austen K: Arachidonic acid metabolism by the 5-lipoxygenase pathway, and the effects of alternative dietary fatty acids . *Advances in Immunology* 1986;39:145-175.

Tulleken J: Long chain omega-3 polyunsaturated fatty acids in rheumatoid arthritis. *The Netherlands. Rijksuniversiteit Groningen* 1991;

Rejected Condition

Abate N, Jialal I: Therapy and clinical trials. *Current Opinion in Lipidology* 2002;13:457-460.

Adam O: Nutrition as adjuvant therapy for chronic polyarthritis. *Zeitschrift fur Rheumatologie* 1993;52:275-280.

Adam O, Schubert A, Adam A, Antretter N, Forth W: Effects of omega-3 fatty acids on renal function and electrolyte excretion in aged persons. *European Journal of Medical Research* 1998; 3:111-118.

Almallah YZ, El Tahir A, Heys SD, Richardson S, Eremin O: Distal procto-colitis and n-3 polyunsaturated fatty acids: the mechanism(s) of natural cytotoxicity inhibition. *European Journal of Clinical Investigation* 2000;30:58-65.

Arrington JL, McMurray DN, Switzer KC, Fan YY, Chapkin RS: Docosahexaenoic acid suppresses function of the CD28 costimulatory membrane receptor in primary murine and Jurkat T cells. *Journal of Nutrition* 2001;131:1147-1153.

Assmann G, Backer Gde Bagnara S, Betteridge J, et al: International consensus statement on olive oil and the Mediterranean diet: implications for health in Europe. *European Journal of Cancer Prevention* 1997;30:

Baird D, Umbach D, Lansdell L, et al: Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. *J Clin Endocrinol Metab* 1995;80:1685-90.

Baker PW, Gibbons GF: Effect of dietary fish oil on the sensitivity of hepatic lipid metabolism to regulation by insulin. *Journal of Lipid Research* 2000;48:

Barham JB, Edens MB, Fonteh AN, Johnson MM, Easter L, Chilton FH: Addition of eicosapentaenoic acid to gamma-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. *Journal of Nutrition* 2000;130:1925-1931.

Berlin E, Bhathena SJ, Judd JT, et al: Effects of omega-3 fatty acid and vitamin E supplementation on erythrocyte membrane fluidity, tocopherols, insulin binding, and lipid composition in adult men. *Journal of Nutritional Biochemistry* 1992;3:392-400.

Bhathena SJ, Berlin E, Judd JT, et al: Effects of omega 3 fatty acids and vitamin E on hormones involved in carbohydrate and lipid metabolism in men. *American Journal of Clinical Nutrition* 1991;54:684-688.

Bordin P, Bodamer OA, Venkatesan S, Gray RM, Bannister PA, Halliday D: Effects of fish oil supplementation on apolipoprotein B100 production and lipoprotein metabolism in normolipidaemic males. *European Journal of Clinical Nutrition* 1998;52:104-109.

Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV: The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. *New England Journal of Medicine* 1993;42 :4

Bourre JM, Dumont O, Piciotti M, et al: Essentiality of omega-3 fatty acids for brain structure and function, in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:103-117.

Broadhurst CL: Balanced intakes of natural triglycerides for optimum nutrition: an evolutionary and phytochemical perspective. *Medical Hypotheses* 1997;49:247-261.

Brooks Angela Todd: The influence of ground flaxseed or flaxseed oil on indicators for diabetes in adults. *Masters Abstracts International* 40-05: 1222-

Brzezinski A, Adlercreutz: Short term effects of phytoestrogen-rich diet on postmenopausal women. *Menopause* 1997;4:89-94.

Burn JH: Early observations and their importance today. I. Diabetes in childhood, II. Theophylline in myasthenia gravis, III. Properties of cod liver oil. *Journal of Pharmacy & Pharmacology* 1978;30:779-782.

Burnett JR, Watts GF: Therapeutic considerations for postprandial dyslipidaemia. *Diabetes, Obesity & Metabolism* 2001;3:143-156.

Campbell JM, Fahey GC, Demichele SJ, Garleb KA: Metabolic characteristics of healthy adult males as affected by ingestion of a liquid nutritional formula containing fish oil, oligosaccharides, gum arabic and antioxidant vitamins. *Food & Chemical Toxicology* 1997;35:1165-1176.

Campos FG, Waitzberg DL, Habr Gama A, et al: Impact of parenteral n-3 fatty acids on experimental acute colitis. *British Journal of Nutrition* 2002;87:S83-S88

Candela M, Cherubini G, Chelli F, Danieli G, Gabrielli A: Fish-oil fatty acid supplementation in mixed cryoglobulinemia: a preliminary report. *Clinical & Experimental Rheumatology* 1994;12:509-513.

Carroll DN, Roth MT: Evidence for the cardioprotective effects of omega-3 fatty acids. *Annals of Pharmacotherapy* 2002;36:1950-1956.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ: The effect on human tumor necrosis factor alpha and interleukin 1beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *American Journal of Clinical Nutrition* 1996;63:116-122.

Chan DC, Watts GF, Barrett PH, Beilin LJ, Mori TA: Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. *Clinical Chemistry* 2002;48:

Clarke SD: Polyunsaturated fatty acid regulation of gene transcription: a molecular mechanism to improve the metabolic syndrome. *Journal of Nutrition* 2001;131:1129-1132.

Clarke SD, Baillie R, Jump DB, Nakamura MT: Fatty acid regulation of gene expression. Its role in fuel partitioning and insulin resistance. *Annals of the New York Academy of Sciences* 1997;827:178-187.

Cleland L, James M, Neumann M, D'Angelo M, Gibson R: Linoleate inhibits EPA incorporation from dietary fish-oil supplements in human subjects. *Am J Clin Nutr* 1992;55:395-9.

Craig WJ: Phytochemicals: guardians of our health. *Journal of the American Dietetic Association* 1997;97:Suppl-204

Dagnelie PC, Rietveld T, Swart GR, Stijnen T, van den Berg JW: Effect of dietary fish oil on blood levels of free fatty acids, ketone bodies and triacylglycerol in humans. *Lipids* 1994;29:41-45.

Dam RM van Willett WC, Rimm EB, Stampfer MJ, Hu FB, van Dam RM: Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care* 2002;25:417-424.

Das UN: GLUT-4, tumor necrosis factor, essential fatty acids and daf-genes and their role in insulin resistance and non-insulin dependent diabetes mellitus. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1999;60:13-20.

Davey G: - Randomised controlled trial of a 12-week exercise intervention and omega-3 fatty acids in improving insulin sensitivity among South Asians and Europeans. - *Clinical Science* 1997;Vol.93:25P

de Lorenzo A, Petroni ML, Luca PP de Andreoli A, et al: Use of quality control indices in moderately hypocaloric Mediterranean diet for treatment of obesity. *Diabetes, Nutrition and Metabolism* 2001;14:181-188.

Delarue J, Couet C, Cohen R, Brechot JF, Antoine JM, Lamisse F: Effects of fish oil on metabolic responses to oral fructose and glucose loads in healthy humans. *American Journal of Physiology - Endocrinology & Metabolism* 1996;270:E353-E362

DeMarco D, Santoli D, Zurier R: Effects of fatty acids on proliferation and activation of human synovial compartment lymphocytes. *Journal of Leukocyte Biology* 1994;56:612-615.

Denke MA: Dietary prescriptions to control dyslipidemias. *Circulation* 2002;105:132-135.

DiGiacomo R, Kremer J, Shah D: Fish-oil dietary supplementation in patients with Raynauds phenomenom: A double-blind, controlled, prospective study. *Am J Med* 1989;86:158-164.

Dolecek TA, Grandits G: Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT) , in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:205-216.

Dubois C, Cara L, Armand M, et al: Effects of pea and soybean fibre on postprandial lipaemia and lipoproteins in healthy adults. *European Journal of Clinical Nutrition* 1993;47:508-520.

Durrington PN, Bhatnagar D, Mackness MI, et al: An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. *Heart (British Cardiac Society)* 2001;85:544-548.

Ekblond A, Mellemkjaer L, Tjonneland A, et al: A cross-sectional study of dietary habits and urinary glucose excretion - a predictor of non-insulin-dependent diabetes mellitus. *European Journal of Clinical Nutrition* 2000;54:434-439.

Emeis JJ, van Houwelingen AC, van den Hoogen CM, Hornstra G: A moderate fish intake increases plasminogen activator inhibitor type-1 in human volunteers. *Blood* 1989;74:233-237.

Endres S, Ghorbani R, Kelley V, et al: The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989;320:265-71.

Fisher WR: Hypertriglyceridemia in diabetes. An approach to management. *Journal of the Florida Medical Association* 1991;78:747-750.

Franceschini G, Paoletti R: Pharmacological management of hypertriglyceridemic patients. *Cardiovascular Risk Factors* 1992;2:343-347.

Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE: Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care* 1998;21:494-500.

Ginsberg HN, Illingworth DR: Postprandial dyslipidemia: an atherogenic disorder common in patients with diabetes mellitus. *American Journal of Cardiology* 2001;88:9H-15H.

Gletsu NA, Clandinin MT: Impact of dietary fatty acid composition on insulin action at the nucleus. *Annals of the New York Academy of Sciences* 1997;827:188-199.

Gohlke H: Diet and body weight. *Zeitschrift fur Kardiologie* 2002;91:12-24.

Goulet O, de Potter S, Antebi H, et al: Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. *American Journal of Clinical Nutrition* 1999;70:338-345.

Grimble R, Tappia P: Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. *Zeitschrift fur Ernahrungswissenschaft.* 1998;37:57-65.

Grundt H, Nilsen DW, Hetland O, et al: Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. *Journal of Internal Medicine* 1995;237:249-259.

Guarner F, Vilaseca J, Malagelada JR: Dietary manipulation in experimental inflammatory bowel disease. *Agents & Actions* 1992;35:C10-C14

Gustafsson I-B, Ohrvall M, Ekstrand B, Vessby B: Moderate amounts of n-3 fatty acid enriched seafood products are effective in lowering serum triglycerides and blood pressure in healthy subjects. *Journal of Human Nutrition & Dietetics* 1996;9:135-145.

Haglund O, Wallin R, Wretling S, Hultberg B, Saldeen T: Effects of fish oil alone and combined with long chain (n-6) fatty acids on some coronary risk factors in male subjects. *Journal of Nutritional Biochemistry* 1998;9:629-635.

Hall AV, Parbtani A, Clark WF, et al: Abrogation of MRL/lpr lupus nephritis by dietary flaxseed. *American Journal of Kidney Diseases* 1993;22:326-332.

Harding WR, Russell CE, Davidson F, Prior IAM: Dietary surveys from the Tokelau Island Migrant Study. *Ecology of Food and Nutrition* 1986;19:83-97.

Healy DA, Wallace FA, Miles EA, Calder PC, Newsholme P: Effect of low-to-moderate amounts of dietary fish oil on neutrophil lipid composition and function. *Lipids* 2000;35:763-768.

Henderson WR: Omega-3 supplementation in CF. *6th North American Cystic Fibrosis Conference* 1992;-

Horrobin D: Essential fatty acid and prostaglandin metabolism in Sjogren's syndrome, systemic sclerosis and rheumatoid arthritis. *Scandinavian Journal of Rheumatology Supplement*. 1986;61:242-245.

Hughes D, Pinder A: n-3 Polyunsaturated fatty acids inhibit the antigen-presenting function of human monocytes. *American Journal of Clinical Nutrition* 2000;71:357S-360S.

Hughes DaPA: Influence of n-3 polyunsaturated fatty acids (PUFA) on the antigen-presenting function of human monocytes. *Biochemical.Society Transactions.* 1966;24:389S-

Jabbar MA, Zuhri-Yafi MI, Larrea J: Insulin therapy for a non-diabetic patient with severe hypertriglyceridemia. *Journal of the American College of Nutrition* 1998;17 :458-461.

Joannic JL, Auboiron S, Raison J, Basdevant A, Bornet F, Guy-Grand B: How the degree of unsaturation of dietary fatty acids influences the glucose and insulin responses to different carbohydrates in mixed meals. *American Journal of Clinical Nutrition* 1997;65:1427-1433.

Jula A, Marniemi J, Huupponen R, Virtanen A, Rastas M, Ronnemaa T: Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomized controlled trial. *JAMA* 2002;287:598-605.

Jump DB: The biochemistry of n-3 polyunsaturated fatty acids. *Journal of Biological Chemistry* 2002;78:

Jump DB, Clarke SD, Thelen A, Liimatta M, Ren B, Badin MV: Dietary fat, genes, and human health. *Advances in Experimental Medicine & Biology* 1997;422:167-176.

Kelley DS, Nelson GJ, Branch LB, Taylor PC, Rivera YM, Schmidt PC: Salmon diet and human immune status. *European Journal of Clinical Nutrition* 1992;46:397-404.

Kelley VE: Dietary effects on the progression of autoimmune glomerulonephritis. *Clinics in Immunology & Allergy* 1986;6:367-381.

Knapp H, Fitzgerald G: The antihypertensive effect of fish oil: A controlled lstudy of polyunsaturated fatty acid supplementation in essential hypertension. *N Engl J Med* 1989;320:1037

Koletzko B: Relevance of essential fatty acids in medicine and nutrition. *Aktuelle Endokrinologie und Stoffwechsel* 1986;7:18-27.

Kothny W, Angerer P, Stork S, Von Schacky C: Short term effects of omega-3 fatty acids on the radial artery of patients with coronary artery disease. *Atherosclerosis* 1998;140:181-186.

Krauss RM, Eckel RH, Howard B, et al: Revision 2000: a statement for healthcare professionals from the nutrition committee of the American Heart Association. *Journal of Nutrition* 2001;205:

Kriketos AD, Robertson RM, Sharp TA, et al: Role of weight loss and polyunsaturated fatty acids in improving metabolic fitness in moderately obese, moderately hypertensive subjects. *Journal of Hypertension* 2001;19:1745-1754.

Kris-Etherton PM, Harris WS, Appel LJ: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2747-2757.

Lahoz C, Alonso R, Porres A, Mata P: Diets enriched in monounsaturated fatty acids and polyunsaturated omega 3 fatty acids decrease blood pressure without modifying plasma insulin concentration in healthy subjects. *Medicina Clinica Barcelona* 1999;40:

Lardinois CK: The role of omega 3 fatty acids on insulin secretion and insulin sensitivity. *Medical Hypotheses* 1987;24:243-248.

Lardinois CK, Starich GH, Mazzaferri EL: The postprandial response of gastric inhibitory polypeptide to various dietary fats in man. *Journal of the American College of Nutrition* 1988;7:241-247.

Leaf A, Weber PC: Cardiovascular effects of n-3 fatty acids. *N Engl J Med* 1988;318:549-57.

Leiba A, Amital H, Gershwin M, Shoenfeld Y: Diet and lupus. *Lupus.* 2001;10:246-248.

Leigh-Firbank EC, Minihane AM, Leake DS, et al: Eicosapentaenoic acid and docosahexaenoic acid from fish oils: Differential associations with lipid responses. *British Journal of Nutrition* 2002;87:435-445.

Louheranta AM, Turpeinen AK, Schwab US, Vidgren HM, Parviainen MT, Uusitupa MIJ: A high-stearic acid diet does not impair glucose tolerance and insulin sensitivity in healthy women. *Metabolism, Clinical and Experimental* 1998;44 ref.:5, 529-553444.

Lovegrove JA, Brooks CN, Murphy MC, Gould BJ, Williams CM: Use of manufactured foods enriched with fish oils as a means of increasing long-chain n-3 polyunsaturated fatty acid intake.[comment]. *British Journal of Nutrition* 1997;78:223-236.

Mackness MI, Bhatnagar D, Durrington PN, et al: Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. *European Journal of Clinical Nutrition* 1994;48:859-865.

Mann JI, Asp NG, Frayn K, Vessby B: Can dietary intervention produce long-term reduction in insulin resistance? *Diet and the metabolic syndrome* 25:

Mantzioris E, Cleland L, Gibson R, Neumann M, Demasi M, James MJ: Biochemical effects of a diet containing foods enriched with n-3 fatty acids. *American Journal of Clinical Nutrition* 2000;72:42-48.

Margolis S, Dobs AS: Nutritional management of plasma lipid disorders. *Journal of the American College of Nutrition* 1989;8:Suppl-45S

Marotta F, Chui DH, Safran P, Rezakovic I, Zhong GG, Ideo G: Shark fin enriched diet prevents mucosal lipid abnormalities in experimental acute colitis. *Digestion* 1995;56:46-51.

Matalas AL, Franti CE, Grivetti LE: Comparative study of diet and disease prevalence in Greek Chians part I rural and urban residents of chios. *Ecology of Food and Nutrition* 1999;

Matalas AL, Franti CE, Grivetti LE: Comparative study of diets and disease prevalence in Greek Chians part II Chian immigrants to Athens and to the United States. *Ecology of Food and Nutrition* 1999;38:381-414.

Maurin AC, Chavassieux PM, Vericel E, Meunier PJ: Role of polyunsaturated fatty acids in the inhibitory effect of human adipocytes on osteoblastic proliferation. *Bone* 2002;31:260-266.

Meydani SN, Endres S, Woods MM, et al: Effect of oral n-3 fatty acid supplementation on the immune response of young and older women. *Advances in Prostaglandin, Thromboxane, & Leukotriene Research* 1991;21A:245-248.

Meydani S, Lichtenstein A, Cornwall S, et al: Immunologic effects of national cholesterol education panel step-2 diets with and without fish-derived N-3 fatty acid enrichment. *J Clin Invest* 1993;92:105-13.

Mori TA, Bao DQ, Burke V, Puddey IB, Watts GF, Beilin LJ: Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *American Journal of Clinical Nutrition* 1999;70:817-825.

Mori TA, Burke V, Puddey IB, et al: Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *American Journal of Clinical Nutrition* 2000;71:1085-1094.

Mori T: The effect of fish oil on plasma lipids, platelet and neutrophil function in patients with vascular disease. *Australian & New Zealand Journal of Medicine* 1991;21:516

Morris MC , Manson JE , Rosner B, Ruing JE, Willett WC, Hennekens CH: Fish consumption and cardiovascular disease in the physicians' health study: A prospective study. *American Journal of Epidemiology* 1995;142:166-175.

Mueller BA, Talbert RL: Biological mechanisms and cardiovascular effects of omega-3 fatty acids. *Clinical Pharmacy* 1988;7:795-807.

Murkies A, Lombard C, Strauss B, Wilcox G, Burger H, Morton M: Dietary flour supplementation decreases post-menopausal hot flushes: effect of soy and wheat. *Maturitas* 1995;21:189-95.

Naughton JM, O'Dea K, Sinclair AJ: Animal foods in traditional Australian aboriginal diets: polyunsaturated and low in fat. *Lipids* 1986;21:684-690.

Niculescu D, Tomescu E, Ionescu C, et al: Ultrastructural changes in cartilage after intra-articular administration of osmium tetroxide and the sodium salts of fish oil fatty acids. *Scandinavian Journal of Rheumatology* 1976;5:133-140.

Nydahl M, Gustafsson IB, Ohrvall M, Vessby B: Similar effects of rapeseed oil (canola oil) and olive oil in a lipid-lowering diet for patients with hyperlipoproteinemia. *Journal of the American College of Nutrition* 1995;41:

Okumura T, Fujioka Y, Morimoto S, et al: Eicosapentaenoic acid improves endothelial function in hypertriglyceridemic subjects despite increased lipid oxidizability. *American Journal of the Medical Sciences* 2002;324:247-253.

Parke DV: The role of nutrition in the prevention and treatment of degenerative disease. *Saudi Medical Journal* 1994;48 ref.:

Pedersen A, Marckmann P, Sandstrom B: Postprandial lipoprotein, glucose and insulin responses after two consecutive meals containing rapeseed oil, sunflower oil or palm oil with or without glucose at the first meal. *British Journal of Nutrition* 1999;82:97-104.

Pestka JJ, Zhou HR, Jia QS, Timmer AM: Dietary fish oil suppresses experimental immunoglobulin A nephropathy in mice. *Journal of Nutrition* 2002;

Pieke B, von Eckardstein A, Gulbahce E, et al: Treatment of hypertriglyceridemia by two diets rich either in unsaturated fatty acids or in carbohydrates: effects on lipoprotein subclasses, lipolytic enzymes, lipid transfer proteins, insulin and leptin. *International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity* 2000;24:1286-1296.

Pschierer V, Richter WO, Schwandt P: Primary chylomicronemia in patients with severe familial hypertriglyceridemia responds to long-term treatment with (n-3) fatty acids. *Journal of Nutrition* 1995;125:1490-1494.

Radack K, Deck C, Huster G: Dietary supplementation with low-dose fish oils lowers fibrinogen levels: a randomized, double-blind controlled study. *Ann Intern Med* 1989;9:757-758.

Raptis S, Dollinger HC, von Berger L, et al: Effect of lipids on insulin, growth hormone and exocrine pancreatic secretion in man. *European Journal of Clinical Investigation* 1975;5:521-526.

Richter WO, Jacob BG, Ritter MM, Schwandt P: Treatment of primary chylomicronemia due to familial hypertriglyceridemia by omega-3 fatty acids. *Metabolism: Clinical & Experimental* 1992;41:1100-1105.

Robertson MD, Jackson KG, Fielding BA, Williams CM, Frayn KN: Acute effects of meal fatty acid composition on insulin sensitivity in healthy post-menopausal women. *British Journal of Nutrition* 2002;88:635-640.

Robinson DR, Kremer JM: Rheumatoid arthritis and inflammatory mediators, in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:44-47.

Rossetti R, Seiler C, DeLuca P, Laposata M, Zurier R: Oral administration of unsaturated fatty acids: Effects on human peripheral blood T lymphocyte proliferation. *Journal of Leukocyte Biology* 1997;62:438-443.

Saso L, Valentini G, Casini M, et al: Inhibition of protein denaturation by fatty acids, bile salts and other natural substances: A new hypothesis for the mechanism of action of fish oil in rheumatic diseases. *Japanese Journal of Pharmacology* 1999;79:89-99.

Sawazaki S, Hamazaki T, Yazawa K, Kobayashi M: The effect of docosahexaenoic acid on plasma catecholamine concentrations and glucose tolerance during long-lasting psychological stress: a double-blind placebo-controlled study. *Journal of Nutritional Science and Vitaminology* 1999;45:655-665.

Schimke E, Honigmann G, Hildebrandt R: Effect of linolenic acid-rich diet on lipoproteins in diabetic subjects. *Deutsche Gesundheitswesen* 1984;39:223-225.

Schwab US, Niskanen LK, Maliranta HM, Savolainen MJ, Kesaniemi YA, Uusitupa MI: Lauric and palmitic acid-enriched diets have minimal impact on serum lipid and lipoprotein concentrations and glucose metabolism in healthy young women. *Journal of Nutrition* 1995;125:466-473.

Sebokova E, Klimes I, Hermann M, et al: Modulation of the hypolipidemic effect of fish oil by inhibition of adipose tissue lipolysis with Acipimox, a nicotinic acid analog. *Dietary lipids and insulin action Second International Smolenice Insulin Symposium* 20:183-191.

Sherertz EF: Improved acanthosis nigricans with lipodystrophic diabetes during dietary fish oil supplementation. *Archives of Dermatology* 1988;124:1094-1096.

Silva JM, Souza I, Silva R, Tavares P, Teixeira F, Silva PS: The triglyceride lowering effect of fish oils is affected by fish consumption. *International Journal of Cardiology* 1996;57:75-80.

Simopoulos AP: Nutrients in the control of metabolic diseases. *World Review of Nutrition and Dietetics* 1992;

Simopoulos AP, Johnston PK, Sabate J: Essential fatty acids in health and chronic disease. *Third International Congress on Vegetarian Nutrition* 98:

Sinclair HM: Essential fatty acids in perspective. *Human Nutrition - Clinical Nutrition* 1984;38:245-260.

Singer P, Wirth M, Berger I, et al: Influence on serum lipids, lipoproteins and blood pressure of mackerel and herring diet in patients with type IV and V hyperlipoproteinemia. *Atherosclerosis* 1985;56:111-118.

Soucy J, LeBlanc J: The effects of a beef and fish meal on plasma amino acids, insulin and glucagon levels. *Nutrition Research* 1999;22 ref.:

Sperling R, Benincaso A, Knoell C, Larkin J, Austen K, Robinson D: Dietary omega-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. *J Clin Invest* 1993;91:651-60.

Stammers T, Sibbald B, Freeling P: Fish oil in osteoarthritis. *Lancet* 1989;121:503

Storlien LH, Kriketos AD, Calvert GD, Baur LA, Jenkins AB: Fatty acids, triglycerides and syndromes of insulin resistance. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1997;57:379-385.

Storlien LH, Kriketos AD, Jenkins AB, et al: Does dietary fat influence insulin action? *Annals of the New York Academy of Sciences* 1997;827:287-301.

Storlien LH, Pan DA, Kriketos AD, et al: Skeletal muscle membrane lipids and insulin resistance. *Lipids* 1996;31:

Tchorzewski H, Banasik M, Glowacka E, Lewkowicz P: Modification of innate immunity in humans by active components of shark liver oil. *Polski Merkuriusz Lekarski* 2002;13:329-332.

Tezabwala BU, Bennett M, Grundy SM: Immunotoxicity of polyunsaturated fatty acids in serum-free medium. *Immunopharmacology & Immunotoxicology* 1995;17:365-383.

Toft I, Bonaa KH, Ingebretsen OC, Nordoy A, Jenssen T: Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial.[comment]. *Annals of Internal Medicine* 1995;123:911-918.

Urakaze M, Hamazaki T, Yano S, Kashiwabara H, Oomori K, Yokoyama T: Effect of fish oil concentrate on risk factors of cardiovascular complications in renal transplantation. *Transplantation Proceedings* 1989;21:

Vialettes B: The CHO in fat ratio and glucose tolerance. *Cahiers de Nutrition et de Dietetique* 2001;36:327-330.

Wardle EN: Eicosanoids and renal allograft rejection. *Nephron* 1995;70:151-154.

Weisburger JH: Dietary fat and risk of chronic disease: mechanistic insights from experimental studies. *Journal of the American Dietetic Association* 1997;97:

Williams CM, Moore F, Morgan L, Wright J: Effects of n-3 fatty acids on postprandial triacylglycerol and hormone concentrations in normal subjects. *British Journal of Nutrition* 1992;68:655-666.

Xu N, Zhang GZ, Chen SH: The effect of eicosapentaenoic acid enriched marine oil on the platelet function in hypercoagulable state. *Chung-Hua Nei Ko Tsa Chih Chinese Journal of Internal Medicine* 1990;29:406-409.

Yam D, Eliraz A, Berry EM: Diet and disease - the Israeli paradox: possible dangers of a high omega-6 polyunsaturated fatty acid diet. *Israel Journal of Medical Sciences* 1996;135:

Yaqoob P, Pala H, Cortina-Borja M, Newsholme E, Calder P: Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. *Eur J Clin Invest* 2000;30:260-74.

Zak A, Hrabak P, Zeman M, Svarcova H, Vrana A, Mares P: Effect of fish oils on plasma lipids, glucose tolerance and insulin secretion in persons with endogenous hypertriglyceridemia. *Casopis Lekaru Ceskych* 1988;127 :881-884.

Zak A, Zeman M, Hrabak P, Vrana A, Svarcova H , Mares P: Changes in the glucose tolerance and insulin secretion in hypertriglyceridemia: effects of dietary n-3 fatty acids. *Nutrition Reports International* 1989;39:235-242.

Zak A, Zeman M, Tvrzicka E, Pisarikova A, Sindelkova E, Vrana A: Glucose tolerance, insulin secretion, plasma lipid fatty acids, and the hypolipidemic effects of fish oil. *Annals of the New York Academy of Sciences* 1993;683:378-379.

Zampelas A, Murphy M, Morgan LM, Williams CM: Postprandial lipoprotein lipase, insulin and gastric inhibitory polypeptide responses to test meals of different fatty acid composition: comparison of saturated, n-6 and n-3 polyunsaturated fatty acids. *European Journal of Clinical Nutrition* 1994;48:849-858.

Zurier R, Rossetti R, Seiler C, Laposata M: Human peripheral blood T lymphocyte proliferation after activation of the T cell receptor: Effects of unsaturated fatty acids. *Prostaglandins Leukotrienes and Essential Fatty Acids* 1999; 60:371-375.

Rejected Topic

AnonymousPrinciples of nutrition for the patient with diabetes mellitus. *Diabetes* 1967;16:738

Abushufa R, Reed P, Weinkove C, Wales S, Shaffer J: Essential fatty acid status in patients on long-term home parenteral nutrition. *Journal of Parenteral & Enteral Nutrition* 1995;19:286-290.

Adachi JD, Bensen WG, Bell MJ, et al: Salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis. *British Journal of Rheumatology* 1997;36:255-259.

Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL: A randomized controlled trial of weight reduction and exercise for diabetes management in older African-American subjects. *Diabetes Care* 1997;20:1503-1511.

Anderson EJ, Richardson M, Castle G, et al: Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial. The DCCT Research Group. *Journal of the American Dietetic Association* 1993;93:768-772.

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. *Journal of Internal Medicine* 1996;240:203-209.

Andersson A, Sjodin A, Olsson R, Vessby B: Effects of physical exercise on phospholipid fatty acid composition skeletal muscle. *American Journal of Physiology - Endocrinology & Metabolism* 1998;274:E432-E438

Arai Y, Uehara M, Kimira M, Watanabe S: Effects of soybean isoflavones on bone mineral density and bone metabolism in women: correlation among isoflavone concentrations in biological fluids, sex-hormone binding globulin and bone biomarkers. *Soy Protein Research* 2001;26:135-14126.

Arai Y, Uehara M, Oshima K, Takada N, Kimira M, Watanabe S: Effects of soybean isoflavones on bone mineral density and bone metabolism in human. *Soy.Protein.Research,.Japan.* 2000;28 ref.:79-86.

Arisaka M, Arisaka O, Yamashiro Y: Fatty acid and prostaglandin metabolism in children with diabetes mellitus. II. The effect of evening primrose oil supplementation on serum fatty acid and plasma prostaglandin levels. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1991;43:197-201.

Arnaiz-Villena A, Vicario JL, Serrano-Rios M: Glomerular basement membrane antibodies and HLA-DR2 in Spanish rapeseed oil disease. *New England Journal of Medicine* 1982;307 :1404-1405.

Astrup A, Ryan L, Grunwald GK, et al: The role of dietary fat in body fatness: evidence from a preliminary meta-analysis of ad libitum low-fat dietary intervention studies. *British Journal of Nutrition* 2000;83:S25-S32

Austin HA, Boumpas DT: Treatment of lupus nephritis. *Seminars in Nephrology* 1996;16:527-535.

Baart de la Faille H: Lupus therapy. *Clinical Investigator* 1994;72:749-753.

Bang HO, Dyerberg J: Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. *Acta Medica Scandinavica* 1972;192:85-94.

Bantle JP: Current recommendations regarding the dietary treatment of diabetes mellitus. *Endocrinologist* 1994;4:189-195.

Bassi A, Avogaro A, Crepaldi C, et al: Short-term diabetic ketosis alters n-6 polyunsaturated fatty acid content in plasma phospholipids. *Journal of Clinical Endocrinology & Metabolism* 1996;81:1650-1653.

Baur LA, O'Connor J, Pan DA, Kriketos AD, Storlien LH: The fatty acid composition of skeletal muscle membrane phospholipid: its relationship with the type of feeding and plasma glucose levels in young children. *Metabolism: Clinical & Experimental* 1998;47:106-112.

Belch J, Hill A: Evening primrose oil and borage oil in rheumatologic conditions. *American Journal of Clinical Nutrition* 2000;71:352S-356S.

Belluzzi A, Brignola C, Campieri M, et al: Short report: zinc sulphate supplementation corrects abnormal erythrocyte membrane long-chain fatty acid composition in patients with Crohn's disease. *Alimentary Pharmacology & Therapeutics* 1994;8:127-130.

Belury MA: Dietary conjugated linoleic acid in health: physiological effects and mechanisms of action. *Annual Review of Nutrition* 2002;22:505-531.

Beri D, Malaviya AN, Shandilya R, Singh RR: Effect of dietary restrictions on disease activity in rheumatoid arthritis. *Annals.of.the.Rheumatic.Diseases* 1988;47:69-72.

Biernat J, Iwanicka Z, Szymczak J, Wasikowa R: Effect of essential unsaturated fatty acids diet on selected indices of lipid metabolism in children with diabetes mellitus. *Przeglad Lekarski* 1982;39:353-356.

Bisschop PH de Metz: Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *American Journal of Clinical Nutrition* 2001;73:554-559.

Bloomgarden ZT: International Diabetes Federation Meeting, 1997: Nephropathy, retinopathy, and glycation. *Diabetes Care* 1998;21:1560-1566.

Bohannon NJV: Lipid metabolism in type II diabetes. *Postgraduate Medicine* 1992;92:105-113.

Bohov P, Gelienova K, Sebokova E, Klimes I: Abnormal serum fatty acid composition in non-insulin-dependent diabetes mellitus. *Annals of the New York Academy of Sciences* 1993;683:367-370.

Bomalaski JS, Goldstein CS, Dailey AT, Douglas SD, Zurier RB: Uptake of fatty acids and their mobilization from phospholipids in cultured monocyte-macrophages from rheumatoid arthritis patients. *Clinical Immunology & Immunopathology.* 1986;39:198-212.

Bourn DM, Mann JI, McSkimming BJ, Waldron MA, Wishart JD: Impaired glucose tolerance and NIDDM: Does a lifestyle intervention program have an effect? *Diabetes Care* 1994;17:1311-1319.

Brand JC, Snow BJ, Nabhan GP, Truswell AS: Plasma glucose and insulin responses to traditional Pima Indian meals. *American Journal of Clinical Nutrition* 1990;51:416-420.

Bruce WR, Wolever TM, Giacca A: Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. *Nutrition & Cancer* 2000;37:19-26.

Brynes AE, Edwards CM, Jadhav A, Ghatei MA, Bloom SR , Frost GS: Diet-induced change in fatty acid composition of plasma triacylglycerols is not associated with change in glucagon-like peptide 1 or insulin sensitivity in people with type 2 diabetes. *American Journal of Clinical Nutrition* 2000;72:1111-1118.

Brzeski M: Evening primrose oil in patients with rheumatoid arthritis and side-effects of non-steroidal anti-inflammatory drugs. *British Journal of Rheumatology* 1991;30:370-372.

Buller H, Chin S, Kirschner B, et al: Inflammatory bowel disease in children and adolescents: Working group report of the first World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology & Nutrition* 2002;35:S151-S158

Calle Pascual AL: Diet and day-to-day variability in a sample of Spanish adults with IDDM or NIDDM. *Hormone and Metabolic Research* 1997;29:450-453.

Calle-Pascual AL, Manzano P, Camarero E, et al: Diabetes nutrition and complications trial (DNCT): Food intake and targets of diabetes treatment in a sample of Spanish people with diabetes. *Diabetes Care* 1997;20:1078-1080.

Calle-Pascual AL, Saavedra A, Benedi A, et al: Changes in nutritional pattern, insulin sensitivity and glucose tolerance during weight loss in obese patients from a Mediterranean area. *Hormone & Metabolic Research* 1995;27:499-502.

Cattran D, Delmore T, Roscoe J, Cole ECC, Charron R , Ritchie S: A randomized controlled trial of prednisone in patients with idiopathic membranous nephropathy. *N Engl J Med* 1989;320:210-5.

Celaya S, Sanz A, Homs C, et al: Experience with an enteral diet with fiber and a high fat content in ICU patients with glucose intolerance. *Nutricion Hospitalaria* 1992;7:260-269.

Chaintreuil J, Monnier L, Colette C, et al: Effects of dietary gamma-linolenate supplementation on serum lipids and platelet function in insulin-dependent diabetic patients. *Human Nutrition - Clinical Nutrition* 1984;38:121-130.

Christiansen E, Schnider S, Palmvig B, Tauber-Lassen E, Pedersen O: Intake of a diet high in trans monounsaturated fatty acids or saturated fatty acids. Effects on postprandial insulinemia and glycemia in obese patients with NIDDM. *Diabetes Care* 1997;20:881-887.

Clarke SD: Nonalcoholic steatosis and steatohepatitis. I. Molecular mechanism for polyunsaturated fatty acid regulation of gene transcription. *American Journal of Physiology - Gastrointestinal & Liver Physiology* 2001;281:G865-G869

Clarke SD, Jump DB: Dietary polyunsaturated fatty acid regulation of gene transcription. *Annual Review of Nutrition* 1994;14:83-98.

Clifton PM, Nestel PJ: Relationship between plasma insulin and erythrocyte fatty acid composition. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1998;59:191-194.

Collier GR, Wolever TM, Wong GS, Josse RG: Prediction of glycemic response to mixed meals in noninsulin-dependent diabetic subjects. *American Journal of Clinical Nutrition* 1986;44:349-352.

Costacou T, Levin S, Mayer Davis EJ: Dietary patterns among members of the Catawba Indian nation. *Journal of the American Dietetic Association* 2000;22:

Costantino L, Rastelli G, Vianello P, Cignarella G, Barlocco D: Diabetes complications and their potential prevention: Aldose reductase inhibition and other approaches. *Medicinal Research Reviews* 1999;19:3-23.

Cunnane SC, Ainley CC, Keeling PW, Thompson RP, Crawford MA: Diminished phospholipid incorporation of essential fatty acids in peripheral blood leucocytes from patients with Crohn's disease: correlation with zinc depletion. *Journal of the American College of Nutrition* 1986;5:451-458.

D'Amico G, Remuzzi G, Maschio G, et al: Effect of dietary proteins and lipids in patients with membranous nephropathy and nephrotic syndrome. *Clinical Nephrology* 1991;35 :237-242.

Dahlquist GG, Blom LG, Persson LA, Sandstrom AI, Wall SG: Dietary factors and the risk of developing insulin dependent diabetes in childhood. *BMJ* 1990;300:1302-1306.

Das UN: Essential fatty acid metabolism in patients with essential hypertension, diabetes mellitus and coronary heart disease. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1995; 52:387-391.

Das UN: Metabolic syndrome X is common in South Asians, but why and how? *Nutrition* 2002;18:774-776.

Das UN, Kumar KV, Prabha PS, Murthy BV, Neela P: Oxy-radicals, lipid peroxides and essential fatty acids in patients with glomerular disorders. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1993;49:603-607.

Das UN, Kumar KV, Ramesh G: Essential fatty acid metabolism in south Indians. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1994;50:253-255.

De Leeuw IH, Van Gaal L, Rillaerts E, Dalemans C: Effects of the relative enrichment of polyunsaturated fatty acids in insulin-dependent diabetic patients. *Diabete et Metabolisme* 1986;12:246-249.

Decsi T, Minda H, Hermann R, et al: Polyunsaturated fatty acids in plasma and erythrocyte membrane lipids of diabetic children. *Prostaglandins Leukotrienes & Essential Fatty Acids* 2002;67:203-210.

Decsi T, Molnar D, Koletzko B: Long-chain polyunsaturated fatty acids in plasma lipids of obese children. *Lipids* 1996;37:305-331.

Desai S, Allen E, Deodhar A: Miller Fisher syndrome in adult onset Still's disease: Case report and review of the literature of other neurological manifestations. *Rheumatology* 2002;41:216-222.

Dimitriadis E, Griffin M, Collins P, Johnson A, Owens D, Tomkin GH: Lipoprotein composition in NIDDM: effects of dietary oleic acid on the composition, oxidisability and function of low and high density lipoproteins. *Diabetologia* 1996;39:667-676.

Dohi K, Kanauchi M: Etiology and therapy of chronic primary glomerulonephritis. *Nippon Naika Gakkai Zasshi - Journal of Japanese Society of Internal Medicine* 1998;87:1271-1276.

Donaghue KC, Pena MM, Chan AK, et al: Beneficial effects of increasing monounsaturated fat intake in adolescents with type 1 diabetes. *Diabetes Research & Clinical Practice* 2000;48:193-199.

Dorfler H, Rauh G, Bassermann R: Lipoatrophic diabetes. *Clinical Investigator* 1993;71:264-269.

Dreval AV, Anykina NV, Tishin DP, et al: Effect of soybean protein isolate on energy substrate oxidation in patients with insulin-dependent diabetes mellitus. *Problemy Endokrinologii* 1994;40:21-25.

Dullaart RP, Beusekamp BJ, Meijer S, Hoogenberg K, van Doormaal JJ, Sluiter WJ: Long-term effects of linoleic-acid-enriched diet on albuminuria and lipid levels in type 1 (insulin-dependent) diabetic patients with elevated urinary albumin excretion. *Diabetologia* 1992;35:165-172.

Dullaart RP, Hoogenberg K, Riemens SC, et al: Cholesteryl ester transfer protein gene polymorphism is a determinant of HDL cholesterol and of the lipoprotein response to a lipid-lowering diet in type 1 diabetes. *Diabetes* 1997;46:2082-2087.

Dutta-Roy AK: Insulin mediated processes in platelets, erythrocytes and monocytes/macrophages: effects of essential fatty acid metabolism. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1994;51:385-399.

Ebbesson SO, Kennish J, Ebbesson L, Go O, Yeh J : Diabetes is related to fatty acid imbalance in Eskimos. *International Journal of Circumpolar Health* 1999;58:108-119.

Edelman SV: Type II diabetes mellitus. *Advances in Internal Medicine* 1998;43:449-500.

El Boustani S, Descomps B, Monnier L, et al: In vivo conversion of dihomogamma linolenic acid into arachidonic acid in man. *Progress in Lipid Research* 1986;25:67-71.

Ernest I, Linner E, Svanborg A: Carbohydrate-rich, fat-poor diet in diabetes. *American Journal of Medicine* 1965;39:594-600.

Esteve Comas M, Ramirez M, Fernandez Banares F, et al: Plasma polyunsaturated fatty acid pattern in active inflammatory bowel disease. *Gut* 1992;33:1365-69.

Esteve M, Navarro E, Klaassen J, et al: Plasma and mucosal fatty acid pattern in colectomized ulcerative colitis patients. *Digestive Diseases & Sciences* 1998;43:1071-1078.

Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, Waldhausl W: No effect of short-term dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. *Annals of Nutrition & Metabolism* 1996;40:116-122.

Ferro-Luzzi A, James WP, Kafatos A: The high-fat Greek diet: a recipe for all? *European Journal of Clinical Nutrition* 2002;56:796-809.

Feskens EJ, Bowles CH, Kromhout D: Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes Care* 1991;14:935-941.

Feskens EJM, Virtanen SM, Rasanen L, et al: Dietary factors determining diabetes and impaired glucose tolerance: A 20- year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes Care* 1995;18:1104-1112.

Fischbach W: Drug therapy for inflammatory bowel disease. *Leber, Magen, Darm* 1992;22:49-55.

Fisher RL: Newer therapies for inflammatory bowel disease. *Chinese Journal of Gastroenterology* 1992;9:230-232.

Florent CH: Inflammatory bowel diseases (IBD): Therapeutic actualities. *Acta Endoscopica* 1995;25:571-574.

French MA, Parrott AM, Kielo ES, et al: Polyunsaturated fat in the diet may improve intestinal function in patients with Crohn's disease. *Biochimica et Biophysica Acta* 1997;1360:262-270.

Fujita H, Yamagami T, Ohshima K: Long-term ingestion of a fermented soybean-derived Touchi-extract with alpha-glucosidase inhibitory activity is safe and effective in humans with borderline and mild type-2 diabetes. *Journal of Nutrition* 2001;131:2105-2108.

Garaulet M, Perez-Llamas F, Perez-Ayala M, et al: Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity. *American Journal of Clinical Nutrition* 2001;74:585-591.

Garg A: High-monounsaturated fat diet for diabetic patients. Is it time to change the current dietary recommendations? *Diabetes Care* 1994;17:242-246.

Garg A: High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *American Journal of Clinical Nutrition* 1998;67:582S

Garg A, Grundy SM: Diabetic dyslipidemia and its therapy. *Diabetes Reviews* 1997;5:425-433.

Garg A, Klimes I, Howard BV, Storlien LH, Sebokova E: Dietary monounsaturated fatty acids for patients with diabetes mellitus. *Annals New York Academy of Sciences* 27:199-206.

Gatti E, Noe D, Pazzucconi F, et al: Differential effect of unsaturated oils and butter on blood glucose and insulin response to carbohydrate in normal volunteers. *European Journal of Clinical Nutrition* 1992;46:161-166.

Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrugger RW, Brummer RJ: Diet as a risk factor for the development of ulcerative colitis. *American Journal of Gastroenterology* 2000;95:1008-1013.

Georgopoulos A: Postprandial triglyceride metabolism in diabetes mellitus. *Clinical Cardiology* 1999;22:II28-II33

Georgopoulos A, Bantle JP, Noutsou M, Hoover HA: A high carbohydrate versus a high monounsaturated fatty acid diet lowers the atherogenic potential of big VLDL particles in patients with type 1 diabetes. *Journal of Nutrition* 2000;130:2503-2507.

Gilbertson HR, Thorburn AW, Brand-Miller JC, Chondros P, Werther GA: Effect of low-glycemic-index dietary advice on dietary quality and food choice in children with type 1 diabetes. *American Journal of Clinical Nutrition* 2003;77:83-90.

Glassock RJ: Concluding remarks and summary of the 7th International Symposium on IgA Nephropathy (Singapore, 1-2 October 1996). *Nephrology* 1997;3:131-135.

Goodfriend TL, Ball DL, Elliott ME, et al: Fatty acids may regulate aldosterone secretion and mediate some of insulin's effects on blood pressure. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1993;48:43-50.

Gorska A, Nawrocki A, Urban M, Florys B: Composition of phospholipid fatty acids in erythrocyte membranes of children with chronic juvenile arthritis: Clinical and biochemical correlations. *Medical Science Monitor* 2000;6:30-39.

Griffin ME, Dimitriadis E, Lenehan K, et al: Non-insulin-dependent diabetes mellitus: dietary monounsaturated fatty acids and low-density lipoprotein composition and function. *QJM* 1996;89:211-216.

Grober U: Orthomolecular medicine: Usefulness of micronutrients in diabetes mellitus. *Deutsche Apotheker Zeitung* 2002;142:46-52.

Hallgren B, Lundquist CG, Svanborg A: The fatty acid composition of mitochondrial lipids from musculus pectoralis minor in non-diabetics and diabetics. *Acta Medica Scandinavica* 1966;179:447-452.

Halpern G: Anti-inflammatory effects of a stabilized lipid extract of Perna canaliculus (Lyprinolrho). *Allergie et Immunologie* 2000;32:272-278.

Hansen TM, Lerche A, Kassis V: Treatment of rheumatoid arthritis with prostaglandin E1 precursors cis-linoleic acid and gamma-linolenic acid. *Scandinavian Journal of Rheumatology* 1983;12:85-88.

Harding AH, Sargeant LA, Welch A, et al: Fat consumption and HbA(1c) levels: the EPIC-Norfolk study. *Diabetes Care* 2001;24:1911-1916.

Hauner H: Nutritional therapy in diabetic nephropathy. *Aktuelle Ernahrungsmedizin* 2001;5:519-525.

Healey JH, Paget SA, Williams-Russo: A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. *Calcified.Tissue International* 1996;58:73-80.

Heine RJ, Mulder C, Popp-Snijders C, van der Meer J, van der Veen EA: Linoleic-acid-enriched diet: long-term effects on serum lipoprotein and apolipoprotein concentrations and insulin sensitivity in noninsulin-dependent diabetic patients. *American Journal of Clinical Nutrition* 1989;49:448-456.

Hernell O, Holmgren G, Jagell SF, Johnson SB, Holman RT: Suspected faulty essential fatty acid metabolism in Sjogren-Larsson syndrome. *Pediatric.Research* 1982;16:45-49.

Higashi K, Shige H, Ito T, et al: Effect of a low-fat diet enriched with oleic acid on postprandial lipemia in patients with type 2 diabetes mellitus. *Lipids* 2001;36:1-6.

Hirai K, Nomura M, Nakajima Y, Minamoto K, Abe H: Serum levels of retinol, inorganic phosphate and polyunsaturated fatty acid and their relationship in diabetic patients with early nephropathy. *Nutrition Research* 1994;

Hirayama T: National burden of disease of urinary organs--an epidemiological consideration. *Hinyokika Kiyo - Acta Urologica Japonica* 1987;33:1550-1555.

Hockaday TD, Hockaday JM, Mann JI, Turner RC: Prospective comparison of modified fat-high-carbohydrate with standard low-carbohydrate dietary advice in the treatment of diabetes: one year follow-up study. *British Journal of Nutrition* 1978;39:357-362.

Hornych A, Oravec S, Girault F, Forette B, Horrobin DF: The effect of gamma-linolenic acid on plasma and membrane lipids and renal prostaglandin synthesis in older subjects. *Bratislavske Lekarske Listy* 2002;103:101-107.

Horrobin D: Essential fatty acid metabolism in diseases of connective tissue with special reference to scleroderma and to Sjogren's syndrome. *Medical Hypotheses* 1984;14:233-247.

Horrobin DF: Essential fatty acids in the management of impaired nerve function in diabetes. *Diabetes* 1997;46:S90-S93

Horrobin DF: Fatty acid metabolism in health and disease: the role of delta-6-desaturase. *American Journal of Clinical Nutrition* 1993;57:732S-737S.

Horrobin DF: Nutritional and medical importance of gamma-linolenic acid. *Progress in Lipid Research* 1992;31:163-194.

Horrobin DF, Campbell A, McEwen CG: Treatment of the Sicca syndrome and Sjogren's syndrome with E.F.A., pyridoxine and vitamin C. *Progress in Lipid Research* 1981;20:253-254.

Horrobin DF, Cunnane SC: Interactions between zinc, essential fatty acids and prostaglandins: relevance to acrodermatitis enteropathica, total parenteral nutrition, the glucagonoma syndrome, diabetes, anorexia nervosa and sickle cell anaemia. *Medical Hypotheses* 1980;6:277-296.

Horrobin DF, Jantti J: Effects of evening primrose oil in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1989;48:965-966.

Horrobin DF, Manku MS: How do polyunsaturated fatty acids lower plasma cholesterol levels? *Lipids* 1983;18:558-562.

Houtsmuller AJ, Hal-Ferwerda J, Zahn KJ, Henkes HE: Favorable influences of linoleic acid on the progression of diabetic micro- and macroangiopathy in adult onset diabetes mellitus. *Progress in Lipid Research* 1981;20:377-386.

Houtsmuller AJ, Zahn KJ, Henkes HE: Unsaturated fats and progression of diabetic retinopathy. *Documenta Ophthalmologica* 1980;48:363-371.

Howard BV: Dietary fatty acids, insulin resistance, and diabetes. *Annals of the New York Academy of Sciences* 1997;827:215-220.

Jalili T, Wildman REC, Medeiros DM: Nutraceutical roles of dietary fiber. *Journal of Nutraceuticals, Functional & Medical Foods* 2000;2:19-34.

Jang Y, Lee JH, Kim OY, Park HY, Lee SY: Consumption of whole grain and legume powder reduces insulin demand, lipid peroxidation, and plasma homocysteine concentrations in patients with coronary artery disease -- randomized controlled clinical trial. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2001;21:2065-2071.

Jantti J, Nikkari T, Solakivi T, Vapaatalo H, Isomaki H: Evening primrose oil in rheumatoid arthritis: Changes in serum lipids and fatty acids. *Annals of the Rheumatic Diseases* 1989;48:124-127.

Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB: Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA* 2002;288:2554-2560.

Joe LA, Hart LL: Evening primrose oil in rheumatoid arthritis. *Annals of Pharmacotherapy* 1993;27:1475-1477.

Jones DB, Carter RD, Haitas B, Mann JI: Low phospholipid arachidonic acid values in diabetic platelets. *British Medical Journal Clinical Research Ed* 1983;286:173-175.

Jones DB, Carter RD, Mann JI: Indirect evidence of impairment of platelet desaturase enzymes in diabetes mellitus. *Hormone & Metabolic Research* 1986;18:341-344.

Jones G, Riley M, Dwyer T: Maternal diet during pregnancy is associated with bone mineral density in children: a longitudinal study. *European Journal of Clinical Nutrition.* 2000;54:749-756.

Julius U, Hanefeld M: Management of lipid disorders in diabetes mellitus. *Munchener Medizinische Wochenschrift* 1994;136:46-50.

Karamanos B, Thanopoulou A, Angelico F, et al: Nutritional habits in the Mediterranean Basin. The macronutrient composition of diet and its relation with the traditional Mediterranean diet. Multi-centre study of the Mediterranean Group for the Study of Diabetes (MGSD). *European Journal of Clinical Nutrition* 2002;56:983-991.

Kast R: Borage oil reduction of rheumatoid arthritis activity may be mediated by increased cAMP that suppresses tumor necrosis factor-alpha. *International.Immunopharmacology* 2001;1:2197-2199.

Katsilambros N: Mediterranean diet and diabetes mellitus. *Cahiers de Nutrition et de Dietetique* 1996;31:209-211.

Kearney MT, Chowienczyk PJ, Brett SE, Sutcliffe A, Ritter JM, Shah AM: Acute haemodynamic effects of lipolysis-induced increase of free fatty acids in healthy men. *Clinical Science* 2002;102:495-500.

Keen H, Payan J, Allawi J, et al: Treatment of diabetic neuropathy with gamma-linolenic acid. The gamma-Linolenic Acid Multicenter Trial Group. *Diabetes Care* 1993;16:8-15.

Keller U, Turkalj I, Laager R, Bloesch D, Bilz S: Effects of medium- and long-chain fatty acids on whole body leucine and glucose kinetics in man. *Metabolism, Clinical and Experimental* 2002;36:

Khoshoo V, Reifen R, Neuman MG, Griffiths A, Pencharz PB: Effect of low- and high-fat, peptide-based diets on body composition and disease activity in adolescents with active Crohn's disease. *Journal of Parenteral & Enteral Nutrition* 1996;20:401-405.

Kimberly R: Treatment. Corticosteroids and anti-inflammatory drugs. *Rheumatic Diseases Clinics of North America.* 1988;14:203-221.

Kleijnen J: Evening primrose oil. *BMJ* 1994:824-825.

Knauf VC, Facciotti D: Genetic engineering of foods to reduce the risk of heart disease and cancer. *Advances in Experimental Medicine & Biology* 1995;369:221-228.

Korelitz BI: Where do we stand on drug treatment for ulcerative colitis? *Annals of Internal Medicine* 1992;116:692-694.

Kotaniemi A, Piirainen H, Paimela L, et al: Is continuous intranasal salmon calcitonin effective in treating axial bone loss in patients with active rheumatoid arthritis receiving low dose glucocorticoid therapy? *Journal of Rheumatology* 1996;23:1875-1879.

Kreider R, Ferreira M, Greenwood M, Wilson M, Almada AL: Effects of conjugated linoleic acid supplementation during resistance training on body composition, bone density, strength, and selected hematological markers. *Journal of Strength & Conditioning Research.* 2002;16:325-334.

Kuroki F, Iida M, Matsumoto T, Aoyagi K, Kanamoto K, Fujishima M: Serum n3 polyunsaturated fatty acids are depleted in Crohn's disease. *Digestive Diseases & Sciences* 1997;42:1137-1141.

Laaksonen DE, Lakka TA, Lakka HM, et al: Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. *Diabetic Medicine* 2002;19:456-464.

Laitinen J, Uusitupa M, Ahola I, Siitonen O: Metabolic and dietary determinants of serum lipids in obese patients with recently diagnosed non-insulin-dependent diabetes. *Annals of Medicine* 1994;26:119-124.

Laitinen JH, Ahola IE, Sarkkinen ES, Winberg RL, Harmaakorpi-Iivonen PA, Uusitupa MI: Impact of intensified dietary therapy on energy and nutrient intakes and fatty acid composition of serum lipids in patients with recently diagnosed non-insulin-dependent diabetes mellitus. *Journal of the American Dietetic Association* 1993;93:276-283.

Lauritsen K, Laursen LS, Kjeldsen J, Bukhave K, Rask-Madsen J: Inhibition of eicosanoid synthesis and potential therapeutic benefits of 'dual pathway inhibition'. *Pharmacology & Toxicology, Supplement* 1994;75:9-13.

Lerman-Garber I, Gulias-Herrero A, Palma ME, et al: Response to high carbohydrate and high monounsaturated fat diets in hypertriglyceridemic non-insulin dependent diabetic patients with poor glycemic control. *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 1995;8:339-345.

Lerman-Garber I, Ichazo-Cerro S, Zamora-Gonzalez J, Cardoso-Saldana G, Posadas-Romero C: Effect of a high-monounsaturated fat diet enriched with avocado in NIDDM patients . *Diabetes Care* 1994;17:311-315.

Lesnichi AV: Use of unsaturated fatty acids in diabetes mellitus. *Problemy Endokrinologii* 1972;18:20-22.

Lichtenstein AH, Ausman LM, Jalbert SM, et al: Efficacy of a Therapeutic Lifestyle Change/Step 2 diet in moderately hypercholesterolemic middle-aged and elderly female and male subjects. *Journal of Lipid Research* 2002;43:264-273.

Lopez Ledesma R, Frati Munari AC, Hernandez Dominguez BC, et al: Monounsaturated fatty acid (avocado) rich diet for mild hypercholesterolemia. *Archives of Medical Research* 1996;27:519-523.

Louis Eand Belaiche J: The immunopathology and therapeutic perspectives of Chrohn's disease. *Medecine et Hygiene* 1991;49:3402-3406.

Lovejoy JC, Champagne CM, Smith SR, et al: Relationship of dietary fat and serum cholesterol ester and phospholipid fatty acids to markers of insulin resistance in men and women with a range of glucose tolerance. *Metabolism: Clinical & Experimental* 2001;50:86-92.

Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC: Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. *American Journal of Clinical Nutrition* 2002;76:1000-1006.

Lovejoy JC, Smith SR, Champagne CM, et al: Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care* 2002;25:1283-1288.

Madigan C, Ryan M, Owens D, Collins P, Tomkin GH: Dietary unsaturated fatty acids in type 2 diabetes: higher levels of postprandial lipoprotein on a linoleic acid-rich sunflower oil diet compared with an oleic acid-rich olive oil diet. *Diabetes Care* 2000;23:1472-1477.

Madsen JR, Laursen LS, Lauritsen K: [Chronic inflammatory bowel disease. *Nordisk Medicin* 1992;107:254-260.

Mallick NP: Dietary protein and progression of chronic renal disease. Large randomised controlled trial suggests no benefit from restriction. *BMJ British Medical Journal* 1994;309:1101-1102.

Mani UV, Desai S, Iyer U: Studies on the long-term effect of spirulina supplementation on serum lipid profile and glycated proteins in NIDDM patients. *Journal of Nutraceuticals, Functional and Medical Foods* 2000;2:25-32.

Marckmann P: Dietary treatment of thrombogenic disorders related to the metabolic syndrome. *British Journal of Nutrition* 2000;83:S121-S126

Marinides GN: Progression of chronic renal disease and diabetic nephropathy: A review of clinical studies and current therapy. *Journal of Medicine* 1993;24:266-288.

Matsueda K: Therapeutic efficacy of elemental enteral alimentation in Crohn's disease. *Journal of Gastroenterology* 2000;35:19-

Matsui T, Ueki M, Yamada M, Sakurai T, Yao T: Indications and options of nutritional treatment for Crohn's disease. A comparison of elemental and polymeric diets. *Journal of Gastroenterology* 1995;30:

Mayer-Davis EJ, Levin S, Bergman RN, et al: Insulin secretion, obesity, and potential behavioral influences: results from the Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes/Metabolism Research Reviews* 2001;17:137-145.

Mayer Davis EJ, Monaco JH, Hoen HM, et al: Dietary fat and insulin sensitivity in a triethnic population\the role of obesity. The Insulin Resistance Atherosclerosis Study (IRAS). *American Journal of Clinical Nutrition* 1997;65:79-87.

McAuley KA, Williams SM, Mann JI, et al: Intensive lifestyle changes are necessary to improve insulin sensitivity: a randomized controlled trial. *Diabetes Care* 2002;25:445-452.

McCarty MF: Toward practical prevention of type 2 diabetes. *Medical Hypotheses* 2000;54 :786-793.

McCarty MFand Rubin EJ: Rationales for micronutrient supplementation in diabetes. *Medical Hypotheses* 1984;13:139-151.

McKendry R: Treatment of Sjogren's syndrome with essential fatty acids, pyridoxine and vitamin C. *Prostaglandins Leukotrienes & Medicine* 1982:403-408.

Merrin PK, Elkeles RS: Treatment of diabetes: The effect on serum lipids and lipoproteins. *Postgraduate Medical Journal* 1991;67:931-937.

Metcalf PA, Stevens J, Shimakawa T, et al: Comparison of diets of NIDDM and non-diabetic African Americans and whites: the atherosclerosis risk in communities study. *Nutrition Research* 1998;

Mikhailidis DP, Jeremy JY, Dandona P: The role of prostaglandins, leukotrienes and essential fatty acids in the pathogenesis of the complications associated with diabetes mellitus. [Review] [19 refs]. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1988;33:205-206.

Milne RM, Mann JI, Chisholm AW, Williams SM: Long-term comparison of three dietary prescriptions in the treatment of NIDDM. *Diabetes Care* 1994;17:74-80.

Mironova MA, Klein RL, Virella GT, Lopes-Virella MF: Anti-modified LDL antibodies, LDL-containing immune complexes, and susceptibility of LDL to in vitro oxidation in patients with type 2 diabetes. *Diabetes* 2000;49:1033-1041.

Miwa H, Yamamoto M, Futata T, Kan K, Asano T: Thin-layer chromatography and high-performance liquid chromatography for the assay of fatty acid compositions of individual phospholipids in platelets from non-insulin-dependent diabetes mellitus patients: effect of eicosapentaenoic acid ethyl ester administration. *Journal of Chromatography B: Biomedical Applications* 1996;677:217-223.

Moncada S, Higgs EA: Arachidonate metabolism in blood cells and the vessel wall. *Clinics in Haematology* 1986;15:273-292.

Murata M, Kaji H, Iida K, Okimura Y, Chihara K: Dual action of eicosapentaenoic acid in hepatoma cells: up-regulation of metabolic action of insulin and inhibition of cell proliferation. *Journal of Biological Chemistry* 2001;276:

Murphy NJ, Schraer CD, Thiele MC, et al: Dietary change and obesity associated with glucose intolerance in Alaska Natives. *Journal of the American Dietetic Association* 1995;95:676-682.

Nakamura H, Faludi G, Spitzer JJ: Changes of individual free fatty acids during glucose tolerance test. *Diabetes* 1967;16:175-180.

Nakamura N, Hamazaki T, Jokaji H, Minami S, Kobayashi M: Effect of HMG-CoA reductase inhibitors on plasma polyunsaturated fatty acid concentrations in patients with hyperlipidemia. *International Journal of Clinical & Laboratory Research* 1998;28 :192-195.

Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S: Toward improved management of NIDDM: a randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Preventive Medicine* 1999;

Niemann J, Lippert C: Prospective development of the food industry and healthy nutrition. *Elelmezesi Ipar* 1990;

Nishida T, Miwa H, Shigematsu A, Yamamoto M, Iida M, Fujishima M: Increased arachidonic acid composition of phospholipids in colonic mucosa from patients with active ulcerative colitis. *Gut* 1987;28:1002-1007.

Nobmann ED, Byers T, Lanier AP, Hankin JH, Jackson MY: The diet of Alaska Native adults: 1987-1988. *American Journal of Clinical Nutrition* 1992;55:1024-1032.

Novak E: Maintaining remission of Crohn's disease. *CMAJ* 1988;139:14-

O'Morain C, O'Sullivan M: Nutritional support in Crohn's disease: current status and future directions. *Journal of Gastroenterology* 1995;30:

Odes HS: The pharmacological treatment of inflammatory bowel diseases: Recent concepts and advances. *Archives of Gastroenterohepatology* 1993;12:170-173.

Oguogho A, Aghajanian AA, Sinzinger H: Prostaglandin synthesis in human lymphatics from precursor fatty acids. *Lymphology* 2000;33:62-66.

Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H: The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *European Journal of Cancer* 2000;36:1235-1247.

Parfitt VJ, Desomeaux K, Bolton CH, Hartog M: Effects of high monounsaturated and polyunsaturated fat diets on plasma lipoproteins and lipid peroxidation in type 2 diabetes mellitus. *Diabetic Medicine* 1994;11:85-91.

Parfitt VJ, Hopton M, Taberner J, Bolton C, Hartog M: The effects of high monounsaturated and polyunsaturated fat diets on vascular endothelium and the coagulation system in non-insulin dependent diabetes mellitus--related to changes in lipid peroxidation? *Biochemical Society Transactions* 1993;21:103S-

Pedrera JD, Lopez MJ, Canal ML, et al: Quantitative phalangeal bone ultrasound is normal after long-term gluten-free diet in young coeliac patients. *European.Journal.of.Gastroenterology.and.Hepatology* 2001;13:1169-1173.

Pelikanova T, Kazdova L, Chvojkova S, Base J: Serum phospholipid fatty acid composition and insulin action in type 2 diabetic patients. *Metabolism: Clinical & Experimental* 2001;50:1472-1478.

Peppercorn MA: A 66-year-old woman with ulcerative colitis. *Journal of the American Medical Association* 1998;279:949-954.

Pereira SP, Cassell TB, Engelman JL, Sladen GE, Murphy GM, Dowling RH: Plasma arachidonic acid-rich phospholipids in Crohn's disease: response to treatment. *Clinical Science* 1996;91:509-512.

Perez-Jimenez F, Lopez-Miranda J, Pinillos MD, et al: A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. *Diabetologia* 2001;44:2038-2043.

Perry TL, Mann JI, Lewis-Barned NJ, Duncan AW, Waldron MA, Thompson C: Lifestyle intervention in people with insulin-dependent diabetes mellitus (IDDM). *European Journal of Clinical Nutrition* 1997;51:757-763.

Pi-Sunyer FX, Maggio CA, McCarron DA, et al: Multicenter randomized trial of a comprehensive prepared meal program in type 2 diabetes. *Diabetes Care* 1999;22:191-197.

Poisson JP, Narce M: Lipid metabolism. *Current Opinion in Lipidology* 2000;11:329-330.

Poppitt SD, Keogh GF, Prentice AM, et al: Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. *American Journal of Clinical Nutrition* 2002;75:11-20.

Pottathil R, Huang SW, Chandrabose KA: Essential fatty acids in diabetes and systemic lupus erythematosus (SLE) patients. *Biochemical & Biophysical Research Communications.* 1985;128:803-808.

Prescott J, Owens D, Collins P, Johnson A, Tomkin GH: The fatty acid distribution in low density lipoprotein in diabetes. *Biochimica et Biophysica Acta, Molecular and Cell Biology of Lipids* 1999;1439:110-116.

Randle PJ: Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metabolism Reviews* 1998;174:

Rao S, Erasmus RT: A pilot study on plasma fatty acids in poorly controlled non insulin dependent (type 2) Melanesian diabetics. *Central African Journal of Medicine* 1996;42:295-297.

Recht L, Helin P, Rasmussen J, Jacobsen J, Lithman T, Schersten B: Hand handicap and rheumatoid arthritis in a fish-eating society (the Faroe Islands). *Journal of Internal Medicine* 1990:49-55.

Requirand P, Gibert P, Tramini P, Cristol JP, Descomps B: Serum fatty acid imbalance in bone loss: example with periodontal disease. *Clinical Nutrition.* 2000;19:271-276.

Riccardi G, Rivellese A: Effects of dietary fiber and carbohydrate on glucose and lipoprotein metabolism in diabetic patients. *Diabetes Care* 1991;14:1115-25.

Riley MD, Dwyer T: Microalbuminuria is positively associated with usual dietary saturated fat intake and negatively associated with usual dietary protein intake in people with insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1998;67:50-57.

Riserus U, Arner P, Brismar K, Vessby B: Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. *Diabetes Care* 2002;25:1516-1521.

Rocca AS, LaGreca J, Kalitsky J, Brubaker PL: Monounsaturated fatty acid diets improve glycemic tolerance through increased secretion of glucagon-like peptide-1. *Endocrinology* 2001;142:1148-1155.

Rossetti R, Seiler C, Laposata M, Zurier R: Differential regulation of human T lymphocyte protein kinase C activity by unsaturated fatty acids. *Clinical Immunology & Immunopathology* 1995;76:220-224.

Rossing P: Promotion, prediction, and prevention of progression in diabetic nephropathy. *Danish Medical Bulletin* 1998;45:354-369.

Rowe BR, Bain SC, Pizzey M, Barnett AH: Rapid healing of ulcerated necrobiosis lipoidica with optimum glycaemic control and seaweed-based dressings. *British Journal of Dermatology* 1991;125:603-604.

Royall D, Jeejeebhoy KN, Baker JP, et al: Comparison of amino acid v peptide based enteral diets in active Crohn's disease: Clinical and nutritional outcome. *Gut* 1994;35:783-787.

Ruiz-Gutierrez V, Stiefel P, Villar J, Garcia-Donas MA, Acosta D, Carneado J: Cell membrane fatty acid composition in type 1 (insulin-dependent) diabetic patients: relationship with sodium transport abnormalities and metabolic control. *Diabetologia* 1993;36:850-856.

Ryan EA, Pick ME, Marceau C: Use of alternative medicines in diabetes mellitus. *Diabetic Medicine* 2001; 18:242-245.

Ryan M, McInerney D, Owens D, Collins P, Johnson A, Tomkin GH: Diabetes and the Mediterranean diet: a beneficial effect of oleic acid on insulin sensitivity, adipocyte glucose transport and endothelium-dependent vasoreactivity. *QJM* 2000;93:85-91.

Sabino KCC, Gayer CRM, Vaz LCA, Santos LRL, Felzenszwalb I, Coelho MGP: In vitro and in vivo toxicological study of the Pterodon pubescens seed oil. *Toxicology.Letters* 1999;29:

Sakamaki N, Kikutani N, Iguchi M, et al: Studies on fat contents and fatty acids composition in foods for dietary therapy of diabetes. *Annual Report of the Tokyo Metropolitan Research Laboratory of Public Health* 1996;11:202-206.

Salamone L, Cauley J, Black D, et al: Effect of a lifestyle intervention on bone mineral density in premenopausal women: a randomized trial. *American Journal of Clinical Nutrition.* 1999; 70:97-103.

Salmeron J, Hu FB, Manson JE, et al: Dietary fat intake and risk of type 2 diabetes in women. *American Journal of Clinical Nutrition* 2001;73:1019-1026.

Sanchez E, Jansen S, Castro P, et al: Mediterranean diet improves lipid profile in smoking males better than the American Cholesterol Program diet (NCEP-I). *Medicina Clinica Barcelona* 1999;39:

Sanfelippo ML, Swenson RS, Reaven GM: Reduction of plasma triglycerides by diet in subjects with chronic renal failure. *Kidney International* 1977;39:

Sarzi-Puttini P, Comi D, Boccassini L, et al: Diet therapy for rheumatoid arthritis. A controlled double-blind study of two different dietary regimens. *Scandinavian Journal of Rheumatology* 2000;29:302-307.

Schalch A, Ybarra J, Adler D, Deletraz M, Lehmann T, Golay A: Evaluation of a psycho-educational nutritional program in diabetic patients. *Patient Education & Counseling* 2001;44:171-178.

Scheffer PG, Bakker SJL, Popp-Snijders C, Heine RJ, Schutgens RBH, Teerlink T: Composition of LDL as determinant of its susceptibility to in vitro oxidation in patients with well-controlled type 2 diabetes. *Diabetes/Metabolism Research Reviews* 2001;17:459-466.

Schiff M: Emerging treatments for rheumatoid arthritis. *American Journal of Medicine* 1997;102:11S-15S.

Schmidt LE, Arfken CL, Heins JM: Evaluation of nutrient intake in subjects with non-insulin-dependent diabetes mellitus. *Journal of the American Dietetic Association* 1994;94:773-774.

Schwab U, Uusitupa M, Karhapaa P, et al: Effects of two fat-modified diets on glucose and lipid metabolism in healthy subjects. *Dietary lipids and insulin action Second International Smolenice Insulin Symposium* 1:279-280.

Schwarz JM, Linfoot P, Dare D, Aghajanian K: Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. *American Journal of Clinical Nutrition* 2003;77:43-50.

Schwingshandl J, Rippel S, Unterluggauer M, Borkenstein M: Effect of the introduction of dietary sucrose on metabolic control in children and adolescents with type I diabetes. *Acta Diabetologica* 1994;31:205-209.

Seigneur M, Freyburger G, Gin H, et al: Serum fatty acid profiles in type I and type II diabetes: metabolic alterations of fatty acids of the main serum lipids. *Diabetes Research & Clinical Practice* 1994;23:169-177.

Shanahan F: Probiotics: Science or snake oil? *Clinical Perspectives in Gastroenterology* 2001;4:47-50.

Shoda R, Matsueda K, Yamato S, Umeda N, Shanahan F : Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. *American Journal of Clinical Nutrition* 1996;63:741-745.

Sidery MB, Gallen IW, Macdonald IA: The initial physiological responses to glucose ingestion in normal subjects are modified by a 3 d high-fat diet. *British Journal of Nutrition* 1990; 64:705-713.

Sidossis LS, Stuart CA, Shulman GI, Lopaschuk GD, Wolfe RR: Glucose plus insulin regulate fat oxidation by controlling the rate of fatty acid entry into the mitochondria . *Journal of Clinical Investigation* 1996;28:

Siguel EN, Lerman RH: Prevalence of essential fatty acid deficiency in patients with chronic gastrointestinal disorders. *Metabolism: Clinical & Experimental* 1996;45:12-23.

Sileghem A: Intranasal calcitonin for the prevention of bone erosion and bone loss in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1992;51:761-764.

Simopoulos AP: Is insulin resistance influenced by dietary linoleic acid and trans fatty acids? *Free Radical Biology & Medicine* 1994;17:367-372.

Singer P, Gnauck G, Honigmann G, Schliack V: Fatty acid pattern of the triglycerides in severe diabetic macroangiopathy. *Deutsche Gesundheitswesen* 1978;33:2179-2183.

Singer P, Gnauck G, Honigmann G, Schliack V, Laeuter J: The fatty acid composition of triglycerides in arteries, depot fat and serum of amputated diabetics. *Atherosclerosis* 1977;28:87-92.

Singer P, Honigmann G, Buntrock P, Schliack V: Eicosapentaenoic acid in liver, serum and adipose tissue triglycerides in relation to the form of fatty liver in diabetics. *Deutsche Gesundheitswesen* 1981;36:1264-1272.

Singer P, Honigmann G, Schliack V: Fatty infiltration of the liver and fatty acid composition of the liver and adipose tissue triglycerides in diabetics without or with arterial hypertension. *Deutsche Gesundheitswesen* 1981;36:1693-1699.

Singer P, Honigmann G, Schliack V: Negative correlation of eicosapentaenoic acid and lipid accumulation in hepatocytes of diabetics. *Biomedica Biochimica Acta* 1984;43:S438-S442

Smedman A, Vessby B: Conjugated linoleic acid supplementation in humans - Metabolic effects. *Lipids* 2001;36:773-781.

Smith U: Carbohydrates, fat, and insulin action. *American Journal of Clinical Nutrition* 1994;59:686S-689S.

Soriguer F, Serna S, Valverde E, et al: Lipid, protein, and calorie content of different Atlantic and Mediterranean fish, shellfish, and molluscs commonly eaten in the south of Spain. *European Journal of Epidemiology* 1997;13:451-463.

Staprans I, Pan XianMang Hardman DA, Feingold KR , Pan XM: Effect of oxidized lipids in the diet on oxidized lipid levels in postprandial serum chylomicrons of diabetic patients. *Diabetes Care* 1999;22:300-306.

Stojceva-Taneva O, Polenakovic M, Grozdanovski R , Sikole A: Lipids, protein intake, and progression of diabetic nephropathy. *Nephrology Dialysis Transplantation* 2001;16:90-91.

Storlien LH, Hulbert AJ, Else PL: Polyunsaturated fatty acids, membrane function and metabolic diseases such as diabetes and obesity. *Current Opinion in Clinical Nutrition and Metabolic Care* 1998;46:

Strain GW, Champagne C, Roman SH: An ethnic comparison of nutritional patterns and health habits in elderly patients with diabetes. *Journal of Nutrition for the Elderly* 1998;18:37-47.

Straznicky NE, Barrington VE, Branley P, Louis WJ: A study of the interactive effects of oral contraceptive use and dietary fat intake on blood pressure, cardiovascular reactivity and glucose tolerance in normotensive women. *Journal of Hypertension* 1998;16:357-368.

Sukumar P, Loo A, Magur E, Nandi J, Oler A, Levine RA: Dietary supplementation of nucleotides and arginine promotes healing of small bowel ulcers in experimental ulcerative ileitis. *Digestive Diseases and Sciences* 1997;42:1530-1536.

Suryaprabha P, Das UN, Ramesh G, Kumar KV, Kumar GS: Reactive oxygen species, lipid peroxides and essential fatty acids in patients with rheumatoid arthritis and systemic lupus erythematosus. *Prostaglandins Leukotrienes & Essential.Fatty Acids* 1991;43:251-255.

Swinburn BA, Metcalf PA, Ley SJ: Long-term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 2001;24:619-624.

Takayasu K, Tada T, Okada F, Yoshikawa I: Human plasma fatty acid composition: the features of hyperlipoproteinemia and the influence of -linolenate and clofibrate. *Japanese Circulation Journal* 1971;35:1059-1069.

Teahon K, Venkatesan S: Fatty acid profile of plasma lipids from patients with Crohn's disease before and after 4 weeks on elemental diet ([double prime] 0 28 [double prime] or [double prime] Vivonex [double prime]). *Biochemical Society Transactions* 1991;19:322S-

Theander E, Horrobin D, Jacobsson L, Manthorpe R: Gammalinolenic acid treatment of fatigue associated with primary sjogren's syndrome. *Scandinavian Journal of Rheumatology* 2002;31:72-79.

Thomsen C, Rasmussen OW, Hansen KW, Vesterlund M, Hermansen K: Comparison of the effects on the diurnal blood pressure, glucose, and lipid levels of a diet rich in monounsaturated fatty acids with a diet rich in polyunsaturated fatty acids in type 2 diabetic subjects. *Diabetic Medicine* 1995;12:600-606.

Tilvis RS, Miettinen TA: Fatty acid compositions of serum lipids, erythrocytes, and platelets in insulin-dependent diabetic women. *Journal of Clinical Endocrinology & Metabolism* 1985;61:741-745.

Tilvis RS, Taskinen MR, Miettinen TA: Effect of insulin treatment on fatty acids of plasma and erythrocyte membrane lipids in type 2 diabetes. *Clinica Chimica Acta* 1988;171:293-303.

Tinahones FJ, Pareja A, Soriguer F, Gomez Zumaquero JM, Esteva I: Metabolic effects of a diet deficient in essential fatty acids. *Diabetes, Nutrition and Metabolism* 1998;11:325-329.

Toeller M, Klischan A, Heitkamp G, et al: Nutritional intake of 2868 IDDM patients from 30 centres in Europe. EURODIAB IDDM Complications Study Group. *Diabetologia* 1996;39:929-939.

Torrioli E, Citti C, Picchi L: Clinical and therapeutic studies of synthetic salmon calcitonin in some osteopathies. *Clinica.Terapeutica*. 1982:123-129.

Traianedes K, Collier GR, O'Dea K: Ingestion of different types of fat in the evening meal does not affect metabolic responses to a standard breakfast. *American Journal of Clinical Nutrition* 1990;52:442-445.

Trichopoulou A, Georgiou E, Bassiakos Y, et al: Energy intake and monounsaturated fat in relation to bone mineral density among women and men in Greece. *Preventive Medicine* 1997;26:395-400.

Tsihlias EB, Gibbs AL, McBurney MI, Wolever TM: Comparison of high- and low-glycemic-index breakfast cereals with monounsaturated fat in the long-term dietary management of type 2 diabetes. *American Journal of Clinical Nutrition* 2000;72:439-449.

Tuna N, Frankhauser S, Goetz FC: Total serum fatty acids in diabetes: relative and absolute concentrations of individual fatty acids. *American Journal of the Medical Sciences* 1968;255:120-131.

Tuomilehto J, Lindstrom J, Eriksson JG: Changes in diet and physical activity prevented type 2 diabetes mellitus in people with impaired glucose tolerance. *Evidence Based Medicine* 2001;6:176-

Tuomilehto J, Lindstrom J, Eriksson JG, et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* 2001;344:1343-1350.

Uccella R, Contini A, Sartorio M: Action of evening primrose oil on cardiovascular risk factors in insulin-dependent diabetics. *Clinica Terapeutica* 1989;129:381-388.

Uesugi T, Fukui Y, Yamori Y: Beneficial effects of soybean isoflavone supplementation on bone metabolism and serum lipids in postmenopausal japanese women: a four-week study. *Journal of the American College of Nutrition.* 2002;21:97-102.

Uusitupa M, Schwab U, Makimattila S, et al: Effects of two high-fat diets with different fatty acid compositions on glucose and lipid metabolism in healthy young women. *American Journal of Clinical Nutrition* 1994;59:1310-1316.

van Doormaal JJ, Idema IG, Muskiet FA, Martini IA, Doorenbos H: Effects of short-term high dose intake of evening primrose oil on plasma and cellular fatty acid compositions, alpha-tocopherol levels, and erythropoiesis in normal and type 1 (insulin-dependent) diabetic men. *Diabetologia* 1988;31:576-584.

van Doormaal JJ, Muskiet FA, van Ballegooie E, Sluiter WJ, Doorenbos H: The plasma and erythrocyte fatty acid composition of poorly controlled, insulin-dependent (type I) diabetic patients and the effect of improved metabolic control. *Clinica Chimica Acta* 1984;144:203-212.

van Epps-Fung M, Williford J, Wells A, Hardy RW: Fatty acid-induced insulin resistance in adipocytes. *Endocrinology Philadelphia* 1997;138:4338-4345.

van Oostrom AJ, Cabezas MC, Rabelink TJ: Insulin resistance and vessel endothelial function. *Journal of the Royal Society of Medicine* 2002;95:S61

Vassilopoulos D, Zurier R, Rossetti R, Tsokos G: Gammalinolenic acid and dihomogammalinolenic acid suppress the CD3mediated signal transduction pathway in human T cells. *Clinical Immunology & Immunopathology* 1997;83:237-244.

Vazquez IM, Millen B, Bissett L, Levenson SM, Chipkin SR: Buena Alimentacion, Buena Salud: A preventive nutrition intervention in Caribbean Latinos with type 2 diabetes. *American Journal of Health Promotion* 1998;13:116-119.

Vessby B, Aro A, Skarfors E, Berglund L, Salminen I, Lithell H: The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. *Diabetes* 1994;43:1353-1357.

Vessby B, Unsitupa M, Hermansen K, et al: Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. *Diabetologia* 2001;44:312-319.

Wahrburg U, Kratz M, Cullen P: Mediterranean diet, olive oil and health. *European Journal of Lipid Science and Technology* 2002;104:698-705.

Walker KZ, O' Dea K: Is a low fat diet the optimal way to cut energy intake over the long term in overweight people? *Nutrition Metabolism and Cardiovascular Diseases* 2001;

Walker KZ, O'Dea K, Nicholson GC, Muir JG: Dietary composition, body weight, and NIDDM: Comparison of high-fiber, high-carbohydrate, and modified-fat diets. *Diabetes Care* 1995;18:401-403.

Wallace AJ, Sutherland WHF, Mann JI, Williams SM: The effect of meals rich in thermally stressed olive and safflower oils on postprandial serum paraoxonase activity in patients with diabetes. *European Journal of Clinical Nutrition* 2001;55:951-958.

Wallace DJ: Systemic lupus erythematosus and Sjogren's syndrome. *Current Opinion in Rheumatology* 1994;6:459-460.

Watson J, Byars ML, McGill P, Kelman AW: Cytokine and prostaglandin production by monocytes of volunteers and rheumatoid arthritis patients treated with dietary supplements of blackcurrant seed oil. *British Journal of Rheumatology* 1993;32:1055-1058.

Watts GF: Coronary disease, dyslipidaemia and clinical trials in type 2 diabetes mellitus. *Practical Diabetes International* 2000;17:54-59.

Welch IM, Bruce C, Hill SE, Read NW: Duodenal and ileal lipid suppresses postprandial blood glucose and insulin responses in man: possible implications for the dietary management of diabetes mellitus. *Clinical Science* 1987;72:209-216.

West KM: Diet therapy of diabetes: an analysis of failure. *Annals of Internal Medicine* 1973;79:425-434.

Williams DEM, Prevost AT, Whichelow MJ, Cox BD, Day NE, Wareham NJ: A cross-sectional study of dietary patterns with glucose intolerance and other features of the metabolic syndrome. *British Journal of Nutrition* 2000;83:257-266.

Williams WV, Rosenbaum H, Zurier RB: Effects of unsaturated fatty acids on expression of early response genes in human T lymphocytes. *Pathobiology* 1996;64:27-31.

Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Elaine HB: Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Archives of Internal Medicine* 1991;151 :1334-1340.

Wolever TMS, Mehling C: High-carbohydrate-low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance. *British Journal of Nutrition* 2002;87:477-487.

Wuesten O, Balz CH, Kloer HU, Bretzel RG, Linn T: Enhancement of beta-cell sensitivity to glucose by oral fat load. *Hormone & Metabolic Research* 2001;33:548-553.

Wyatt RJ, Hogg RJ: Evidence-based assessment of treatment options for children with IgA nephropathies. *Pediatric Nephrology* 2001;16:156-167.

Yamamoto K, Asakawa H, Tokunaga K, et al: Long-term ingestion of dietary diacylglycerol lowers serum triacylglycerol in type II diabetic patients with hypertriglyceridemia. *Journal of Nutrition* 2001;131:3204-3207.

Yaqoob P, Knapper JA, Webb DH, Williams CM, Newsholme EA, Calder PC: Effect of olive oil on immune function in middle-aged men. *American Journal of Clinical Nutrition* 1998;67:129-135.

Young TK, Gerrard JM, O'Neil JD: Plasma phospholipid fatty acids in the central Canadian arctic: biocultural explanations for ethnic differences. *American Journal of Physical Anthropology* 1999;109:9-18.

Zock PL, Mensink RP, Harryvan J, De Vries JHM, Katan MB: Fatty acids in serum cholesteryl esters as quantitative biomarkers of dietary intake in humans. *American Journal of Epidemiology* 1997;145:1114-1122.

Rejected Population

Bonnema SJ, Jespersen LT, Marving J, Gregersen G: Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 1995;8:81-87.

Cameron NE, Cotter MA: Effects of antioxidants on nerve and vascular dysfunction in experimental diabetes. *Diabetes Research & Clinical Practice* 1999;45:137-146.

Cathcart E, Gonnerman WA: Fish oil fatty acids and experimental arthritis. *Rheum Dis Clin North Am* 1991;17:235-42.

Clandinin MT, Cheema S, Field CJ, Baracos VE: Dietary lipids influence insulin action. *Annals of the New York Academy of Sciences* 1993;683:151-163.

Edrees GMF, Othman AB, Amer MA: Influence of zinc supplementation and soybean feeding in controlling some diabetic disorders. *Egyptian Journal of Food Science* 1991;20 ref.:1-2, 217.

Field CJ, Goruk SD, Wierzbicki AA, Clandinin MT: The effect of dietary fat content and composition on adipocyte lipids in normal and diabetic states. *International Journal of Obesity* 1989;13:747-756.

Gerbi A, Maixent JM, Barbey O, et al: Neuroprotective effect of fish oil in diabetic neuropathy. *Lipids* 1999;7:

Haines AP, Sanders TA, Imeson JD, et al: Effects of a fish oil supplement on platelet function, haemostatic variables and albuminuria in insulin-dependent diabetics. *Thrombosis Research* 1986;43:643-655.

Lungershausen YK, Howe PRC, Clifton PM, et al: Evaluation of an omega-3 fatty acid supplement in diabetics with microalbuminuria. *Annals of the New York Academy of Sciences* 1997;827:369-381.

Mori TA, Vandongen R, Masarei JR, Rouse IL, Dunbar D: Comparison of diets supplemented with fish oil or olive oil on plasma lipoproteins in insulin-dependent diabetics. *Metabolism: Clinical & Experimental* 1991;40:241-246.

Ogborn MR, Nitschmann E, Bankovic-Calic N, Weiler HA, Aukema H: Dietary flax oil reduces renal injury, oxidized LDL content, and tissue n-6/n-3 FA ratio in experimental polycystic kidney disease. *Lipids* 2002;37:1059-65.

Ohtake T, Kimura M, Takemura H, Hishida A: Effects of dietary lipids on daunomycin-induced nephropathy in mice: comparison between cod liver oil and soybean oil. *Lipids* 2002;4:

Reifen R: Nutrition and autoimmunity. *Israel Journal of Medical Sciences* 1997;33:269-272.

Robinson DR, Knoell CT, Urakaze M, et al: Suppression of autoimmune disease by omega-3 fatty acids. *Biochemical Society Transactions* 1995;23:287-291.

Robinson DXL, Tateno S, Guo M, Colvin R: Suppression of autoimmune disease by dietary n-3 fatty acids. *Journal of Lipid Research* 1993;34:1435-1444.

Shohat J, Boner G: Role of lipids in the progression of renal disease in chronic renal failure: evidence from animal studies and pathogenesis. *Israel Journal of Medical Sciences* 1993;29:228-239.

Stiefel P, Ruiz-Gutierrez V, Gajon E, et al: Sodium transport kinetics, cell membrane lipid composition, neural conduction and metabolic control in type 1 diabetic patients. Changes after a low-dose n-3 fatty acid dietary intervention. *Annals of Nutrition & Metabolism* 1999;43:113-120.

Tariq T, Close C, Dodds R, Viberti GC, Lee T, Vergani D: The effect of fish-oil on the remission of type 1 (insulin-dependent) diabetes in newly diagnosed patients. *Diabetologia* 1989;32:765-

Thaiss F, Schoeppe W, Germann P, Stahl RAK: Dietary fish oil intake: effects on glomerular prostanoid formation, hemodynamics, and proteinuria in nephrotoxic serum nephritis. *Journal of Laboratory and Clinical Medicine* 1990;33 ref.:

Watkins B, Lippman H, Le Bouteiller L, Li Y, Seifert M: Bioactive fatty acids: role in bone biology and bone cell function. *Progress in Lipid Research.* 2001;40:125-148.

Weise WJ, Natori Y, Levine JS, et al: Fish oil has protective and therapeutic effects on proteinuria in passive Heymann nephritis. *Kidney International* 1993;48:

Yagasaki K: Evaluation of therapeutic potential of dietary manipulations and food factors against nephritis and cancer by in vivo and in vitro disease models. *Nippon Eiyo Shokuryo Gakkaishi = Journal of the Japanese Society of Nutrition and Food Science* 2000;45:

Rejected Study Design Descriptive

AnonymousII. International conference on the health effects of omega-3 polyunsaturated fatty acids in seafoods. *Zeitschrift fur Arztliche Fortbildung* 1991;85:196-

AnonymousInflammatory bowel diseases. *Medecine et Chirurgie Digestives* 1991;20:365-371.

AnonymousSomething fishy for them joints? *Hospitals & Health Networks* 1995;69:12-

American Diabetes Association: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Journal of the American Dietetic Association* 2002;7:

Ballou SP: Systemic lupus erythematosus. Controversies in management. *Postgraduate Medicine* 1987;81:157-164.

Barth C: Prognostic risk factors as an indication for the early treatment of IgA nephritis. *Deutsche Medizinische Wochenschrift* 2000;125:1009-

Benedek T: Treatment of systemic lupus erythematosus: from cod-liver oil to cyclosporin. *Lancet*. 1998;352:901-902.

Cotton P: New approaches may aid patients with inflammatory bowel disease. *JAMA* 1990;263:3121-3122.

Daniel H, Metzger B: The pathogenesis and therapy of chronic inflammatory bowel diseases. *Deutsche Apotheker Zeitung* 1990;130:2461-2468.

Das UN: Insulin resistance and hyperinsulinaemia: Are they secondary to an alteration in the metabolism of essential fatty acids? *Medical Science Research* 1994;22:243-245.

Donadio JV, Bergstralh EJ, Offord KP, Holley KE, Spencer DC: Clinical and histopathologic associations with impaired renal function in IgA nephropathy. Mayo Nephrology Collaborative Group. *Clinical Nephrology* 1994;41:65-71.

Ernst E: Complementary/alternative medicine in rheumatology-between negligence, ignorance and arrogance. *Osteoarthritis & Cartilage* 2002;10:671-672.

Funk C: Current drug therapy of colitis. *Ars Medici* 1990;80:466-473.

Gassull MA: Polyunsaturated fatty acids in inflammatory bowel diseases. *Pediatrika* 1997;17:75-76.

Harrison R, Harrison B, Volker D, Garg M: Fish oils are beneficial to patients with established rheumatoid arthritis. *Journal of Rheumatology* 2001;28:2563-2565.

Hart F, Karmali R, Birtwistle S, McEwen L: Dietary fatty acids and rheumatoid arthritis. *Lancet* 1985;1:699-700.

Hogg RJ: A randomized, placebo-controlled, multicenter trial evaluating alternate-day prednisone and fish oil supplements in young patients with immunoglobulin A nephropathy. *American Journal of Kidney Diseases* 1995;26:792-796.

Howard WJ: Is it time for a clinical trial of dietary fish oil supplementation in individuals with NIDDM? *Annals of the New York Academy of Sciences* 1993;683:341-342.

Korelitz BI, Stenson WF, Cort D, et al: Fish oil supplementation in ulcerative colitis. *Deutsche Medizinische Wochenschrift* 1993;118:925-

Kremer J: Omega-3 fatty acids in rheumatoid arthritis. *Delaware.Medical Journal* 1988:679-681.

Kromhout Dand Feskens EJ: Nutrition and diabetes: the role of fat. *Acta Cardiologica* 1993;48:444-445.

Lauritzen K, Fabech B, Bager S, Larsen C: Fish oil. *Ugeskrift for Laeger* 2002;164:1062-1063.

Lorenz-Meyer H, Purrmann J, Scheurlen C, et al: Ergebnisse der Studie zur Erhaltung der Remission bei Morbus Crohn mit o-3 FS bzw. einer kohlenhydratarmen Kost. *Z Gastroenterol* 1992;30:654

Luostarinen R, Wallin R, Wibell L, Saldeen T: Vitamin E supplementation counteracts the fish oil-induced increase of blood glucose in humans. *Nutrition Research* 1995;15:953-968.

Petrie KJ, Cundy T: Alternative medicine recommendations to patients with Type 2 diabetes visiting health product shops and pharmacies. *Diabetic Medicine* 2002;19:1035-

Shanahan F, Targan S: Medical treatment of inflammatory bowel disease. *Annual Review of Medicine* 1992;43:125-133.

Siguel E: Low- and high-fat, peptide-based diets in adolescents with active Crohn's disease. *Journal of Parenteral & Enteral Nutrition* 1997;21:304-

Singer P: Third International Congress on Essential Fatty Acids and Eicosanoids. *Aktuelle Ernahrungsmedizin Klinik und Praxis* 1992;17:244-245.

Stotland BR, Cirigliano MD, Lchtenstein GR: Medical therapies for inflammatory bowel disease. *Hospital Practice* 1998;33:141-168.

Rejected Study Design Review/Meta-Analysis

Anonymous Fish oil. *Alternative Medicine Review* 2000;5:576-580.

Anonymous Fish oil supplements. *Geneesmiddelenbulletin* 1999;33:37-42.

Anonymous Fish oils in rheumatoid arthritis. *Lancet* 1987;2:720-721.

Anonymous Minerva. *BMJ* 1996;312:322-

Anonymous Nonspecific immunosuppressive therapies still the mainstay for SLE. *Drugs & Therapy Perspectives* 1996;8:5-9.

Adam O: Anti-inflammatory diet in rheumatic diseases. *European Journal of Clinical Nutrition* 1995;49:703-717.

Adam O: Nutrition and immun system: Rheumatism. *Aktuelle Ernahrungsmedizin* 2002;27:245-249.

Alarcon de la Lastra Barranco M, Motilva V, Herrerias J: Mediterranean diet and health: Biological importance of olive oil. *Current Pharmaceutical Design* 2001;7:933-950.

Albertazzi P, Coupland K: Polyunsaturated fatty acids. Is there a role in postmenopausal osteoporosis prevention? *Maturitas.* 2002;42:13-22.

Alexander J: Immunonutrition: The role of omega-3 fatty acids. *Nutrition* 1998;14:627-633.

Anderson JW, Smith BM, Washnock CS: Cardiovascular and renal benefits of dry bean and soybean intake. *American Journal of Clinical Nutrition* 1999;70:464S-474S.

Andreani D, Di Mario U, Pozzilli P: Prediction, prevention, and early intervention in insulin-dependent diabetes. *Diabetes-Metabolism Reviews* 1991;7:61-77.

Angelin B, Palmblad J: Fish liver oil instead of pharmaceuticals? *Lakartidningen* 1988;

Ariza-Ariza R, Mestanza-Peralta M, Cardiel M: Omega-3 fatty acids in rheumatoid arthritis: An overview. *Seminars in Arthritis & Rheumatism* 1998;27:366-370.

Axelrod L: Omega-3 fatty acids in diabetes mellitus. Gift from the sea? *Diabetes* 1989;38:539-543.

Bagdade JD: HDL and reverse cholesterol transport in diabetes. *Diabetes Reviews* 1997;5:392-409.

Barre D: Potential of evening primrose, borage, black currant, and fungal oils in human health. *Annals.of.Nutrition.and.Metabolism* 2001;45:47-57.

Barrett PH, Watts GF: HDL kinetics, fish oils and diabetes. *Atherosclerosis* 2001;159:243-244.

Barrett PH, Watts GF: Kinetic studies of lipoprotein metabolism in the metabolic syndrome including effects of nutritional interventions. *Current Opinion in Lipidology* 2003;14:61-68.

Bates EJ: Eicosanoids, fatty acids and neutrophils: Their relevance to the pathophysiology of disease. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1995;53:75-86.

Belaiche J, Louis E: Management of postoperative Crohn's disease recurrence. *Acta Endoscopica* 1999;29:253-262.

Belch J: Fish oil and rheumatoid arthritis: Does a herring a day keep rheumatologists away? *Annals of the Rheumatic Diseases* 1990;49:71-72.

Belch JJF: Is there a role for natural remedies in rheumatoid arthritis? *Scottish Medical Journal* 1992;37:100-102.

Belluzzi A: N-3 and n-6 fatty acids for the treatment of autoimmune diseases. *European.Journal.of.Lipid.Science.and.Technology* 2001;103:399-407.

Belluzzi A: N-3 fatty acids for the treatment of inflammatory bowel diseases. *Proceedings of the Nutrition Society* 2002;61:391-395.

Belluzzi A, Boschi S, Brignola C, Munarini A, Cariani G, Miglio F: Polyunsaturated fatty acids and inflammatory bowel disease. *American Journal of Clinical Nutrition* 2000;71:339S-342S.

Belluzzi A, Boschi S, Miglio F, et al: Long-chain fatty acids for the treatment of inflammatory bowel disease. *Essential fatty acids and eicosanoids: invited papers from the Fourth International Congress, Edinburgh, Scotland, UK, July 20 24, 1997* 1998;30:

Belluzzi A, Miglio F: n-3 Fatty acids in the treatment of Crohn's Disease. *Medicinal Fatty Acids in Inflammation* 1998;91-101.

Berry EM: Dietary fatty acids in the management of diabetes mellitus. *American Journal of Clinical Nutrition* 1997;66:991S-997S.

Berry EM: Who's afraid of n-6 polyunsaturated fatty acids? Methodological considerations for assessing whether they are harmful. *Nutrition Metabolism & Cardiovascular Diseases* 2001;11:181-188.

Best JD, O'Neal DN: Diabetic dyslipidaemia: Current treatment recommendations. *Drugs* 2000;59:1101-1111.

Bickston SJ, Cominelli F: Inflammatory Bowel disease: Short- and long-term treatments. *Disease-a-Month* 1998;44:144-172.

Bickston SJ, Cominelli F: Recent developments in the medical therapy of inflammatory bowel disease. *Current Opinion in Gastroenterology* 1998;14:6-10.

Bilo HJ, Gans RO: Fish oil: a panacea? *Biomedicine & Pharmacotherapy* 1990;44:169-174.

Bilo HJ, Homan van der Heide JJ Gans RO, Donker AJ: Omega-3 polyunsaturated fatty acids in chronic renal insufficiency. *Nephron* 1991;57:385-393.

Blok W, Katan M, Van der Meer J: Modulation of inflammation and cytokine production by dietary (n-3) fatty acids. *Journal of Nutrition* 1996;126:1515-1533.

Boucher BJ: Inadequate vitamin D status: Does it contribute to the disorders compris ing syndrome 'X'? *British Journal of Nutrition* 1998;79:315-327.

Buchanan HM, Preston SJ, Brooks PM, Buchanan WW: Is diet important in rheumatoid arthritis? *British Journal of Rheumatology* 1991;30:125-134.

Burke A, Lichtenstein GR, Rombeau JL: Nutrition and ulcerative colitis. *Baillieres Clinical Gastroenterology* 1997;11:153-174.

Cabre E, Gassull MA: Nutrition in inflammatory bowel disease: Impact on disease and therapy. *Current Opinion in Gastroenterology* 2001;17:342-349.

Cabre Gelada I, Esteve Comas I: Polysaturated fatty acids and their metabolites in chronic inflammatory bowel disease. *Gastroenterologia y Hepatologia* 1995;18:515-525.

Calder J, Issenman R, Cawdron R: Health information provided by retail health food outlets. *Canadian Journal of Gastroenterology* 2000;14:767-771.

Calder PC: Polyunsaturated fatty acids, inflammation, and immunity. *Lipids* 2001;36:1007-1024.

Calder P: Dietary fatty acids and the immune system. *Lipids* 1999;34:S137-S140

Calder P: Dietary modification of inflammation with lipids. *Proceedings of the Nutrition Society* 2002;61:345-358.

Calder P: n-3 polyunsaturated fatty acids and cytokine production in health and disease. *Annals of Nutrition & Metabolism* 1997;41:203-234.

Calder P: N-3 polyunsaturated fatty acids, inflammation and immunity: Pouring oil on troubled waters or another fishy tale? *Nutrition Research* 2001;21:309-341.

Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA: Fatty acids and lymphocyte functions. *British Journal of Nutrition* 2002;87:S31-S48

Calder P, Zurier R: Polyunsaturated fatty acids and rheumatoid arthritis. *Current Opinion in Clinical Nutrition & Metabolic Care* 2001;4:115-121.

Callegari PE, Zurier RB: Botanical lipids: potential role in modulation of immunologic responses and inflammatory reactions. *Rheumatic Diseases Clinics of North America* 1991;17:415-425.

Campieri M, Gionchetti P, Belluzzi A, Brignola C, Miglioli M, Barbara L: Medical treatment of inflammatory bowel disease. *Current Opinion in Gastroenterology* 1992;8:663-675.

Casellas F, Guarner F: Eicosanoids in inflammatory bowel disease. Therapeutic implications. *Clinical Immunotherapeutics* 1996;6:333-340.

Cathcart ES, Gonnerman WA, Leslie CA, Hayes KC: Dietary n-3 fatty acids and arthritis. *Journal of Internal Medicine Supplement* 1989;225:217-223.

Chowdhury MN: IgA nephropathy and fish oil. *Bangladesh Renal Journal* 2000;19:16-26.

Clark W: Treatment of lupus nephritis: Immunosuppression, general therapy, dialysis and transplantation. *Clinical & Investigative Medicine* 1994;17:588-601.

Clark WF, Parbtani A: Omega-3 fatty acid supplementation in clinical and experimental lupus nephritis. *American Journal of Kidney Diseases* 1994;23:644-647.

Clarke SD: Polyunsaturated fatty acid regulation of gene transcription: a mechanism to improve energy balance and insulin resistance. *British Journal of Nutrition* 2000;83:S59-S66

Cleland LG, Hill CL, James MJ: Diet and arthritis. *Baillieres Clinical Rheumatology* 1995;9:771-785.

Cleland L, James M: Adulthood prevention: Rheumatoid arthritis. *Medical Journal of Australia* 2002;176:S119-S120

Cleland L, James M: Fish oil and rheumatoid arthritis: Antiinflammatory and collateral health benefits. *Journal of Rheumatology* 2000;27:2305-2307.

Cleland LG , James MJ: Rheumatoid arthritis and the balance of dietary N-6 and N-3 essential fatty acids. *British Journal of Rheumatology* 1997;36:513-515.

Cole T, Hawkey CJ: New treatments in inflammatory bowel disease. *British Journal of Hospital Medicine* 1992;47:581-590.

Collier GR, Sinclair AJ: Role of N-6 and N-3 fatty acids in the dietary treatment of metabolic disorders. *Annals of the New York Academy of Sciences* 1993;683:322-330.

Connor WE: Diabetes, fish oil, and vascular disease. *Annals of Internal Medicine* 1995;123:950-952.

Connor WE, DeFrancesco CA, Connor SL: N-3 fatty acids from fish oil. Effects on plasma lipoproteins and hypertriglyceridemic patients. *Annals of the New York Academy of Sciences* 1993;683:16-34.

Cortot A, Desreumaux P: Crohn's disease: How to prevent a flare-up. *Drugs of Today* 1999;35:119-131.

Cukier C, Waitzberg DL: Biological activity of fish oil. *Arquivos.de Gastroenterologia.* 1996:173-178.

D'Amico G: Treatment of IgA nephropathy: An overview. *Nephrology* 1997;3:S725-S730

D'Haens G, Rutgeerts P: Maintenance and prophylactic therapy for Crohn's disease. *Current Opinion in Gastroenterology* 1997;13:312-316.

Darlington LG: Dietary therapy for rheumatoid arthritis. *Clinical & Experimental Rheumatology* 1994;12:235-239.

Darlington L: Do diets rich in polyunsaturated fatty acids affect dis ease activity in rheumatoid arthritis? *Annals.of.the.Rheumatic.Diseases* 1988;47:169-72.

Darlington LG, Ramsey NW: Review of dietary therapy for rheumatoid arthritis. *British Journal of Rheumatology* 1993;32:507-514.

Darlington LG, Ramsey NW: Review of dietary therapy for rheumatoid arthritis. *Comprehensive Therapy* 1994;20:490-494.

Darlington L, Stone T: Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *British Journal of Nutrition* 2001;85:251-269.

Das U: Beneficial action(s) of eicosapentaenoic acid/docosahexaenoic acid and nitric oxide in systemic lupus erythematosus. *Medical Science Research* 1995;23:723-726.

Das UN: Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how? *Prostaglandins Leukotrienes & Essential Fatty Acids* 2000;63:351-362.

Das U: Essential fatty acids: Biology and their clinical implications. *Asia Pacific Journal of Pharmacology* 1991;6:317-330.

Das UN: Essential fatty acids in health and disease. *Journal of the Association of Physicians of India.* 1999;47:906-911.

Das U: Hypothesis: can glucose-insulin-potassium regimen in combination with polyunsaturated fatty acids suppress lupus and other inflammatory conditions? *Prostaglandins,.Leukotrienes.and.Essential.Fatty.Acids* 2001;55:

Das U: Interaction(s) between essential fatty acids, eicosanoids, cytokines, growth factors and free radicals: Relevance to new therapeutic strategies in rheumatoid arthritis and other collagen vascular diseases. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1991;44:201-210.

Das UN: Interaction(s) between nutrients, essential fatty acids, eicosanoids, free radicals, nitric oxide, anti-oxidants and endothelium and their relationship to human essential hypertension. *Medical Science Research* 2000;28:75-83.

Das UN: The lipids that matter from infant nutrition to insulin resistance. *Prostaglandins Leukotrienes & Essential Fatty Acids* 2002;67:1-12.

Das UN: Nutritional factors in the pathobiology of human essential hypertension. *Nutrition* 2001;139:

Daviglus M, Sheeshka J, Murkin E: Health benefits from eating fish. *Comments on Toxicology* 2002;8:345-374.

de Caterina R: Omega 3 fatty acids in renal diseases. *World Review of Nutrition & Dietetics* 1994;76:137-142.

De Caterina R, Endres S, Kristensen SD, Schmidt EB: n-3 fatty acids and renal diseases. *American Journal of Kidney Diseases* 1994;24 :397-415.

De Leeuw IH: Is there a place for N-3 fatty acids in the treatment of diabetic patients? *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 1991;4:149-153.

De Strihou CVY: Fish oil for IgA nephropathy? *New England Journal of Medicine* 1994;331:1227-1229.

Dean JD, Durrington PN: Treatment of dyslipoproteinaemia in diabetes mellitus. *Diabetic Medicine* 1996;13:297-312.

DeLuca P, Rothman D, Zurier R: Marine and botanical lipids as immunomodulatory and therapeutic agents in the treatment of rheumatoid arthritis. *Rheumatic Disease Clinics of North America* 1995;21:759-777.

Dieleman LA, Heizer WD: Nutritional issues in inflammatory bowel disease. *Gastroenterology Clinics of North America* 1998;27:435-451.

Diethelm U: Nutrition and chronic polyarthritis. *Schweizerische Rundschau.fur Medizin Praxis* 1993:359-363.

Dillon JJ: Fish oil therapy for IgA nephropathy: efficacy and interstudy variability. *Journal of the American Society of Nephrology* 1997;8:1739-1744.

Dillon JJ: Treating IgA nephropathy. *Journal of the American Society of Nephrology* 2001;12:846-847.

Donadio JV: n-3 Fatty acids and their role in nephrologic practice. *Current Opinion in Nephrology & Hypertension* 2001;10:639-642.

Donadio J: Omega-3 polyunsaturated fatty acids: a potential new treatment of immune renal disease. *Mayo Clinic Proceedings.* 1991;66:1018-1028.

Donadio JV: Use of fish oil to treat patients with immunoglobulin a nephropathy. *American Journal of Clinical Nutrition* 2000;71:5S

Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM: Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrology Dialysis Transplantation* 2002;17:1197-1203.

Donadio JV, Grande JP: IgA nephropathy. *New England Journal of Medicine Online* 2002;347:738-748.

Driss F, Darcet P, Lagarde M, et al: Polyunsaturated fatty acids: drug or food? *World Review of Nutrition & Dietetics* 1984;43:170-173.

Empey LR, Fedorak RN: Prostaglandins in inflammatory bowel disease therapy. *Canadian Journal of Gastroenterology* 1993;7:173-178.

Endres S, De Caterina R, Schmidt EB, Kristensen SD: n-3 Polyunsaturated fatty acids: Update 1995. *European Journal of Clinical Investigation* 1995;25:629-638.

Endres S, Eisenhut T, Sinha B: n-3 polyunsaturated fatty acids in the regulation of human cytokine synthesis. *Biochemical.Society Transactions.* 1995:277-281.

Endres S, Lorenz R, Loeschke K: Lipid treatment of inflammatory bowel disease. *Current Opinion in Clinical Nutrition & Metabolic Care* 1999;2:117-120.

Endres S, von Schacky C: n-3 polyunsaturated fatty acids and human cytokine synthesis. *Current Opinion in Lipidology* 1996;7:48-52.

Ergas D, Eilat E, Mendlovic S, Sthoeger Z: n-3 fatty acids and the immune system in autoimmunity. *Israel Medical Association Journal: Imaj* 2002;4:34-38.

Ernst E: Complementary and alternative medicine in rheumatology. *Best Practice & Research in Clinical Rheumatology* 2000;14:731-749.

Ernst E , Chrubasik S: Phyto-anti-inflammatories: A systemic review of randomized, placebocontrolled, double-blind trials. *Rheumatic Disease Clinics of North America* 2000;26:13-27.

Ernst E, Nielsen G, Schmidt E: Fish oils and rheumatoid arthritis. *Ugeskrift for Laeger* 1994;156:3490-3495.

Esteve-Comas M, Gassull MA, Jeppesen PB, Hoy C-E, Mortensen PB: Abnormal fatty acid status in patients with Crohn disease. *American Journal of Clinical Nutrition* 2001;73:661-662.

Farmer A, Montori V, Dinneen S, Clar C: Fish oil in people with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2001;CD003205

Farrell RJ, Peppercorn MA: Ulcerative colitis. *Lancet* 2002;359:331-340.

Feehally J: Immunoglobulin A nephropathy: fish oils and beyond. [Review] [27 refs]. *Current Opinion in Nephrology & Hypertension* 1996;5:442-446.

Fernandes G, Venkatraman J: Role of omega-3 fatty acids in health and disease. *Nutrition Research* 1993;13:S19-S45

Feskens EJ, Kromhout D: Epidemiologic studies on Eskimos and fish intake. *Annals of the New York Academy of Sciences* 1993;683:9-15.

Fisher SE: Nutritional therapy of chronic ulcerative colitis. *Journal of Pediatric Gastroenterology & Nutrition* 1993;16:224-

Fleming CR, Jeejeebhoy KN: Advances in clinical nutrition. *Gastroenterology* 1994;106:1365-1373.

Floege J, Feehally J: IgA nephropathy: Recent developments. *Journal of the American Society of Nephrology* 2000;11:2395-2403.

Floege J, Mertens P: Therapy of patients with IgA-nephropathy: a critical appraisal. *Kidney & Blood Pressure Research* 2000;23:207-209.

Flynn MAT: Dietary fat and chronic diseases. *Bahrain Medical Bulletin* 1998;20:77-80.

Fogazzi GB, Sheerin NS: IgA-associated renal diseases. *Current Opinion in Nephrology & Hypertension* 1996;5:134-140.

Forbes A: Crohn's disease -- the role of nutritional therapy. *Alimentary Pharmacology and Therapeutics* 2002;

Fortin P, Lew R, Liang M, et al: Validation of a meta-analysis: The effects of fish oil in rheumatoid arthritis. *Journal of Clinical Epidemiology* 1995;48:1379-1390.

Franz MJ, Bantle JP, Beebe CA, et al: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002;25:148-198.

Friedman AL: Etiology, pathophysiology, diagnosis, and management of chronic renal failure in children. *Current Opinion in Pediatrics* 1996;8:147-151.

Friedman M, Brandon DL: Nutritional and health benefits of soy proteins. *Journal of Agricultural & Food Chemistry* 2001;49:1069-1086.

Fung SM, Ferrill MJ, Norton LL: Fish oil therapy in IgA nephropathy. *Annals of Pharmacotherapy* 1997;31:112-115.

Garg A: Treatment of diabetic dyslipidemia. *American Journal of Cardiology* 1998;81:47B-51B.

Garg A, Grundy SM: Treating dyslipidemia in patients with non-insulin-dependent diabetes mellitus. *Cardiovascular Reviews & Reports* 1988;9:30-36+39.

Gerster H: The use of n-3 PUFAs (fish oil) in enteral nutrition. *International Journal for Vitamin.& Nutrition Research* 1995;65:3-20.

Geusens P: Lipoids: Omega-3-polyunsaturated fatty acids, their anti-inflammatory role, example of rheumatoid polyarthritis. *Nutrition Clinique et Metabolisme* 1996;10:33-34.

Gibson RA: The effect of diets containing fish and fish oils on disease risk factors in humans. *Australian & New Zealand Journal of Medicine* 1988;18:713-722.

Gil A: Polyunsaturated fatty acids and inflammatory diseases. *Biomedicine & Pharmacotherapy* 2002;56:388-396.

Glassock RJ: The treatment of IgA nephropathy: status at the end of the millenium. *Journal of Nephrology* 1999;12:288-296.

Gorson DM, Tobin A, Stenson WF: Fish oil supplementation and ulcerative colitis. *Annals of Internal Medicine* 1992;117:535-536.

Graham TO, Kandil HM: Nutritional factors in inflammatory bowel disease. *Gastroenterology Clinics of North America* 2002;31:203-218.

Grande JP, Donadio JV: Role of dietary fish oil supplementation in IgA nephropathy. Mechanistic implications. *Minerva Urologica e Nefrologica* 2001;53:201-209.

Grassi M, Raffa S, Damiani VC, Fontana M: Current orientation in medical management of ulcerative colitis. *Clinica Terapeutica* 1995;146:327-341.

Griffiths AM: Inflammatory bowel disease. *Nutrition* 1998;14:788-791.

Grimble RF: Modification of inflammatory aspects of immune function by nutrients. *Nutrition Research* 1998;18:1297-1317.

Grimm H, Mayer K, Mayser P, Eigenbrodt E: Regulatory potential of n-3 fatty acids in immunological and inflammatory processes. *British Journal of Nutrition* 2002;87:S59-S67

Harris WS: Dietary fish oil and blood lipids. *Current Opinion in Lipidology* 1996;7:3-7.

Hawkey CJ, Mahida YR, Hawthorne AB: Therapeutic interventions in gastrointestinal disease based on an understanding of inflammatory mediators. *Agents & Actions* 1992;Spec:6

Heine G, Sester U, Kohler H, et al: IgA nephropathy [3] (multiple letters). *New England Journal of Medicine* 2003;348:79-81.

Heine RJ: Dietary fish oil and insulin action in humans. *Annals of the New York Academy of Sciences* 1993;683:110-121.

Heller A, Koch T, Schmeck J, Van Ackern C: Lipid mediators in inflammatory disorders. *Drugs* 1998;55:487-496.

Hitchens K: Managing inflammatory bowel disease. *American Druggist* 1997;214:58-65.

Hodgson HJ: Keeping Crohn's disease quiet. *New England Journal of Medicine* 1996;334:1599-1600.

Hogg RJ, Waldo B: Advances in treatment: immunoglobulin A nephropathy. *Seminars in Nephrology* 1996;16:511-516.

Horrobin DF: Essential fatty acids and the complications of diabetes mellitus. *Wiener Klinische Wochenschrift* 1989;101:289-293.

Horrobin D: Low prevalences of coronary heart disease (CHD), psoriasis, asthma and rheumatoid arthritis in Eskimos: are they casued by high dietary intake of eicosapentaenoic acid (EPA), a genetic variation of essential fatty acid (EFA) metabolism or a combination of. *Medical.Hypotheses* 1987;26:

Horrobin DF: The roles of essential fatty acids in the development of diabetic neuropathy and other complications of diabetes mellitus. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1988;31:181-197.

Horrocks L, Keo Y: Health benefits of docosahexaenoic acid (DHA). *Pharmacological Research* 1999;40:211-225.

Hu FB: The role of n-3 polyunsaturated fatty acids in the prevention and treatment of cardiovascular disease. *Drugs of Today* 2001;37:49-56.

Hu FB, van Dam RM, Liu S: Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. [Review] [111 refs]. *Diabetologia* 2001;44:805-817.

Hubbard R, Mejia A, Horning M: The potential of diet to alter disease processes. *Nutrition Research* 1994;14:1853-1895.

Hummell DS: Dietary lipids and immune function. *Progress in Food & Nutrition Science* 1993;17:287-329.

Illingworth DR: N-3 fatty acids and prevention of atherosclerosis. *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 1989;2:71-81.

Ilowite NT: Hyperlipidemia and the rheumatic diseases. *Current Opinion in Rheumatology.* 1996;8:455-458.

Imai E, Kawamura T: Current therapeutic strategies for IgA nephropathy. *Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs* 2000;2:330-338.

Ioannou Y, Isenberg D: Current concepts for the management of systemic lupus erythematosus in adults: A therapeutic challenge. *Postgraduate Medical Journal* 2002;78:599-606.

Isseroff R: Fish again for dinner! the role of fish and other dietary oils in the therapy of skin disease. *Journal.of.the.American.Academy.of.Dermatology* 1988;19:1073-80.

James M, Cleland L: Dietary n-3 fatty acids and therapy for rheumatoid arthritis. *Seminars in Arthritis & Rheumatism* 1997;27:85-97.

James MJ, Cleland LG, Gibson RA, Hawkes JS: Strategies for increasing the antiinflammatory effect of fish oil. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1991;44:123-126.

James M, Gibson R, Cleland L: Dietary polyunsaturated fatty acids and inflammatory mediator production. *American Journal of Clinical Nutrition* 2000;71:343S-348S.

Jensen T: Dietary supplementation with omega-3 fatty acids in insulin-dependent diabetes mellitus, in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:417-424.

Jensen T: Dietary supplementation with omega 3 fatty acids in insulin-dependent diabetes mellitus. *World Review of Nutrition & Dietetics* 1991;66:417-424.

Jorquera Plaza F, Espinel Diez J, Olcoz Goni JL: Inflammatory bowel disease: importance of nutrition today]. *Nutricion Hospitalaria* 1997;12:289-298.

Julian BA: Treatment of IgA nephropathy. *Seminars in Nephrology* 2000;20:277-285.

Julian BA, Bake AWL: Treatment options in IgA nephropathy. *Nephrology* 1997;3:103-108.

Kasim SE: Dietary marine fish oils and insulin action in type 2 diabetes. *Annals of the New York Academy of Sciences* 1993;683:250-257.

Katsilambros NL: Nutrition in diabetes mellitus. *Experimental & Clinical Endocrinology & Diabetes* 2001;109:8

Katz S: Update in medical therapy in inflammatory bowel disease: A clinician's view. *Digestive Diseases* 1999;17:163-171.

Kehn P, Fernandes G: The importance of omega-3 fatty acids in the attenuation of immune-mediated diseases. *Journal of Clinical Immunology* 2001;21:99-101.

Kelly DG, Fleming CR: Nutritional considerations in inflammatory bowel diseases. *Gastroenterology Clinics of North America* 1995;24:597-611.

Kelly GS: Insulin resistance: Lifestyle and nutritional interventions. *Alternative Medicine Review* 2000;5:109-132.

Kettler D: Can manipulation of the ratios of essential fatty acids slow the rapid rate of postmenopausal bone loss? *Alternative Medicine Review* 2001;6:61-77.

Kim YI: Can fish oil maintain Crohn's disease in remission? *Nutrition Reviews* 1996;54:248-252.

Korelitz BI: Ulcerative colitis: Guidelines for optimal treatment. *Drug Therapy* 1993;23:43-44+47.

Koretz RL: Maintaining remissions in Crohn's disease: a fat chance to please. *Gastroenterology* 1997;112:

Korstanje M, Bilo H, Peltenburg H, Stoof T: Fish-oil; food or drug? *Nederlands Tijdschrift voor Geneeskunde* 1991;135:828-833.

Kremer J: Clinical studies of omega-3 fatty acid supplementation in patients who have rheumatoid arthritis. *Rheumatic Disease Clinics of North America* 1991;17:391-402.

Kremer J: Effects of modulation of inflammatory and immune parameters in patients with rheumatic and inflammatory disease receiving dietary supplementation of n-3 and n-6 fatty acids. *Lipids* 1996;31:S243-S247

Kremer J: n-3 Fatty acid supplements in rheumatoid arthritis. *American Journal of Clinical Nutrition* 2000;71:349S-351S.

Kremer JM, Robinson DR: Studies of dietary supplementation with omega-3 fatty acids in patients with rheumatoid arthritis, in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:367-382.

Kubitschek J: Cardiovascular diseases: Fish oil improved arterial compliance in 20 patients with type II diabetes mellitus. *Deutsche Apotheker Zeitung* 1995;135:69-

Kyriakopoulos A: Rheumatoid arthritis and fish oil. *Annals of Internal Medicine* 1987:941-

Lackey VA, Noble TA: Omega-3 fatty acid supplementation in noninsulin-dependent diabetes. *DICP* 1990;24:258-260.

Landgraf R: PUFA supplementation and hypertension in type 1 diabetes. *Annals of the New York Academy of Sciences* 1993;683:331-336.

Larkin J: Alternative medicine and rheumatoid arthritis. *Rheumatology Review* 1994;3:61-71.

Lau C, Gallacher C, Ross P, Belch J: Rheumatoid arthritis: Fish oil? or snake oil? *British Journal of Rheumatology* 1991;30:72-73.

Le Goff P, Baron D, Youinou P: Effects of dietary modification with fatty acids in rheumatoid arthritis. *Rhumatologie* 1992;44:145-149.

Lee T, Arm J: Benefits from oily fish. May help in coronary artery disease and several inflammatory conditions. *BMJ.British Medical Journal* 1988;297:1421-1422.

Lefebvre PJ, Scheen AJ: Management of non-insulin-dependent diabetes mellitus. *Drugs* 1992;44:29-38.

Lichenstein GR: Medical therapies for inflammatory bowel disease. *Current Opinion in Gastroenterology* 1994;10:390-403.

Lichtenstein AH, Schwab US: Relationship of dietary fat to glucose metabolism. *Atherosclerosis* 2000;150:227-243.

Lin C-Y: Treatment of IgA nephropathy. *Springer Seminars in Immunopathology* 1994;16:121-127.

Ling S, Griffiths A: Nutrition in inflammatory bowel disease. *Current Opinion in Clinical Nutrition & Metabolic Care* 2000;3:339-344.

Linn FV, Peppercorn MA: Drug therapy for inflammatory bowel disease: Part II. *American Journal of Surgery* 1992;164:178-185.

Locatelli F, Pozzi C, Del Vecchio L, et al: New therapeutic approaches in primary IgA nephropathy. *Advances in Nephrology From the Necker Hospital* 1999;29:73-91.

Lombard L, Augustyn MN, Ascott-Evans BH: The metabolic syndrome - Pathogenesis, clinical features and management. *Cardiovascular Journal of Southern Africa* 2002;13:181-186.

Lorenz R, Loeschke K: Placebo-controlled trials of omega 3 fatty acids in chronic inflammatory bowel disease. *World Review of Nutrition & Dietetics* 1994;76:143-145.

Malasanos TH, Stacpoole PW: Biological effects of omega-3 fatty acids in diabetes mellitus. *Diabetes Care* 1991;14:1160-1179.

Mangge H, Hermann J, Schauenstein K: Diet and rheumatoid arthritis A review. *Scandinavian Journal of Rheumatology* 1999;28:201-209.

Mazieres B, Cantagrel A: Rheumatoid arthritis. Modern treatments. *European Journal of Internal Medicine, Supplement* 1992;3:91-101.

McCarthy GM, Kenny D: Dietary fish oil and rheumatic diseases. *Seminars in Arthritis & Rheumatism* 1992;21:368-375.

McCarty MF: A central role for protein kinase C overactivity in diabetic glomerulosclerosis: implications for prevention with antioxidants, fish oil, and ACE inhibitors. *Medical Hypotheses* 1998;50:155-165.

McCarty MF: Complementary measures for promoting insulin sensitivity in skeletal muscle. *Medical Hypotheses* 1998;51:451-464.

McCarty M: Upregulation of lymphocyte apoptosis as a strategy for preventing and treating autoimmune disorders: a role for whole-food vegan diets, fish oil and dopamine agonists. *Medical.Hypotheses* 2001;

McCarty M, Russell A: Niacinamide therapy for osteoarthritis--does it inhibit nitric oxide synthase induction by interleukin 1 in chondrocytes? *Medical Hypotheses* 1999:350-360.

McCowen KC, Pei Ra Ling Bistrian BR, Jeppesen PB , Hoy C-E, Mortensen PB: Arachidonic acid concentrations in patients with Crohn disease [1] (multiple letters). *American Journal of Clinical Nutrition* 2000;71:1008-1009.

Meier R: Chronic inflammatory bowel diseases and nutrition. *Schweizerische Medizinische Wochenschrift - Supplementum* 1996;79:14S-24S.

Meletis C, Bramwell B: Rheumatoid arthritis: Etiology and naturopathic treatments. *Alternative & Complementary Therapies* 2001;7:347-354.

Meltzer E, Arber N: Inflammatory bowel disease - Current and future medical therapy. *Ceska a Slovenska Gastroenterologie* 2000;54:187-195.

Mera SL: Diet and disease. *British Journal of Biomedical Science* 1994;51:189-206.

Messina M: Legumes and soybeans: overview of their nutritional profiles and health effects. *American Journal of Clinical Nutrition.* 1999;70:450S

Messina M: Soy foods and soybean isoflavones and menopausal health. *Nutrition in Clinical Care* 2002;5:272-82.

Miller ML: Treatment of systemic lupus erythematosus in adults and children. *Current Opinion in Rheumatology* 1990;2:712-716.

Milly Tand Simoncic R: Is fish oil supplementation (n-3 fatty acids) important for the diabetic? *Bratislavske Lekarske Listy* 1993;94:521-525.

Montori VM, Farmer A, Wollan PC, Dinneen SF: Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care* 2000;23:1407-1415.

Murch SH, Walker-Smith JA: Medical management of chronic inflammatory bowel disease. *Baillieres Clinical Gastroenterology* 1994;8:133-148.

Murch SH, Walker-Smith JA: Nutrition in inflammatory bowel disease. *Baillieres Clinical Gastroenterology* 1998;12:719-738.

Murphy NG , Zurier RB: Treatment of rheumatoid arthritis. *Current Opinion in Rheumatology* 1991;3:441-448.

Murray F: Fish oils in rheumatoid arthritis. *Lancet* 1987:1157-1158.

Mutanen M, Freese R: Fats, lipids and blood coagulation. *Current Opinion in Lipidology* 2001;12:25-29.

Nestel PJ: Polyunsaturated fatty acids (n-3, n-6). *American Journal of Clinical Nutrition* 1987;45:1161-7.

Nolin L, Courteau M: Management of IgA nephropathy: evidence-based recommendations. *Kidney International - Supplement* 1999;70:S56-S62

Nosari I, Cortinovis F, Lepore G, Maglio ML, Pagani G: Utilization of omega-3 fatty acids in diabetic patients. [Italian]. *Clinica Terapeutica* 1994;144:213-221.

O'Morain C, Tobin A, McColl T, Suzuki Y: Fish oil in the treatment of ulcerative colitis. *Canadian Journal of Gastroenterology* 1990;4:420-423.

O'Morain CA: Nutritional therapy in ambulatory patients. *Digestive Diseases & Sciences* 1987;32:95S-99S.

Okuyama H, Kobayashi T, Watanabe S: Dietary fatty acids - the N-6/N-3 balance and chronic elderly diseases. Excess linoleic acid and relative N-3 deficiency syndrome seen in Japan. *Progress in Lipid Research* 1996;

Palmblad J: Omega3 and omega6 fatty acids and inflammation. *Scandinavian Journal of Nutrition/Naringsforskning* 1996;40:125-128.

Pan CG: Glomerulonephritis in childhood. *Current Opinion in Pediatrics* 1997;9:154-159.

Panush R: Nutritional therapy for rheumatic diseases. *Annals of Internal Medicine* 1987:619-621.

Parke AL: Gastrointestinal disorders and rheumatic diseases. *Current Opinion in Rheumatology* 1993;5:79-84.

Patavino T, Brady DM: Natural medicine and nutritional therapy as an alternative treatment in systemic lupus erythematosus. *Alternative Medicine Review* 2001;6:460-471.

Peet M, Edwards RW: Lipids, depression and physical diseases. *Current Opinion in Psychiatry* 1997;10:477-480.

Pelton R: Treating arthritis naturally. *American Druggist* 1999;216:60-62.

Peppercorn MA: Advances in drug therapy for inflammatory bowel disease. *Annals of Internal Medicine* 1990;112:50-60.

Pepping J: Omega-3 essential fatty acids. *Am J Healht-Syst Pharm* 1999;56:719-724.

Peterson DB: Long-chain fatty acids and cardiovascular disease risk in non-insulin-dependent diabetes. *Nutrition* 1998;14:316-318.

Petri M: Diet and systemic lupus erythematosus: From mouse and monkey to woman? *Lupus* 2001;10:775-777.

Pike M: Antiinflammatory effects of dietary lipid modification. *Journal of Rheumatology* 1989:718-720.

Podell RN: Nutritional treatment of rheumatoid arthritis. Can alterations in fat intake affect disease course? *Postgraduate Medicine* 1985;77:65-72.

Podolsky DK: Inflammatory bowel disease. *New England Journal of Medicine* 2002;347:417-429.

Popova D: The diet in diabetes mellitus - Composition and comparative analysis. *Bulgarian Medicine* 1997;5:32-34.

Popp-Snijders C, Bilo HJ, Heine RJ: Fish oil and glycemic control: importance of dose . *Diabetes Care* 1990;13:80-81.

Popp-Snijders C, Schouten JA, Heine RJ, van der Veen EA: Dietary (n-3) polyunsaturated fatty acids lower plasma triacyglycerol concentrations in non-insulin-dependent diabetes mellitus. *Atherosclerosis* 1986;61:253-256.

Prince MJ, Deeg MA: Do n-3 fatty acids improve glucose tolerance and lipemia in diabetics? *Current Opinion in Lipidology* 1997;8:7-11.

Prokhorovich EA, Zharov EI, Martynov AI, Vertkin AL, Martynov DA, Svetova IuB: An experimental and clinical study of the biological action of marine fish fats. *Kardiologiia* 1990;30:99-102.

Raccah D, Coste T, Gerbi A, Vague P: Polyunsatured fatty acids and diabetes. *Cahiers de Nutrition et de Dietetique* 1997;32:349-358.

Rachmilewitz D: New forms of treatment for inflammatory bowel disease. *Gut* 1992;33:1301-1302.

Raheja BS, Sadikot SM, Phatak RB: Insulin resistance in syndrome X. *Lancet* 1993;342:554-555.

Raheja BS, Sadikot SM, Phatak RB, Rao MB: Significance of the N-6/N-3 ratio for insulin action in diabetes. *Annals of the New York Academy of Sciences* 1993;683:258-271.

Rampton DS: New drugs for inflammatory bowel disease. *European Journal of Internal Medicine* 1996;7:141-148.

Rapport L, Lockwood B: (5) flaxseed and flaxseed oil. *Pharmaceutical Journal* 2001;266:287-289.

Rebstock W: Modern concepts in therapy of glomerulonephritis. *Nieren- und Hochdruckkrankheiten* 1998;27:258-261.

Rhodes J, Thomas G, Evans BK: Inflammatory bowel disease management. Some thoughts on future drug developments. *Drugs* 1997;53:189-194.

Richter B, Clar C, Berger M: The Cochrane collaboration and its possible impact on diabetes care. *Diabetes Care* 2000;23:1217-1218.

Richter WO, Bertsch S, Muller S-D: Omega-3 fatty acids in diabetic hypertriglyceridemia. *Deutsche Apotheker Zeitung* 2001;141:43-62.

Ringertz B: Dietary treatment of rheumatoid arthritis. *Annals of Medicine* 1991:

Rivellese AA: Monounsaturated and marine omega-3 fatty acids in NIDDM patients. *Annals of the New York Academy of Sciences* 1997;827:302-309.

Robin J: Potential value of eicosapentaenoic acid. *Allergie.et Immunologie.* 1987:13

Rodgers J: n-3 Fatty acids in the treatment of ulcerative colitis, in Anonymous*Medicinal Fatty Acids in Inflammation*. Basel, Birkhauser Verlag; 1998:103-109.

Roediger WEW: Dietary therapy for Crohn's and ulcerative colitis: The importance of fatty acids and sulphur amino acids. *Cme Journal Gastroenterology, Hepatology & Nutrition* 2001;4:55-57.

Rombeau JL: Nutritional-metabolic aspects of inflammatory bowel disease. *Current Opinion in Gastroenterology* 1993;9:566-570.

Ross E: The role of marine fish oils in the treatment of ulcerative colitis. *Nutrition Reviews* 1993;51:47-49.

Rostoker G: Therapy of IgA nephropathy. *Biodrugs* 1998;9:279-301.

Rubba P, Iannuzzi A: N-3 to n-6 fatty acids for managing hyperlipidemia, diabetes, hypertension and atherosclerosis: is there evidence? *European Journal of Lipid Science and Technology* 2001;103:407-418.

Rustan AC, Nenseter MS, Drevon CA: Omega-3 and omega-6 fatty acids in the insulin resistance syndrome. Lipid and lipoprotein metabolism and atherosclerosis. *Annals of the New York Academy of Sciences* 1997;827:310-326.

Sadikot SM: Diabetes, obesity and insulin resistance/hyperinsulinemia. *Journal of the Diabetic Association of India* 1993;33:62-74.

Sanderson IR: Diet and gut inflammation. *Current Opinion in Gastroenterology* 1997;13:518-524.

Sarkkinen E, Uusitupa M: The role of fish oil in the prevention and treatment of diseases. *Duodecim* 1996:1755-1763.

Sasinka M, Filka J, Podracka L, Roland R, Gayova E, Vargova V: Does non-immunological therapy and diet determining factors in the treatment of autoimmune diseases?. *Vnitrni Lekarstvi* 1992;38:1018-1027.

Schacky Cvon, Von Schacky C: Omega-3 fatty acids, Mediterranean diet, low-fat diet -- what actually does protect against myocardial infarction? *MMW Fortschritte der Medizin* 2002;3-4, 37.

Scheinman JI, Trachtman H, Lin C-Y, Langman CB, Chan JCM: IgA nephropathy: To treat or not to treat? *Nephron* 1997;75:251-258.

Schmidt EB, Dyerberg J: Omega-3 fatty acids. Current status in cardiovascular medicine. *Drugs* 1994;47:405-424.

Schmitz PG, Antony KA: Omega-3 fatty acids in ESRD: Should patients with ESRD eat more fish? *Nephrology Dialysis Transplantation* 2002;17:11-14.

Seidman E, LeLeiko N, Ament M, et al: Nutritional issues in pediatric inflammatory bowel disease. *Journal of Pediatric Gastroenterology & Nutrition* 1991;12:424-438.

Sewell KL: Immunotherapy and other novel therapies, including biologic response modifiers, apheresis, and dietary modifications. *Current Opinion in Rheumatology* 1993;5 :293-298.

Siguel E: Deficiencies and abnormalities of essential fats in gastrointestinal and coronary artery disease. *Journal of Clinical Ligand Assay* 2000;23:104-111.

Silvis N: Nutritional recommendations for individuals with diabetes mellitus. *South African Medical Journal* 1992;81:162-166.

Simopoulos A: Essential fatty acids in health and chronic disease. *American Journal of Clinical Nutrition* 1999;70:560S-569S.

Simopoulos A: The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedicine & Pharmacotherapy* 2002;56:365-379.

Simopoulos A: Omega-3 fatty acids in health and disease and in growth and development. *American Journal of Clinical Nutrition* 1991;54:438-463.

Simopoulos A: Omega-3 fatty acids in inflammation and autoimmune diseases. *Journal of the American College of Nutrition* 2002;21:495-505.

Simopoulos AP: Omega-6/omega-3 fatty acid ratio and trans fatty acids in non-insulin-dependent diabetes mellitus. *Annals of the New York Academy of Sciences* 1997;827:327-338.

Simopoulos AP, Kifev RR, Martin RE, Barlow SM: Health effects of omega-3 polyunsaturated fatty acids in seafoods. *World Review of Nutrition and Dietetics* 1991;xxiv-

Sinclair HM: Food fats, good and bad. *British Journal of Clinical Practice* 1987;41:1033-1036.

Sinclair R: Good, bad or essential fats: what is the story with Omega-3? *Nutrition.and.Food.Science* 2000;9:4-5.

Sirtori CR, Galli C: N-3 fatty acids and diabetes. *Biomedicine & Pharmacotherapy* 2002;56:397-406.

Socha P, Ryzko J: Application of fish oil to the treatment of inflammatory bowel disease. *Pediatria Polska* 1998;73:929-935.

Sorisky A, Robbins DC: Fish oil and diabetes. The net effect. *Diabetes Care* 1989;12:302-304.

Spencer-Green G: Drug treatment of arthritis: Update on conventional and less conventional methods. *Postgraduate Medicine* 1993;93:129-140.

Sperling RI: Dietary omega-3 fatty acids: Effects on lipid mediators of inflammation and rheumatoid arthritis. *Rheumatic Disease Clinics of North America* 1991;17:373-389.

Sperling RI: Diet therapy in rheumatoid arthritis. *Current Opinion in Rheumatology* 1989;1:33-38.

Sperling R: Eicosanoids in rheumatoid arthritis. *Rheumatic Diseases Clinics of North America* 1995:741-758.

Stein Gand Funfstuck R: (omega)3-Unsaturated fatty acids in the treatment of mesangioproliferative glomerulonephritis? *Nieren- und Hochdruckkrankheiten* 1997;26:353-356.

Stenson WF, Alpers DH: Nutritional therapy in inflammatory bowel disease: A historical overview. *Current Opinion in Gastroenterology* 1997;13:135-139.

Stoll BA: Essential fatty acids, insulin resistance, and breast cancer risk. *Nutrition & Cancer* 1998;31:72-77.

Stone NJ: Fish consumption, fish oil, lipids, and coronary heart disease. *Circulation* 1996;94:2337-2340.

Swinburn BA: Effect of dietary lipid on insulin action. Clinical studies. *Annals of the New York Academy of Sciences* 1993;683:102-109.

Teitelbaum JE, Walker WA: Review: The role of omega 3 fatty acids in intestinal inflammation. *Journal of Nutritional Biochemistry* 2001;12:21-32.

Tidow-Kebritchi S: Effects of diets containing fish oil and vitamin E on rheumatoid arthritis. *Nutrition Reviews* 2001;59:335-338.

Topping DL, Illman RJ, Storer GB: Dietary (n-3) polyunsaturated fatty acids and the control of hypertriglyceridaemia in insulin-dependent and insulin-independent diabetics. *Atherosclerosis* 1986;61:255-256.

Trentham DE: Novel therapies. *Current Opinion in Rheumatology* 1990;2:506-509.

Tritos NA, Mantzoros CS: Clinical Review 97: Syndromes of severe insulin resistance. *Journal of Clinical Endocrinology & Metabolism* 1998;83:3025-3030.

Tulleken J, van Rijswijk M: Fish oil in the treatment of rheumatoid arthritis patients. *Nederlands Tijdschrift voor Geneeskunde* 1988;132:1875-1877.

Van Der Merwe CF: A different and physiological approach to manipulating the inflammatory response. *European Journal of Gastroenterology & Hepatology* 1993;5:433-436.

van Riel PLCM, van de Putte LBA: Clinical assessment and clinical trials in rheumatoid arthritis. *Current Opinion in Rheumatology* 1994;6:132-139.

van Ypersele de Strihou: Fish oil for IgA nephropathy? *New England Journal of Medicine* 1994;331:1227-1229.

Velardo B, Lagarde M, Guichardant M, et al: Decrease of platelet activity after intake of small amounts of eicosapentaenoic acid in diabetics. *Thrombosis & Haemostasis* 1982;48:344-

Vergroesen AJ: Physiological effects of dietary linoleic acid. *Nutrition Reviews* 1977;35:1-5.

Vessby B: Dietary supplementation with N-3 polyunsaturated fatty acids in type 2 diabetes. Effects on glucose homeostasis. *Annals of the New York Academy of Sciences* 1993;683:244-249.

Vessby B: Effects of omega-3 fatty acids on glucose and lipid metabolism in non-insulin-dependent diabetes mellitus, in Simopoulos AP, Kifer RR, Martin RE, Barlow SM (eds): *Health effects of omega-3 polyunsaturated fatty acids in seafoods.* Basel, Karger, World Rev Nutr Diet; 1991:407-416.

Vessby B: Effects of omega 3 fatty acids on glucose and lipid metabolism in non-insulin-dependent diabetes mellitus. *World Review of Nutrition & Dietetics* 1991;66:407-416.

Vessby B: n-3 fatty acids and blood glucose control in diabetes mellitus. *Journal of Internal Medicine Supplement* 1989;225:207-210.

Wardle E: Fish oils and glomerulonephritis. *Nephrology Dialysis Transplantation* 2002;17 :2033-

Wardle EN: Fish oils and nephritis or hypertension. *Nephron* 1987;46:399-

Wardle EN: IgA nephropathy: To treat or not to treat? *Nephron* 1998;79:221-

Wasielewski S: Fewer relapses in Crohn's disease with fish-oil capsules? *Deutsche Apotheker Zeitung* 1996;136:37-39.

Watkins B, Li Y, Lippman H, Seifert M: Omega-3 polyunsaturated fatty acids and skeletal health. *Experimental Biology & Medicine.* 2001;226:485-497.

Wilhelmi G: Potential effects of nutrition including additives on healthy and arthrotic joints. I. Basic dietary constituents. *Zeitschrift fur Rheumatologie.* 1993:174-179.

Williams CN: Special issues in nutritional therapy of inflammatory bowel disease. *Canadian Journal of Gastroenterology* 1993;7:196-199.

Wolf JM, Lashner BA: Inflammatory bowel disease: sorting out the treatment options. *Cleveland Clinic Journal of Medicine* 2002;69:621-626.

Woo KT: IgA nephritis: a review of the pathogenetic mechanisms and the rationale for therapy. *Annals of the Academy of Medicine, Singapore* 1989;18:702-706.

Yen P: Fish facts. *Geriatric Nursing* 1993:52-53.

Yetiv J: Clinical applications of fish oils. *Journal of the American Medical Association* 1988;260:665-670.

Yoshikawa N, Iijima K, Ito H: IgA nephropathy in children. *Nephron* 1999;83:1-12.

Yoshikawa N, Tanaka R, Iijima K: Pathophysiology and treament of lgA nephropathy in children. *Pediatric Nephrology* 2001;16:446-457.

Young RJ, Vanderhoof JA: Nutrition in pediatric inflammatory bowel disease. *Nutrition* 2000;16:78-80.

Yunus MB: Investigational therapy in rheumatoid arthritis: A critical review. *Seminars in Arthritis & Rheumatism* 1987;17:163-184.

Zachos M, Griffiths AM: Enteral feeding and Crohn disease. *Current Opinion in Gastroenterology* 2001;17:167-170.

Ziboh V, Gershwin M, German J, Keen C: Nutritional modulation of inflammation by polyunsaturated fatty acids/eicosanoids. *Nutrition.and.immunology:.principles.and.practice* 2000;81:-

Zimmerman KF, Schlesinger PA, Bloss TJ, Stillman MT: Fish-oil supplementation and rheumatoid arthritis. *Annals of Internal Medicine* 1987;107:262-263.

Zimmerman R, Radhakrishnan J, Valeri A, Appel G: Advances in the treatment of lupus nephritis. *Annual Review of Medicine* 2001;52:63-78.

Zurier B: Essential fatty acids and inflammation. *Annals of the Rheumatic Diseases* 1991;50:745-746.

Rejected Inappropriate Study Design

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;17:1498-1501.

Albrink MJ, Ullrich IH, Blehschmidt NG et al: The beneficial effect of fish oil supplements on serum lipids and clotting functions of patients with type II diabetes mellitus. *Diabetes* 1986;35:43A

Almallah YZ, Ewen SW, Mowat NAG, et al: Immunohistological modulation after nutritional supplementation with omega-3 essential fatty acids in patients with inflammatory bowel disease. *British Journal of Surgery* 1998;85:690-691.

Almallah YZ et al: Eicosapentaenoic acid and docosahexaenic acid in the treatment of patients with distal procto-colitis. *British Journal of Surgery* 1996;83:2

Anderson J, Blake JE, Turner J, Smith B: Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. *Am J Clin Nutr* 1998;68:1347S-1353S.

Arslan G, Brunborg LA, Froyland L, Brun JG, Valen M, Berstad A: Effects of duodenal seal oil administration in patients with inflammatory bowel disease. *Lipids* 2002;37:935-940.

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;39:426-431.

Bagdade JD, Ritter M, Subbaiah PV: Marine lipids normalize cholesteryl ester transfer in IDDM. *Diabetologia* 1996;39:487-491.

Bakker DJ, Haberstroh BN, Philbrick DJ, Holub BJ: Triglyceride lowering in nephrotic syndrome patients consuming a fish oil concentrate. *Nutrition Research* 1989;9:27-34.

Belluzzi A, Brignola C, Campieri M, et al: A new enteric coated preparation of omega 3 fatty acids for preventing post-surgical recurrence in Crohn's disease. *Digestive Disease Week* 1997;(Abstract)

Bilo HJG, Schaap GH, Slagt ME, Popp-Snijders C, Oe PL, Donker AJM: Protein intake variation and omega-3 polyunsaturated fatty acids do not influence carbohydrate metabolism in patients with chronic renal insufficiency. *Current Therapeutic Research, Clinical & Experimental* 1988;44:292-303.

Bjerve KS, Brubakk AM, Fougner KJ, Johnsen H, Midthjell K, Vik T: Omega-3 fatty acids: essential fatty acids with important biological effects, and serum phospholipid fatty acids as markers of dietary omega 3-fatty acid intake. *American Journal of Clinical Nutrition* 1993;57:801S-806S.

Branten AJW, Klasen IS, Wetzels JFM, et al: Short-term effects of fish oil treatment on urinary excretion of high- and low-molecular weight proteins in patients with IgA nephropathy. *Clinical Nephrology* 2002;58:267-274.

Butani L, Palmer J: Effect of fish oil in a patient with post-transplantation IgA nephropathy. *Nephrology Dialysis Transplantation* 2000;15:1264-1265.

Byars M, Watson J, McGill P: Blackcurrant seed oil as a source of polyunsaturated fatty acids in the treatment of inflammatory disease. *Biochemical.Society Transactions.* 1992 May;20:139S-

Chan PC, Chan KW, Cheng IK, Chan MK: Focal sclerosing glomerulopathy. Risk factors of progression and optimal mode of treatment . *International Urology & Nephrology* 1991;23:619-629.

Chen YD, Swami S, Skowronski R, Coulston AM, Reaven GM: Effect of variations in dietary fat and carbohydrate intake on postprandial lipemia in patients with noninsulin dependent diabetes mellitus. *Journal of Clinical Endocrinology & Metabolism* 1993;76 :347-351.

Cheng IK, Chan PC, Chan MK: The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. *Nephrology Dialysis Transplantation* 1990;5:241-246.

Chowdhury MdN Rashid HU, Rahman H, Jahan SS, Alam MR, Iqbal M: Effect of hilsha fish oil on lipid profile in patients with nephrotic syndrome. *Bangladesh Renal Journal* 2001;20:14-19.

Christensen JH, Skou HA, Madsen T, Torring I, Schmidt EB: Heart rate variability and n-3 polyunsaturated fatty acids in patients with diabetes mellitus. *Journal of Internal Medicine* 2001;249:545-552.

Clark W, Parbtani A, Huff M, Reid B, Holub BJ, Falardeau P: Omega-3 fatty acid dietary supplementation in systemic lupus erythematosus. *Kidney International.* 1989;36:653-660.

Clark W, Parbtani A, Huff M, et al: Flaxseed: a potential treatment for lupus nephritis. *Kidney International.* 1995;48:475-480.

Cleland LG, Gibson RA, Neumann M, French JK: The effect of dietary fish oil supplement upon the content of dihomo-gammalinolenic acid in human plasma phospholipids. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1990;40:12-Sep

D'Amico G, Gentile MG: Effect of dietary manipulation on the lipid abnormalities and urinary protein loss in nephrotic patients. *Mineral & Electrolyte Metabolism* 1992;18:203-206.

Das U: Beneficial effect of eicosapentaenoic and docosahexaenoic acids in the management of systemic lupus erythematosus and its relationship to the cytokine network. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1994;51:207-213.

De Caterina R, Caprioli R, Giannessi D, et al: n-3 fatty acids reduce proteinuria in patients with chronic glomerular disease. *Kidney International* 1993;44:843-850.

Dichi I, Dichi JB, Frenhane P, Rodrigues MA, Burini RC, Victoria CR: Reactivation of ulcerative rectocolitis with the use of non-steroidal anti-inflammatory drugs. Report of a case and review of the literature. *Arquivos de Gastroenterologia* 1995;32:172-177.

Dichi I, Dichi JB, Frenhane P, Rodrigues MAM, Burini RC, Victoria CR: Ulcerative colitis associated with non-steroidal anti-inflammatory drug. Report of a case and review of the literature. *Arquivos de Gastroenterologia* 1995;32:730-735.

Donadio JV, Jr, Grande JP, et al: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. *Journal of the American Society of Nephrology* 1999;10:1772-1777.

Donnelly JP, McGrath LT, Brennan GM: Lipid peroxidation, LDL glycosylation and dietary fish oil supplementation in type II diabetes mellitus. *Biochemical Society Transactions* 1994;22:34S-

Fahrer H, Hoeflin F, Lauterburg BH, Peheim E, Levy A, Vischer TL: Diet and fatty acids: Can fish substitute for fish oil? *Clinical & Experimental Rheumatology* 1991;9:403-406.

Fasching P, Ratheiser K, Waldhausl W, et al: Metabolic effects of fish-oil supplementation in patients with impaired glucose tolerance. *Diabetes* 1991;40:583-589.

Fisher WR, Zech LA, Stacpoole PW: Apolipoprotein B metabolism in hypertriglyceridemic diabetic patients administered either a fish oil- or vegetable oil-enriched diet. *Journal of Lipid Research* 1998;39:388-401.

Fox J, Manitius J, Debska Slizie Rutkowski B, Nowak J, Bautembach S, Owczarzak A: The effect of administering Omega-3 acids on lipids in serum, functional state of erythrocyte membrane and function of the kidneys in patients with primary glomerulonephritis. *Przeglad Lekarski* 1996;53:858-861.

Frenais R, Ouguerram K, Maugeais C, et al: Effect of dietary omega-3 fatty acids on high-density lipoprotein apolipoprotein AI kinetics in type II diabetes mellitus. *Atherosclerosis* 2001;157:131-135.

Friday KE, Childs MT, Tsunehara CH, Fujimoto WY, Bierman EL, Ensinck JW: Elevated plasma glucose and lowered triglyceride levels from omega-3 fatty acid supplementation in type II diabetes. *Diabetes Care* 1989;12:276-281.

Fujita H, Yamagami T, Ohshima K: Fermented soybean-derived water-soluble Touchi extract inhibits alpha-glucosidase and is antiglycemic in rats and humans after single oral treatments. *Journal of Nutrition* 2001;131:1211-1213.

Geerling BJ, Houwelingen AC, Badart-Smook A, Stockbrugger RW, Brummer RJ: Fat intake and fatty acid profile in plasma phospholipids and adipose tissue in patients with Crohn's disease, compared with controls. *American Journal of Gastroenterology* 1999;94:410-417.

Glauber H, Wallace P, Griver K, Brechtel G: Adverse metabolic effect of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Annals of Internal Medicine* 1988;108:663-668.

Goren A, Stankiewicz H, Goldstein R, Drukker A: Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. *Pediatrics* 1991;88:265-268.

Grimminger F, Fuhrer D, Papavassilis C, et al: Influence of intravenous n-3 lipid supplementation on fatty acid profiles and lipid mediator generation in a patient with severe ulcerative colitis. *European Journal of Clinical Investigation* 1993;23:706-715.

Gruenwald J, Graubaum H, Harde A: Effect of cod liver oil on symptoms of rheumatoid arthritis. *Advances in Therapy* 2002;19:101-107.

Haban P, Simoncic R, Zidekova E, Klvanova J: Effect of application of n-3 polyunsaturated fatty acids on blood serum concentration of von Willebrand factor in type II diabetes mellitus. *Medical Science Monitor* 1999;5:661-665.

Haban P, Zidekova E, Klvanova J: Supplementation with long-chain n-3 fatty acids in non-insulin-dependent diabetes mellitus (NIDDM) patients leads to the lowering of oleic acid content in serum phospholipids. *European Journal of Nutrition* 2000;39:201-206.

Hall AV, Parbtani A, Clark WF, et al: Omega-3 fatty acid supplementation in primary nephrotic syndrome: effects on plasma lipids and coagulopathy. *Journal of the American Society of Nephrology* 1992;3:1321-1329.

Hamazaki T, Nakazawa R, Tateno S, et al: Effects of fish oil rich in eicosapentaenoic acid on serum lipid in hyperlipidemic hemodialysis patients. *Kidney International* 1984;26:81-84.

Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S: Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. *Lipids* 1990;25:541-545.

Hansen G: Nutritional status of Danish patients with rheumatoid arthritis and effects of a diet adjusted in energy intake, fish content and antioxidants. *Ugeskrift for Laeger* 1998;160:3074-3078.

Hiroyuki F, Tomohide Y, Kazunori O: Efficacy and safety of Touchi extract, an a-glucosidase inhibitor derived from fermented soybeans, in non-insulin-dependent diabetic mellitus. *Journal of Nutritional Biochemistry* 2001;12:351-356.

Holman RT, Johnson SB, Bibus D, Spencer DC, Donadio JV Jr: Essential fatty acid deficiency profiles in idiopathic immunoglobulin A nephropathy. *American Journal of Kidney Diseases* 1994;23:648-654.

Hombrouckx RO, Bogaert AM, Leroy FM, et al: Polyunsaturated fatty acids of the n-3 class in chronic dialysis. *ASAIO Journal* 1992;38:M331-M333

Honzlova M, Peliskova Z, Trnavsky K: Initial experience with the treatment of rheumatoid arthritis by dietary manipulation. *Casopis.Lekaru.Ceskych.* 1989;128:149-152.

Horiuchi, Onouchi T, Takahashi M, To H, Orimo H: Effect of soy protein on bone metabolism in postmenopausal Japanese women. *Osteoporosis International.* 2000;11:721-724.

Ilowite N, Copperman N, Leicht T, Kwong T, Jacobson M: Effects of dietary modification and fish oil supplementation on dyslipoproteinemia in pediatric systemic lupus erythematosus. *Journal of Rheumatology.* 1995;22:1347-1351.

Jaschonek K, Clemens MR, Scheurlen M: Decreased responsiveness of platelets to a stable prostacyclin analogue in patients with Crohn's disease. Reversal by n-3 polyunsaturated fatty acids. *Thrombosis Research* 1991;63:667-672.

Jorgensen ME, Bjeregaard P, Borch-Johnsen K, et al: Diabetes and impaired glucose tolerance among the inuit population of Greenland. *Diabetes Care* 2002;25:1766-1771.

Kamada T, Yamashita T, Baba Y, et al: Dietary sardine oil increases erythrocyte membrane fluidity in diabetic patients. *Diabetes* 1986;35:604-611.

Kasim S, Stern B, Khilnani S et al: Omega-3 fish oils increase the serum apoprotein B level and improve blood pressure in non-insulin-dependent diabetes. *Circulation* 1987;76:35

Kasim SE, Stern B, Khilnani S, McLin P, Baciorowski S, Jen KL: Effects of omega-3 fish oils on lipid metabolism, glycemic control, and blood pressure in type II diabetic patients. *Journal of Clinical Endocrinology & Metabolism* 1988;67:1-5.

Kesavulu MM, Kameswararao B, Apparao Ch Kumar EG , Harinarayan CV: Effect of omega-3 fatty acids on lipid peroxidation and antioxidant enzyme status in type 2 diabetic patients. *Diabetes & Metabolism* 2002;28:20-26.

Kless T, Adam O: Effect of fish oil supplementation on erythrocyte fatty acids of patients with rheumatoid arthritis following a common western diet or a lactovegetarian diet . *Aktuelle Ernahrungsmedizin Klinik und Praxis* 1993;18:305-310.

Kremer J, Jubiz W, Michalek A: Fish-oil fatty acid supplementation in active rheumatoid arthritis. A double-blinded, controlled, crossover study. *Annals of Internal Medicine* 1987;106:497-503.

Kutafina EK, Netrebenko OK, Gorelova JU, Levachev MM, Garankina TI: Clinical application of the polyunsaturated n-3 fatty acids usage in pediatric practice. *Zeitschrift fur Ernahrungswissenschaft* 1998;37:Suppl-7

Kutner NG, Clow PW, Zhang R, Aviles X: Association of fish intake and survival in a cohort of incident dialysis patients. *American Journal of Kidney Diseases [Online]* 2002;39:1018-1024.

Lagarde M, Croset M, Vericel E, Calzada C: Effects of small concentrations of eicosapentaenoic acid on platelets. *Journal of Internal Medicine Supplement* 1989;225:177-179.

Landgraf-Leurs MM, Drummer C, Froschl H, Steinhuber R, Von Schacky C, Landgraf R: Pilot study on omega-3 fatty acids in type I diabetes mellitus. *Diabetes* 1990;39:369-375.

Lardinois CK, Starich GH, Mazzaferri EL, DeLett A: Effect of source of dietary fats on serum glucose, insulin, and gastric inhibitory polypeptide responses to mixed test meals in subjects with non-insulin dependent diabetes mellitus. *Journal of the American College of Nutrition* 1988;7:129-136.

Lenzi S, Caprioli R, Rindi P, et al: Omega-3 fatty acid supplementation and lipoprotein(a) concentrations in patients with chronic glomerular diseases. *Nephron* 1996;72:383-390.

Linos A, Kaklamani VG, Kaklamani E, et al: Dietary factors in relation to rheumatoid arthritis: A role for olive oil and cooked vegetables? *American Journal of Clinical Nutrition* 1999;70:1077-1082.

Linos A, Kaklamanis E, Kontomerkos A, et al: The effect of olive oil and fish consumption on rheumatoid arthritis A case control study. *Scandinavian Journal of Rheumatology* 1991;20:419-426.

Madar Z, Arieli B, Trostler N, Norynberg C: Effect of consuming soybean dietary fiber on fasting and postprandial glucose and insulin levels in type II diabetes. *Journal of Clinical Biochemistry and Nutrition* 1988;24 :

Malyszko JS, Malyszko J, Pawlak D, Buczko W, liwiec M: Hemostasis, platelet functions, serotonin and serum lipids during omega-3 fatty acid treatment in patients with glomerulonephritis . *Nephron* 1998;80:94-96.

Manitius J, Sulikowska B, Fox J, et al: The effect of dietary enrichment with fish-oil on urinary excretion of N-acetyl-beta-D-glucosaminidase and renal function in proteinuric patients with primary glomerulopathies. *International Urology & Nephrology* 1997;29:489-495.

McGrath LT, Brennan GM, McVeigh GE, Hayes JR, Johnston GD: Effect of fish oil and olive oil supplements on HDL and VLDL concentrations in normotriglyceridaemic and hypertriglyceridaemic type 2 diabetic patients. *British Journal of Clinical Pharmacology* 1993;35:91P-

McManus RM, Jumpson J, Finegood DT, Clandinin MT, Ryan EA: A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. *Diabetes Care* 1996;19:463-467.

Mertens PR, Floege J: Treatment of IgA nephropathies: a critical viewpoint. *Deutsche Medizinische Wochenschrift* 2000;125:1010-

Meyer KA, Kushi LH, Jacobs DR, Jr, Folsom AR: Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* 2001;24:1528-1535.

Miller ME, Anagnostou AA, Ley B, Marshall P, Steiner M: Effect of fish oil concentrates on hemorheological and hemostatic aspects of diabetes mellitus: a preliminary study . *Thrombosis Research* 1987;47:201-214.

Mollsten AV, Dahlquist GG, Stattin EL, Rudberg S: Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care* 2001;24:805-810.

Molvig J, Pociot F, Worsaae H, et al: Dietary supplementation with omega-3-polyunsaturated fatty acids decreases mononuclear cell proliferation and interleukin-1 beta content but not monokine secretion in healthy and insulin-dependent diabetic individuals. *Scandinavian Journal of Immunology* 1991;34:399-410.

Morcos NC: Modulation of lipid profile by fish oil and garlic combination. *Journal of the National Medical Association* 1997;59 ref.:10, 673-1067859.

Mori T, VAndongen R, Masarei J: Fish oil-induced changes in apolipoproteins in IDDM subjects. *Diabetes Care* 1990;13:725-732.

Mori TA, Vandongen R, Masarei JR, Dunbar D, Stanton KG: Serum lipids in insulin-dependent diabetics are markedly altered by dietary fish oils. *Clinical & Experimental Pharmacology & Physiology* 1988;15:333-337.

Mori TA, Vandongen R, Masarei JR, Stanton KG, Dunbar D: Dietary fish oils increase serum lipids in insulin-dependent diabetics compared with healthy controls. *Metabolism: Clinical & Experimental* 1989;38:404-409.

Naka Y, Nagata K, Maeda E, et al: Clinical efficacy of eicosapentaenoic acid ethylester on diabetic subjects. *Therapeutic Research* 1993;14:335-342.

Navarro E, Esteve M, Olive A, et al: Abnormal fatty acid pattern in rheumatoid arthritis. A rationale for treatment with marine and botanical lipids. *Journal of Rheumatology* 2000;27:298-303.

Nishikawa M, Hishinuma T, Nagata K, Koseki Y, Suzuki K, Mizugaki M: Effects of eicosapentaenoic acid (EPA) on prostacyclin production in diabetics: GC/MS analysis of PGI2 and PGI3 levels. *Methods & Findings in Experimental & Clinical Pharmacology* 1997;19:429-433.

O'Dea K, Sinclair AJ: The effects of low-fat diets rich in arachidonic acid on the composition of plasma fatty acids and bleeding time in Australian aborigines. *Journal of Nutritional Science & Vitaminology* 1985;31:441-453.

Okuda Y, Mizutami M, Tanaka K, Isaka M, Yamashita K: Beneficial effects of eicosapentaenoic acid for diabetic patients with arteriosclerosis obliterans. *Diabetes Research & Clinical Practice* 1992;18:139-140.

Okuda Y, Mizutani M, Ogawa M, et al: Long-term effects of eicosapentaenoic acid on diabetic peripheral neuropathy and serum lipids in patients with type II diabetes mellitus. *Journal of Diabetes & its Complications* 1996;10:280-287.

Olness K, Ader R: Conditioning as an adjunct in the pharmacotherapy of lupus erythematosus. *Journal of Developmental & Behavioral Pediatrics.* 1992;13:124-125.

Panchenko VM, Ershov AA, Isaev VA, ZImovchenko GS, Chernova GI: Poseidonol in the treatment of hyperlipidemia in patients with type 2 diabetes mellitus. *Klinicheskaia Meditsina* 2001;79:47-49.

Pecis M, de Azevedo MJ, Gross JL: Chicken and fish diet reduces glomerular hyperfiltration in IDDM patients. *Diabetes Care* 1994;17:665-672.

Piper CM, Carroll PB, Dunn FL: Diet-induced essential fatty acid deficiency in ambulatory patient with type I diabetes mellitus. *Diabetes Care* 1986;9:291-293.

Popp-Snijders C, Blonk MC: Omega-3 fatty acids in adipose tissue of obese patients with non-insulin-dependent diabetes mellitus reflect long-term dietary intake of eicosapentaenoic and docosahexa enoic acid. *American Journal of Clinical Nutrition* 1995;61:360-365.

Popp-Snijders C, Heine R, van der Veen E: Dietary fish oil augments insulin secretion and insulin clearance in obese and type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1988;31:532A(Abstract)

Popp-Snijders C, Heine R, van der Veen E: Effect of dietary fish oil on erythrocyte composition and insulin sensitivity in obese and non-obese subjects. *Diabetologia* 1987;30:571A(Abstract)

Popp-Snijders C, Schouten JA, Heine RJ, van der Meer J, van der Veen EA: Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Research* 1987;4:141-147.

Rabini RA, Fumelli P, Galassi R, Giansanti R, Ferretti G, Mazzanti L: Action of dietary polyunsaturated fatty acids on the fluidity of erythrocyte and platelet membrane in NIDDM. *Annals of the New York Academy of Sciences* 1993;683:371-372.

Richard MJ, Sirajeddine MK, Cordonnier D, et al: Relationship of omega-3 fatty acid supplementation to plasma lipid peroxidation in predialysis patients with hypertriglyceridaemia. *European Journal of Medicine* 1993;2:15-18.

Rillaerts EG, Engelmann GJ, Van Camp KM, De Leeuw I: Effect of omega-3 fatty acids in diet of type I diabetic subjects on lipid values and hemorheological parameters. *Diabetes* 1989;38:1412-1416.

Rylance PB, Gordge MP, Saynor R, Parsons V, Weston MJ: Fish oil modifies lipids and reduces platelet aggregability in haemodialysis patients. *Nephron* 1986;43:196-202.

Salomon P, Kornbluth AA, Janowitz HD: Treatment of ulcerative colitis with fish oil n--3-omega-fatty acid: an open trial. *Journal of Clinical Gastroenterology* 1990;12:157-161.

Sampson MJ, Davies IR, Brown JC, et al: n-3 polyunsaturated fatty acid supplementation, monocyte adhesion molecule expression and pro-inflammatory mediators in Type 2 diabetes mellitus. *Diabetic Medicine* 2001;18:51-58.

Schaap G, Bilo H, Beukhof J, Gans R, Popp-Snijders C, Donker A: The effects of short-term omega-3 polyunsaturated fatty acid supplementation in patients with chronic renal insufficiency. *Curr Ther Res Clin Exp* 1991;49:1061-1070.

Schectman G, Kaul S, Cherayil GD, Lee M, Kissebah A: Can the hypotriglyceridemic effect of fish oil concentrate be sustained? *Annals of Internal Medicine* 1989;110 :346-352.

Schimke E, Hildebrandt R, Beitz J, et al: Influence of a cod liver oil diet in diabetics type I on fatty acid patterns and platelet aggregation. *Biomedica Biochimica Acta* 1984;43:S351-S353

Schmidt EB, Klausen IC, Kristensen SD, Lervang HH, Faergeman O, Dyerberg J: The effect of n-3 polyunsaturated fatty acids on Lp(a). *Clinica Chimica Acta* 1991;198:271-277.

Schmidt EB, Sorensen PJ, Pedersen JO, et al: The effect of n-3 polyunsaturated fatty acids on lipids, haemostasis, neutrophil and monocyte chemotaxis in insulin-dependent diabetes mellitus. *Journal of Internal Medicine Supplement* 1989;225:201-206.

Selvais PL, Ketelslegers JM, Buysschaert M, Hermans MP: Plasma endothelin-1 immunoreactivity is increased following long-term dietary supplementation with omega-3 fatty acids in microalbuminuric IDDM patients. *Diabetologia* 1995;38:253-

Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M, Nelson JL: Diet and rheumatoid arthritis in women: A possible protective effect of fish consumption. *Epidemiology* 1996;7:256-263.

Shaw CK: An epidemiologic study of osteoporosis in Taiwan. *Annals of Epidemiology.* 1993;3:264-271.

Sheehan JP, Wei IW, Ulchaker M, Tserng KY: Effect of high fiber intake in fish oil-treated patients with non-insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1997;66:1183-1187.

Shimizu H, Sato N, Tanaka Y, Kashima K, Ohtani K , Mori M: Effect of eicosapentaenoic acid ethyl on urine albumin excretion in NIDDM. *Diabetes Care* 1993;16:1406-1408.

Spannagl M, Drummer C, Froschl H, et al: Plasmatic factors of haemostasis remain essentially unchanged except for PAI activity during n-3 fatty acid intake in type I diabetes mellitus. *Blood Coagulation & Fibrinolysis* 1991;2:259-265.

Sperling R, Weinblatt M, Robiin J, Ravalese J, Hoover R, House Fea: Effects of dietary supplementation with marine fish oil on leukoeyte lipid mediators and function in rheumatoid rthritis. *Arthritis Rheum* 1987;30:988-997.

Stacpoole PW, Alig J, Ammon L, Crockett SE: Dose-response effects of dietary marine oil on carbohydrate and lipid metabolism in normal subjects and patients with hypertriglyceridemia. *Metabolism: Clinical & Experimental* 1989;38:946-956.

Stacpoole PW, Alig J, Kilgore LL, et al: Lipodystrophic diabetes mellitus. Investigations of lipoprotein metabolism and the effects of omega-3 fatty acid administration in two patients. *Metabolism: Clinical & Experimental* 1988;37:944-951.

Stene LC, Ulriksen J, Magnus P, Joner G: Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring.[erratum appears in Diabetologia. *Diabetologia* 2000;43:1093-1098.

Stenson W, Cort D, Beeken Wea: A trial of fish oil supplemented diet in ulcerative colitis. *Gastroenterology* 1990;98:A475

Suci M Katica D, Kovacevi V: Effect of dietary fish supplementation on lipoprotein levels in patients with hyperlipoproteinemia. *Collegium Antropologicum* 1998;22:77-83.

Sulikowska B, Manitius J, owski T, ysiak W, Rutkowski B: The effect of therapy with small doses of mega-3 polyunsaturated fatty acid on renal reserve and metabolic disturbances in patients with primary IGA glomerulopathy. *Polskie Archiwum Medycyny Wewnetrznej* 2002;108:753-760.

Takahashi R, Inoue J, Ito H, Hibino H: Evening primrose oil and fish oil in non-insulin-dependent-diabetes. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1993;49:569-571.

Tilvis RS, Rasi V, Viinikka L, Ylikorkala O, Miettinen TA: Effects of purified fish oil on platelet lipids and function in diabetic women. *Clinica Chimica Acta* 1987;164 :315-322.

Tobin A: Eicosapentaenoic acid in chronic ulcerative colitis. *Gut* 1989;30:A1502

Tsujikawa T, Satoh J, Uda K, et al: Clinical importance of n-3 fatty acid-rich diet and nutritional education for the maintenance of remission in Crohn's disease. *Journal of Gastroenterology* 2000;35:99-104.

van Dam RM , Rimm EB, Willett WC, Stampfer MJ, Hu FB, van Dam RM: Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Annals of Internal Medicine* 2002;136:201-209.

Vessby B, Karlstrom B, Boberg M, Lithell H, Berne C: Polyunsaturated fatty acids may impair blood glucose control in type 2 diabetic patients. *Diabetic Medicine* 1992;9:126-133.

Virstiuk N: English walnuts in the combined treatment of rheumatoid arthritis patients . *Likarska.Sprava.* 1997;Mar-Apr:123-126.

Wakai K, Kawamura T, Matsuo S, Hotta N, Ohno Y: Risk factors for IgA nephropathy: a case-control study in Japan. *American Journal of Kidney Diseases* 1999;33:738-745.

Wijendran V, Bendel RB, Couch SC, Philipson EH, Cheruku S, Lammi-Keefe CJ: Fetal erythrocyte phospholipid polyunsaturated fatty acids are altered in pregnancy complicated with gestational diabetes mellitus. *Lipids* 2000;35:927-931.

Williams CM, Moore F, Wright J: Fasting and postprandial triacylglycerol responses to a standard test meal in subjects taking dietary supplements of n-3 fatty acids. *Biochemical Society Transactions* 1990;18:909-910.

Yosefy C, Viskoper JR, Laszt A, et al: The effect of fish oil on hypertension, plasma lipids and hemostasis in hypertensive, obese, dyslipidemic patients with and without diabetes mellitus. *Prostaglandins Leukotrienes & Essential Fatty Acids* 1999;61:83-87.

Zak A, Zeman M, Tvrzicka E, Stolba P: Effects of fish oils in patients with type 2 diabetes with associated dyslipidaemia. *Casopis Lekaru Ceskych* 1996;135:354-359.

Zambon S, Friday KE, Childs MT, Fujimoto WY, Bierman EL, Ensinck JW: Effect of glyburide and omega 3 fatty acid dietary supplements on glucose and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. *American Journal of Clinical Nutrition* 1992;56:447-454.

Rejected Duplicate

Dunstan DW, Mori TA, Puddey IB, et al: A randomised, controlled study of the effects of aerobic exercise and dietary fish on coagulation and fibrinolytic factors in type 2 diabetics. *Thrombosis & Haemostasis* 1999;81:367-372.

Fox J, Manitius J, Debska Slizien A, et al: Influence of omega-3 acids administration on plasma lipids, functional status of erythrocyte membrane and function of the kidney in patients with primary glomerulopathies. *Przeglad Lekarski* 1996;13:12, 858-1286113.

Nielsen G, Faarvang K, Tomsen B, Teglbjaerg K, Ernst E: Effects of supplementation with n-3 fatty acids on clinical disease variables in patients with rheumatoid arthritis . *European Journal of Clinical Investigation* 21:

Tulleken J, Limburg P, Muskiet F, van Rijswijk M: Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis Rheum* 1990;33:1416-9.

Rejected Unable to Find Translator

Faarvang KL, Nielsen GL, Thomsen BS, et al: Fish oils and rheumatoid arthritis. A randomized and double-blind study. *Ugeskrift for Laeger* 1994;156:3495-3498.

Shunto S, Takahashi K, Negishi K, et al: Effects of eicosapentaenoic acid on glycemic control and lipid metabolism in healthy and NIDDM subjects. *Therapeutic Research* 1992;13:257-265.

Skoldstam L, Berglund U, Eriksson A, Akesson B: A diet rich in polyunsaturated fatty acids is of no help in patients with rheumatoid arthritis. *Lakartidningen* 1988;14:4411-

Vargova V: Will administration of omega-3 unsaturated fatty acids reduce the use of nonsteroidal antirheumatic agents in children with chronic juvenile arthritis? *Casopis.Lekaru.Ceskych.* 1998;137:651-653.

Rejected No difference in Omega-3 Content

Buonfantino M, Marano M, Di Nuzzi L, Iorio G, Iuliano P, Tufano L: Use of fatty polyunsaturated acids (Fish oil) in diabetic nephropathy: Results of a preliminary study. *Rassegna Internazionale di Clinica e Terapia* 1995;75:264-267.

Dichi I, Frenhane P, Dichi J, et al: Comparison of omega-3 fatty acids and sulfasalazine in ulcerative colitis. *Nutrition* 2000;16:87-90.

Gassull MA, Fernandez-Banares F, Cabre E, et al: Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. *Gut* 2002;51:164-168.

Haugen MA, Kjeldsen-Kragh J, Bjerve KS, Hostmark AT, Forre O: Changes in plasma phospholipid fatty acids and their relationship to disease activity in rheumatoid arthritis patients treated with a vegetarian diet. *British Journal of Nutrition* 1994;72:555-566.

Herrmann W, Biermann J, Ratzmann KP, Lindhofer HG: Effect of fish oil concentrate on the lipoprotein profile of patients with type II diabetes mellitus. *Medizinische Klinik* 1992;87:12-15.

Katsuyama H, Ideguchi S, Fukunaga M, Saijoh K, Sunami S: Usual dietary intake of fermented soybeans (Natto) is associated with bone mineral density in premenopausal women. *Journal of Nutritional Science & Vitaminology.48(3):207-15*, 2002;-

Leiper K, Woolner J, Mullan MMC, et al: A randomised controlled trial of high versus low long chain triglyceride whole protein feed in active Crohn's disease. *Gut* 2001;49:790-794.

Leventhal LJ, Boyce EG , Zurier RB: Treatment of rheumatoid arthritis with blackcurrant seed oil. *British Journal of Rheumatology* 1994;33:847-852.

Lopez-Espinoza I, Howard-Williams J, Mann JI, Carter RD, Hockaday TD: Fatty acid composition of platelet phospholipids in non-insulin-dependent diabetics randomized for dietary advice. *British Journal of Nutrition* 1984;52:41-47.

Louheranta AM, Sarkkinen ES, Vidgren HM, Schwab US, Uusitupa MI: Association of the fatty acid profile of serum lipids with glucose and insulin metabolism during 2 fat-modified diets in subjects with impaired glucose tolerance. *American Journal of Clinical Nutrition* 2002; 76:331-337.

Potter S, Baum J, Teng H, Stillman RJ, Shay N, Erdman J: Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am J Clin Nutr* 1998;68:1375S-1379S.

Provenzano C, Vero R, Oliva A, et al: Lispro insulin in type 1 diabetic patients on a Mediterranean or normal diet: a randomized, cross-over comparative study with regular insulin. *Diabetes, Nutrition & Metabolism - Clinical & Experimental* 2001;14:133-139.

Rodriguez-Villar C, Manzanares JM, Casals E, et al: High-monounsaturated fat, olive oil-rich diet has effects similar to a high-carbohydrate diet on fasting and postprandial state and metabolic profiles of patients with type 2 diabetes. *Metabolism: Clinical & Experimental* 2000;49:1511-1517.

Sakurai T, Matsui T, Yao T, et al: Short-term efficacy of enteral nutrition in the treatment of active Crohn's disease: a randomized, controlled trial comparing nutrient formulas. *Journal of Parenteral & Enteral Nutrition* 2002;26:98-103.

Summers LK, Fielding BA, Bradshaw HA, et al: Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. *Diabetologia* 2002;45:369-377.

Rejected No Outcomes or Criteria of Interest

Astorga G: Active rheumatoid arthritis: effect of dietary supplementation with omega-3 oils. A controlled double-blind trial. *Revista Medica de Chile* 1991;119:267-272.

Belluzzi A, Brignola C, Campieri M, et al: Effects of a new fish oil derivative on fatty acid phospholipid-membrane pattern in a group of Crohn's disease patients. *Dig Dis Sci* 1994;39:2589-2594.

Dahlan W, Richelle M, Kulapongse S, Rossle C, Deckelbaum RJ, Carpentier YA: Effects of essential fatty acid contents of lipid emulsions on erythrocyte polyunsaturated fatty acid composition in patients on long-term parenteral nutrition. *Clinical Nutrition* 1992;11:262-268.

Espersen G, Grunnet N, Lervang H, et al: Decreased interleukin-1 beta levels in plasma from rheumatoid arthritis patients after dietary supplementation with n-3 polyunsaturated fatty acids. *Clinical Rheumatology* 1992;11:393-395.

Hillier K: Human colon mucosa: effect of marine oils on lipid fatty acid composition and eicosanoid synthesis in inflammatory bowel disease. *British Journal of Clinical Pharmacology* 1988;25:129P-30P.

Hillier K, Jewell R, Dorrell L, Smith C: Incorporation of fatty acids from fish oil and olive oil into colonic mucosal lipids and effects upon eicosanoid synthesis in inflammatory bowel disease. *Gut* 1991;32:1151-1155.

Ikehata A, Hiwatashi N, Kinouchi Y, et al: Effect of intravenously infused eicosapentaenoic acid on the leukotriene generation in patients with active Crohn's disease. *American Journal of Clinical Nutrition* 1992;56:938-942.

Jantti JV, Vapaatalo H, Seppala E, Ruutsalo HM, Isomaki H: Treatment of rheumatoid arthritis with fish oil, selenium, vitamins A and E, and placebo. *Scandinavian Journal of Rheumatology* 1991;20:225

Rubin M, Moser A, Vaserberg N, et al: Structured triacylglycerol emulsion, containing both medium- and long-chain fatty acids, in long-term home parenteral nutrition: a double-blind randomized cross-over study. *Nutrition* 2000;23:2, 95-10023.

Woodman RJ, Mori TA, Burke V, et al: Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. *Atherosclerosis* 2003;166:85-93.

Duplicate Reports of Same Trial

Almallah Y, Ewen S, El Tahir A, et al: Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. *Journal of Clinical Immunology* 2000;20:68-76.

Chan D, Watts G, Barrett P, Beilin L, Redgrave T, Mori T: Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. *Diabetes* 2002;51:2377-2386.

Dunstan D, Mori T, Puddey I, et al: The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care* 1997;20:913-921.

McVeigh G, Brennan G, Cohn J, Finkelstein S, Hayes R, Johnston G: Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. *Arteriosclerosis & Thrombosis* 1994;14:1425-1429.

McVeigh G, Brennan G, Johnston G, et al: Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1993;36:33-38.

Mori T, Dunstan D, Burke V, et al: Effect of dietary fish and exercise training on urinary F2-isoprostane excretion in non-insulin-dependent diabetic patients. *Metabolism: Clinical & Experimental* 1999;48:1402-1408.

Nielsen G, Faarvang K, Tomsen B, Teglbjaerg K, Ernst E: Effects of supplementation with n-3 fatty acids on clinical disease variables in patients with rheumatoid arthritis . *European Journal of Clinical Investigation* 21:

Appendix A. Methodologic Approach

A.1 Preliminary Research Questions

Table A.1.1. Preliminary research questions.

GENERAL QUESTIONS: Questions posed for all three participating EPCs, for years 1 and 2.

1. What is the evidence that variable clinical effects may reflect differences in:

   - Serving size (fish vs. dietary supplement);
   - Source (fish, food, plant) vs. dietary supplement (fish oil, plant oil);
   - Specific type(s) of omega-3 fatty acids (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA), fish, fish oil), or the ratio of omega-6/omega-3 fatty acids used;
   - Manufacturer (different purity, presence of other potentially active agents)?

2. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acids (DHA, EPA, DPA, ALA, fish oil, fish)?

3. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations such as diabetics?

4. What are the mean and median intakes of DHA, EPA, DPA, ALA, fish, fish oil, omega-6, omega-6/omega-3 ratio in the US population?

5. What is the evidence that omega-3 fatty acids influence overall energy balance?

6. What is the evidence that accurate interpretation of the results of clinical studies is dependent on knowing the absolute fatty acid content of the baseline data, the relative fatty acid content of the baseline diet, or the tissue ratios of fatty acids (omega-6/omega-3) during the investigative period?

DISEASE-SPECIFIC QUESTIONS: questions posed to the SCEPC for Year 1 of the project:

Immune-Mediated Diseases

1. What is the evidence that in adults or children with type I diabetes, omega-3 fatty acids increase insulin sensitivity?

2. What is the evidence that in adults or children with rheumatoid arthritis, omega-3 fatty acids decrease pain or the number of swollen joints?

3. What is the evidence that omega-3 fatty acids help maintain bone mineral status?

4. What is the evidence that in adults or children with inflammatory bowel disease (ulcerative colitis and Chrohn's disease), omega-3 fatty acids lower leukotriene B4 or prostaglandin E2 levels?

5. What is the evidence that in adults or children with systemic lupus erythematosis, omega-3 fatty acids prolong longevity?

Gastrointestinal/Renal

1. What is the evidence for the efficacy of omega-3 fatty acids in treatment of Crohn's disease, ulcerative colitis, renal inflammation, and glomerulosclerosis?

2. What is the evidence for the efficacy of omega-3 fatty acids in treatment of the hypertriglyceridemia of type II diabetes, insulin resistance, or the metabolic syndrome?

3. What is the evidence that omega-3 fatty acids influence the regulation of gene expression in the progression/prevention of obesity, and intestinal and liver diseases?

A.2 Technical Expert Panel

The members of our technical expert panels are listed in Table A.2.1. We conducted our TEP meetings via teleconference. We held a conference call with the rheumatoid arthritis, systemic lupus erythematosis, and bone density TEP on February 7, 2003; the renal/diabetes TEP on February 12, 2003; and the gastrointestinal TEP on February 12, 2003. Dr. Rosaly Correa-de-Araujo, the Task Order Officer, and Jacqueline Besteman, Director of the Evidence-Based Practice Center Program, represented AHRQ on these calls; Dr. Anne Thurn, Director of the Evidence-Based Review Program, represented ODS; and Dr. Paul Shekelle, Director of the SCEPC, Dr. Catherine MacLean, the Task Order Director, and Rena Hasenfeld, the Project Manager, represented the SCEPC. The key comments and recommendations of each TEP are summarized in Table A.2.2. The TEP continued to advise the SCEPC throughout the project via mail, fax, e-mail, and phone calls.

Table A.2.1 Technical expert panel members.

Rheumatoid Arthritis, Systemic Lupus Erythematosis, and Bone Density TEP		
Name	**Area of Expertise**	**Institution**
Judith Ashley, PhD, MSPH, RD	Omega-3 Fatty Acids	University of Nevada School of Medicine
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Robert P. Heaney, MD	Bone	Creighton University
David A. Isenberg, MD	SLE	University College London Medical School
Joel Kremer, MD	Rheumatoid Arthritis	The Center for Rheumatology
Bruce A. Watkins, PhD	Omega-3 Fatty Acids	Purdue University
Josiah F. Wedgwood, MD, PhD	Rheumatoid Arthritis	National Institute of Allergy and Infectious Diseases
Renal Disease and Diabetes TEP		
Name	**Area of Expertise**	**Institution**
Judith Ashley, PhD, MSPH, RD	Omega-3 Fatty Acids	University of Nevada School of Medicine
Mayer B. Davidson, MD	Diabetes	Charles R. Drew University of Medicine and Science
James V. Donadio, MD	Renal Diseases	Mayo Medical School
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Michael D. Jensen, MD	Diabetes	Mayo Medical School
William F. Keane, MD	Renal Diseases	Merck and Co., Inc.
Catherine Meyers, MD	Renal Diseases	NIDDK, Division of Kidney, Urologic & Hematologic Diseases
Gastrointestinal Diseases TEP		
Name	**Area of Expertise**	**Institution**
Judith Ashley, PhD, MSPH, RD	Omega-3 Fatty Acids	University of Nevada School of Medicine
Andrea Belluzzi, MD	Irritable Bowel Disease	S Orsola Hospital, Bologna, Italy
Frank Hamilton, MD	Irritable Bowel Disease	NIDDK, Division of Digestive Diseases & Nutrition
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Stephen James, MD	Inflammatory Bowel Disease	NIDDK, Division of Digestive Diseases & Nutrition
Michael Ken May, PhD	Inflammatory Bowel Disease	NIDDK, Division of Digestive Diseases & Nutrition
William F. Stenson, MD	Inflammatory Bowel Disease	Washington University

Table A.2.2. Key TEP comments and recommendations.

Rheumatoid Arthritis, Systemic Lupus Erythematosis, and Bone Density TEP
1. What is the evidence that in adults or children with rheumatoid arthritis, omega-3 fatty acids decrease pain or the number of swollen joints?
• Restrict the search to randomized control trials.
• Include children with juvenile rheumatoid arthritis for now.
• If possible, the outcome measures should include: disease activity, damage, and patient perception (i.e. patient global assessment).

2. What is the evidence that omega-3 fatty acids help maintain bone mineral status?
• Include both randomized controlled trials and observational studies.
• The populations of interest are older women and women with osteoporosis.
• Outcomes for randomized controlled trials will likely be measures of bone density and biologic markers.
• Outcomes for observational studies are more likely to include fracture rates.
• There is a need to adjust for ethnicity in the analyses because bone shape may affect the • rate of fractures.
• In studies that report t-scores, there is a need to note the standard used to compute the t-score; WHO and NHANES are two different standards that may be used.
3. What is the evidence that in adults or children with systemic lupus erythematosus, omega-3 fatty acids prolong longevity?
• Restrict the study to randomized controlled trials.
• Longevity is not the correct outcome to assess.
• Recommended outcomes for assessment include disease activity, damage, and patient perception (i.e. patient global assessment).
General Comments
• Note reported side effects of omega-3 fatty acids when reviewing the literature.
Renal Disease and Diabetes TEP
1. What is the evidence for the efficacy of omega-3 fatty acids in treatment of hypertriglyceridemia of type II diabetes, insulin resistance, or the metabolic syndrome?
• The question should be re-worded in the following way: What is the evidence in adults or children for the efficacy of omega-3 fatty acids in treatment of hyperlipedemia in a) type II diabetes, or b) insulin resistance/the metabolic syndrome?
• Do not to limit the review to hypertriglyceridemia; collect data on other lipids, as well.
• The question pertains specifically to the effect of omega-3 fatty acids on lipids in two different clinical syndromes: type II DM and the insulin resistance/metabolic syndrome.
• The question pertains to both adults and children.
2. What is the evidence that in adults or children with type I diabetes, omega-3 fatty acids increase insulin sensitivity?
• Since insulin resistance is not a feature of type I diabetes, the questions should be re-worded in the following way: What is the evidence in adults and children for an effect of omega-3 fatty acids on insulin sensitivity in a) type II diabetes, or b) the metabolic syndrome?
3. What is the evidence for the efficacy of omega-3 fatty acids in treatment of renal inflammation and glomerulosclerosis?
• There was no consensus on how “renal inflammation” and “glomerulosclerosis” should be defined.
• There was no consensus about whether to assess the effect of omega-3 fatty acids on the progression of renal disease.
• Randomized controlled trials should be examined to determine whether sufficient evidence exists to assess the effect of omega-3 fatty acids on renal inflammation and/or the progression of renal acute or chronic renal insufficiency.
• The question may be re-worded after the literature review has been completed.

Table A.2.2. Key TEP comments and recommendations (continued).

Gastrointestinal Diseases TEP
1. What is the evidence for the efficacy of omega-3 fatty acids in treatment of Crohn's disease and ulcerative colitis?
• There are so few studies on the efficacy of omega-3 fatty acids in treating inflammatory bowel disease that it may be necessary to do a qualitative rather than a quantitative review of the literature.
• Efficacy is not uniformly defined in IBD. However, a recent NIH conference addressed defining efficacy in Crohn's disease.
• There are many potential confounders/effect modifiers for IBD, especially for Crohn's disease, including disease characteristics (severity, presence or absence of fistulas in Crohn's), medication use, and population characteristics.
2. What is the evidence that in adults or children with inflammatory bowel disease (ulcerative colitis and Crohn's disease), omega-3 fatty acids lower leukotriene B4 or prostaglandin E2 levels?
• A review of the effect of omega-3 fatty acids on leukotriene B4 or prostaglandin E2 should not be included in the report since neither is a measure of prevention or efficacy in IBD.
• There are no studies of the effects of omega-3 fatty acids on IBD in children.
General Comments
• Take note of the omega-3 preparation. • Abstract and report side effects.

A.3 Search Strategies

Table A.3.1. Core 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. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((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$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.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. 20 or 27 or 28 or 31

Table A.3.2. Literature searches by disease category.

Diabetes
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. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((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$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.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$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31
33. hyperinsulin?emia.tw.
34. hyperinsulinemia/
35. exp diabetes mellitus/
36. diabetes.tw.
37. insulin.tw.
38. metabolic syndrome$.tw.
39. exp insulin resistance/
40. or/33-39
41. 32 and 40
42. 41 and human/

Table A.3.2. Literature searches by disease category (continued).

Inflammatory Bowel Disease and Renal Disease
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. menhaden oil$.tw,hw,rw. 12. (mediterranean adj diet$).tw. 13. ((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$).tw. 14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 15. (fish adj2 oil$).tw. 16. (cod liver oil$ or marine oil$ or marine fat$).tw. 17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 18. (fish consumption or fish intake or (fish adj2 diet$)).tw. 19. diet$ fatty acid$.tw. 20. or/1-19 21. dietary fats/ 22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 23. random$.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$).mp. 31. 29 and 30 32. 20 or 27 or 28 or 31 33. exp inflammatory bowel diseases/ 34. inflammatory bowel.tw. 35. (hemorrhagic proctocolitis or ulcerative proctocolitis).tw. 36. (hemorrhagic rectocolitis or ulcerative rectocolitis).tw. 37. (ileocolitis or ileitis or enteritis or crohn$ or pancolitis or proctitis or colitis).tw. 38. exp nephritis/ 39. ((renal or kidney) and inflammation).tw. 40. (glomerulo$ or nephritis or nephropath$).tw. 41. or/33-40 42. 32 and 41 43. 42 and human/

Table A.3.2. Literature searches by disease category (continued).

Rheumatoid Arthritis
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. menhaden oil$.tw,hw,rw. 12. (mediterranean adj diet$).tw. 13. ((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$).tw. 14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 15. (fish adj2 oil$).tw. 16. (cod liver oil$ or marine oil$ or marine fat$).tw. 17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 18. (fish consumption or fish intake or (fish adj2 diet$)).tw. 19. diet$ fatty acid$.tw. 20. or/1-19 21. dietary fats/ 22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 23. random$.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$).mp. 31. 29 and 30 32. 20 or 27 or 28 or 31 33. exp arthritis, rheumatoid/ 34. (rheumat$ adj2 arthritis).tw. 35. stills diseas$.tw. 36. caplans syndrome$.tw. 37. feltys syndrome$.tw. 38. rheumatoid nodule$.tw. 39. sjogrens syndrome$.tw. 40. ankylosing spondylitis.tw. 41. rheumat$.tw. 42. or/33-41 43. 32 and 42 44. limit 43 to human

Table A.3.2. Literature searches by disease category (continued).

Systemic Lupus Erythematosus
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. menhaden oil$.tw,hw,rw. 12. (mediterranean adj diet$).tw. 13. ((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$).tw. 14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 15. (fish adj2 oil$).tw. 16. (cod liver oil$ or marine oil$ or marine fat$).tw. 17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 18. (fish consumption or fish intake or (fish adj2 diet$)).tw. 19. diet$ fatty acid$.tw. 20. or/1-19 21. dietary fats/ 22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 23. random$.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. 20 or 27 or 28 or 31 33. exp Lupus Erythematosus, Systemic/ 34. (lupus glomerulonephritis or lupus nephritis).tw. 35. (libman-sacks or lupus erythematosus disseminatus or systemic lupus erythematosus).tw. 36. (lupus vasculitis or lupus meningoencephalitis or central nervous system systemic lupus).tw. 37. or/33-36 38. 32 and 37 39. limit 38 to human

Table A.3.2. Literature searches by disease category (continued).

Bone Density/Osteoporosis
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. menhaden oil$.tw,hw,rw. 12. (mediterranean adj diet$).tw. 13. ((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$).tw. 14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 15. (fish adj2 oil$).tw. 16. (cod liver oil$ or marine oil$ or marine fat$).tw. 17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 18. (fish consumption or fish intake or (fish adj2 diet$)).tw. 19. diet$ fatty acid$.tw. 20. or/1-19 21. dietary fats/ 22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 23. random$.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$).mp. 31. 29 and 30 32. 20 or 27 or 28 or 31 33. bone density/ 34. (bone mineral or bone densit$ or bone mass).tw. 35. exp Bone Demineralization, Pathologic/ 36. Bone Demineral$.tw. 37. exp Bone Resorption/ 38. (bone loss$ or bone resportion).tw. 39. exp Densitometry/ 40. or/33-39 41. 32 and 40 42. limit 41 to human

Table A.3.3. Industry experts that were contacted for data about efficacy of omega-3 fatty acids.

Name	Affiliation
Ian Newton	Roche Vitamins
Herb Wool, PhD	BASF Corporation
Annette Dickinson	Council for Responsible Nutrition

Figure A.3.1. Letter sent to industry experts.

Date

Name
Address
City, State, Zip Code

Dear XXX,

I am writing on behalf of the Evidence Based Practice Centers at RAND, New England Medical Center and the University of Ottawa. We are conducting a systematic review of the efficacy and toxicity of omega-3 fatty acids in the prevention and treatment of a number of different diseases/conditions. This review is being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ).

We are contacting you to see if there is any evidence, including unpublished evidence, that you want considered. Our focus is on clinical trials of omega-3 fatty acids in humans, so animal and chemical studies are not necessary.

The specific questions that all the EPCs will address are detailed in the attachment to this letter.

Please contact me with any information that you might have.

Best regards,

Catherine MacLean, M.D., Ph.D.
RAND1700 Main Street, M 23-C
Santa Monica, CA 90407-2138
Voice: 310 393-0411, x6364
Fax: 310-451-6930

A.4 Inclusion/Exclusion Criteria

Table A.4.1. Inclusion/Exclusion Criteria at Screening Stage.*

Assessed the effect of omega-3 fatty acids on arthritis (including rheumatoid arthritis and juvenile rheumatoid arthritis), bone mineral metabolism, diabetes, IBD, lupus, or renal disease
Presented research on human subjects
Reported the results of randomized or controlled clinical trials or cohort/case control studies;† we accepted observational studies for bone mineral status only.
For cross-over studies, reported outcomes for each arm before the cross-over at the end of the first phase of treatment‡

*Language was not a barrier to inclusion; † We defined a randomized controlled trial (RCT) as one in which the participants were assigned to one of two (or more) study groups using a process of random allocation (e.g., random number generation, coin flips); we defined a controlled clinical trial (CCT) as one in which participants were either: (1) assigned to one of two (or more) study groups using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier), or (2) possibly assigned to one of two (or more) study groups using a process of random or quasi-random allocation; ‡ We did not use data from the end of the study period in studies with a cross-over design because as a result of this design, the treatment and placebo groups from these studies are not comparable to the treatment and placebo groups of the non-cross-over randomized controlled trials with which they would be pooled in a meta-analysis. For example, one half of the placebo group in a cross-over trial will have been exposed to treatment with omega-3 fatty acids prior to placebo and hence the measured effect could be biased by earlier treatment with Omega-3 fatty acids.

A.5 Evidence Grading System

Table A.5.1. Summary Score for Methodologic Quality.

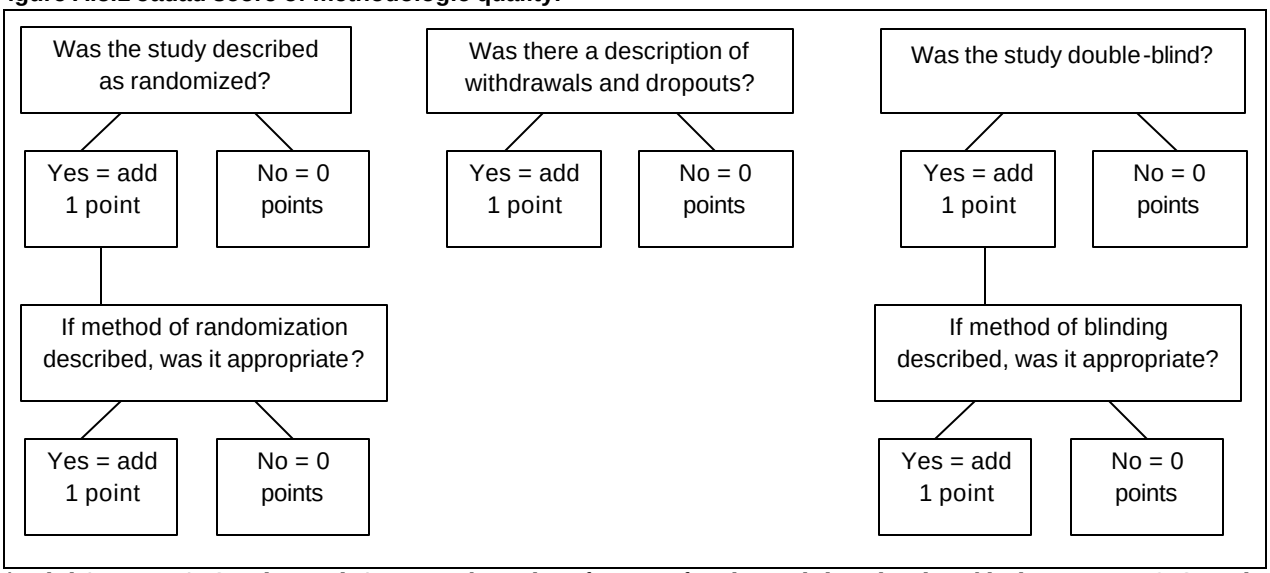
Summary Score	Jadad Score	Concealment of Allocation
A	5	Performed
B	5	Not performed, or Not reported
	3 or 4	Performed, Not performed, or Not reported
	0,1, or 2	Performed
C	0, 1, or 2	Not performed or not reported

Even though a study may focus on a specific target population, limited study size, eligibility criteria and 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 into the applicability scale described in Table A.5.1.

Table A.5.2 Applicability ratings.

Applicability		**Health state**
I	Sample is representative of the U.S. population.	A General population. Typical healthy people similar to Americans without known cardiovascular diseases.
II	Sample is representative of a relevant sub-group of the target population, but not the entire population. For example, a study that is restricted to women or a fish oil study in Japan where the background diet is very different from that of the US would fall into this category.	B Diseased population. Subjects with any of the following: inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus or osteoporosis.
III	Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups. For example, a study of oldest old men or a study of a population on highly controlled diet.	

Figure A.5.1 Jadad score of methodologic quality.*



***** Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17:1-12.

Table A.6.1. Peer Reviewers.

Peer Reviewer	Area of Expertise	Affiliation
Charles Bernstein, MD	Inflammatory Bowel Disease	University of Manitoba
Richard Glassock, MD	nephrology	UCLA
David Heber, MD	nutrition	UCLA
Ted Kraegen, PhD	diabetes, nutrition	Garvan Research Institute, Sydney
Kenneth Saag, MD, MPH	osteoporosis, SLE	University of Alabama
Walter Willett, MD	epidemiology, nutrition	Harvard University
Robert Zurier, MD	rheumatoid arthritis, omega-3 fatty acids	University of Massachusetts Medical School

Appendix B. Coding/Data Abstraction Forms

B.2 Literature Screener Form
B.3 Quality review form

Omega 3 Screening Form
Final Version

1. Article ID: _____
2. First Author: _____
   (Last name of first author)
3. Reviewer: _____

4. Research intervention topic: **(circle one)**
   - Omega 3 or synonymous topic 1
   - Unclear, no English abstract..... 8
     (If unclear, skip to question 8 on language)
   - None of the above ..... 9 **(STOP)**

5. Condition(s)/Subject(s) studied: **(check all that apply)**
   - Arthritis (RA, JRA)..... ❒
   - Bone mineral metabolism ..... ❒
   - Diabetes..... ❒
   - IBD..... ❒
   - Lupus ..... ❒
   - Renal..... ❒

   (If any of the above conditions are checked, ignore stop codes for the following conditions listed below)

   Other conditions:
   - Asthma..... ❒ **(STOP)**
   - Cancer..... ❒ **(STOP)**
   - CVD..... ❒ **(STOP)**
   - Child/maternal health ..... ❒ **(STOP)**
   - Cognitive function..... ❒ **(STOP)**
   - Eye health..... ❒ **(STOP)**
   - Mental health ..... ❒ **(STOP)**
   - Neurological disease..... ❒ **(STOP)**
   - Organ transplant..... ❒ **(STOP)**
   - None of the above ..... ❒ **(STOP)**

6. Study population: **(check all that apply)**
   - Human..... ❒
   - Animal..... ❒ **(STOP)**
   - Unclear..... ❒ **(STOP)**
   - Other (specify:_____)... ❒ **(STOP)**

7. Study design: ..... **(circle one)**
   - Descriptive (historical, editorial, etc.) ..... 1 **(STOP)**
   - Review/ meta-analysis ..... 2 **(STOP)**
   - Randomized clinical trial 3
   - Controlled clinical trial..... 4
   - Cohort /Case control..... 5

   (For cohort/case control, if condition not Bone, then STOP)
   - Case Series/Case Report ..... 6 **(STOP)**
   - Other (specify:_____)..... 8 **(STOP)**

8. Language of article: **(circle one)**
   - English..... 1
   - German..... 2
   - French..... 3
   - Italian..... 4
   - Danish..... 5
   - Other (specify:_____)..... 8

9. Do you think this article might be a duplicate or include the same data as another study?
   - Yes..... 1
   - No..... 2

Notes:

RAND EPC, Omega-3 Project
Quality Review Form

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Is there a difference in Omega-3 content between arms:

		(CIRCLE ONE)
Yes	1	
No	2	(STOP)
Unclear	8	(STOP)

2. Design:

		(CIRCLE ONE)
RCT	1	
CCT	2	
Cohort or Case Control (Bone only)	3	
Other design	4	(STOP)

(STOP IF COHORT/CASE CONTROL AND NOT BONE OR IF OTHER DESIGN)

3. Does the disease meet the appropriate criteria?
Is/are the outcome(s) of interest reported? (CHECK ALL THAT APPLY)
NOTE: for conditions to continue, both criteria and outcomes must be met.

	CRITERIA	OUTCOME(S)
RA	❑	❑
SLE	❑	❑
Bone Mineral Density	❑	❑
Type I Diabetes	❑	❑
Type II Diabetes	❑	❑
Metabolic Syndrome	❑	❑

NOTE: for each condition to continue only one criteria must be met.

Crohn's Disease	❑
Ulcerative colitis	❑
Renal inflammation	❑
Glomerulosclerosis	❑
IgA Nephropathy	❑
Chronic renal disease	❑
Study does not report required components	❑ (STOP)

(SEE THE CODE SHEET FOR APPROPRIATE CRITERIA AND OUTCOMES OF INTEREST.)

4. Is the study described as randomized? (CIRCLE ONE)

Yes	1
No	2

5. If the study was randomized, was method of randomization appropriate? (CIRCLE ONE)

Yes	1
No	2
Method not described	8
Not applicable (not randomized)	9

6. Is the study described as: (CIRCLE ONE)

Double blind	1
Single blind, patient	2
Single blind, outcome assessment	3
Open	4
Blinding not described	8
Not applicable	9

7. If reported, was the method of double blinding appropriate? (CIRCLE ONE)

Yes	1
No	2
Double blinding method not described	8
Not applicable	9

8. If study was randomized, did the method of randomization provide for concealment of allocation? (CIRCLE ONE)

Yes	1
No	2
Concealment not described	8
Not applicable (not randomized)	9

9. Are withdrawals (W) and dropouts (D) described? (CIRCLE ONE)

Yes, reason described for **all** W and D 1
Yes, reason described for **some** W and D 2
Not described 8
Not applicable 9

10. Is this a cross-over study design? (CIRCLE ONE)

Yes 1
No 2
Not described 8

11. Does the study population represent (CHECK ALL THAT APPLY)

	Healthy	Diseased
Typical people	❑	❑
Atypical people (in terms of diet, SES, other factors)	❑	❑
Narrow, atypical people (including highly controlled diet)	❑	❑
Cannot categorize (incomplete data)	❑	❑

12. What was the number of sites involved in the study?
(ENTER NUMBER OF **99** IF NOT REPORTED)

___ ___

13. In what country was the study conducted? (CHECK ALL THAT APPLY)

US ❑
UK ❑
Japan ❑
China ❑
Italy ❑
Netherlands ❑
Canada ❑
Other (enter code) ..... ❑

____ ____, ____ ____, ____ ____, ____ ____

Not specified ..... ❑

14. Are data reported separately for or primarily on over 75% of any of the following populations? (CHECK ALL THAT APPLY)

Children (0-12) ..... ❑
Adolescents (13-17) ..... ❑
Older Adults (=65) ..... ❑

Other (Enter code: ____ ____, ____ ____, ____ ____) . ❑
None of the above ..... ❑

15. What was the racial/ethnic breakdown in percent of the population studied?

Caucasian ..... ____ ____ ____%
African Ancestry ..... ____ ____ ____%
Hispanic ..... ____ ____ ____%
Asian ..... ____ ____ ____%
Native American ..... ____ ____ ____%
Eskimo/Inuit ..... ____ ____ ____%
Other (enter code):
____ ____ ..... ____ ____ ____%
____ ____ ..... ____ ____ ____%
____ ____ ..... ____ ____ ____%
____ ____ ..... ____ ____ ____%
Should TOTAL ... _1__ _0__ _0__
Not described ..... ❑

16. What was the percent of male participants?
(ENTER NUMBER OF 999)

___ ___ ___ %

17. What was reported for the following questions regarding subjects ages? (Enter number 99 for not reported)

Mean Age.....____ ____

Median Age .....____ ____

Age Range.....____ ____ to ___ ____

18. What types of covariates are described? (CHECK ALL THAT APPLY)

Renal insufficiency..... ❑
Proteinuria/ nephrotic ..... ❑
Steroid use (daily) ..... ❑
Other..... ❑
(Enter code: ____ ____, ____ ____, ____ ___, ____ ____)

None described ..... ❑

19. What were the study's inclusion criteria? (Enter code 99 for not reported)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

20. What were the study's exclusion criteria? (Enter code 99 for not reported)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

21. Was there a measure of disease severity reported? (CIRCLE ONE)

Yes..... 1
No..... 2
If "yes", what was that measurement(s)?

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

Interventions

22. Enter sample size and intervention data for each arm beginning with placebo or control, then in order of first mention:

Arm	Sample size	Arm Type Intervention	Components	Total Dose	Units	Is omega 3 quantified?	Duration of treatment	Units	Co-intervention(s)
1	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
2	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
3	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
4	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
5	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported.	Enter Code	Enter code(s)	Enter # or 999 for not reported	Enter a number 1. g 2. mg 3. oz 4. kcal 5. other	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 998. ND 999. NA	Enter a number ***1.Hour*** ***2.Day*** ***3.Week*** ***4.Month*** ***5.Year*** ***8.ND*** ***9.NA***	Enter code(s)

Interventions (continued)

22. Enter sample size and intervention data for each arm :

Arm	Sample size	Arm Type Intervention	Components	Total Dose	Units	Is omega 3 quantified?	Duration of treatment	Units	Co-intervention(s)
6	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
7	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
8	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
9	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
10	_____ N ENTERING _____ N COMPLETING	_____ ARM TYPE _____ INTERVENTION	_____ _____ _____ _____ _____ _____	_____	_____	ALA.....❑ DHA.....❑ EPA.....❑ DPA.....❑ Not Reported..❑	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported.	Enter Code	Enter code(s)	Enter # or 999 for not reported	Enter a number 1. g 2. mg 3. oz 4. kcal 5. other	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 998. ND 999. NA	Enter a number ***1.Hour*** ***2.Day*** ***3.Week*** ***4.Month*** ***5.Year*** ***8.ND*** ***9.NA***	Enter code(s)

Outcomes

23. Type of outcomes measured:

Enter the code for each outcome measured:
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

Evaluation

24. When, relative to the start of the intervention, were outcomes reported?

Enter the number and letters in the appropriate box

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups		

1. Hour
2. Day
3. Week
4. Month
5. Year
8. ND
9. NA

Adverse Events

25. Were any adverse events mentioned?

Enter the code for each adverse event or 99 if not reported:
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

Appendix C. Evidence Tables

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome.

First Author, Year	Study Characteristics	Study design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Alekseeva, 2000[65]	Sample size: 60 Age (mean/range): 58 / 39-65 Race: NR % male: NR # sites: 1 Location: Russia	Design: RCT Duration: 4 wk	Inclusion: Controlled diabetes/Hyperlipidemia/Age Exclusion:NR	Covariates: Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hyperlipidemia/Hypertension	1	Low calorie diet
					2	Linseed oil 18 g/d X 4 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Alekseeva, 2000[65]	Total cholesterol (mg/dl at week 4) Arm 1 mean=251.35 Arm 2 mean=253.67 Mean difference=2.32 (-24.97, 29.60) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Triglyceride (mg/dl at week 4) Arm 1 mean=260.18 Arm 2 mean=313.27 Mean difference=53.10 (-33.55, 139.74) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HDL: NR LDL: NR Fasting blood glucose (mg/dl at week 4) Arm 1 mean=176.58 Arm 2 mean=185.59 Mean difference=9.01 (-24.30, 42.32) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HbA1c: NR	Quality: Jadad: 2 Concealment of allocation:NR Applicability: NR Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Annuzzi, 1991[57]	Sample size: 8 Age (mean/range): 51/45-57 Race: NR % male: 100 # sites: 1 Location: Italy	Design: RXT Duration: 4 wk X-over: week 8 Run-in: None Wash-out: None	Inclusion: Hyperlipidemia/ WHO diabetes criteria Exclusion: Lipid lowering drug use	Covariates: Hypoglycemic treatment/Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160 [Cathy: would just make this into a list as follows, but would have the bullets start further over to the left] Covariates: • Hypoglycemic treatment • Duration of diabetes/Hb A1c • Obesity: BMI=27, kg=72.7, lbs=160	1	Olive oil 10 g/d x 2 wk
					2	Max EPA (fish oil) 10 g/d x 2 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Annuzzi, 1991[57]	Total cholesterol (mg/dl at month 0.5) Arm 1 mean=177.61 Arm 2 mean=183.78 Mean difference=6.18 (-21.65, 34.00) Reported testing: Article reports no significant difference between Arm 1 and Arm 2 by using Wilcoxon's signed rank test. Triglyceride (mg/dl at month 0.5) Arm 1 mean=204.43 Arm 2 mean=171.68 Mean difference=-32.74 (-84.26, 18.77) Reported testing: Article reports significant difference (p<0.05) between Arm 1 and Arm 2 by using Wilcoxon's signed rank test. HDL (mg/dl at month 0.5) Arm 1 mean=22.78 Arm 2 mean=22.78 Mean difference=0.00 (-3.21, 3.21) Reported testing: Article reports no significant difference between Arm 1 and Arm 2 by using Wilcoxon's signed rank test. LDL (mg/dl at month 0.5) Arm 1 mean=109.65 Arm 2 mean=132.82 Mean difference=23.17 (-9.22, 55.56) Reported testing: Article reports significant difference (p<0.025) between Arm 1 and Arm 2 by using Wilcoxon's signed rank test. Fasting blood glucose (mg/dl at month 0.5) Arm 1 mean=153.15 Arm 2 mean=145.22 Mean difference=-7.93 (-66.18, 50.32) Reported testing: Article reports no significant difference between Arm 1 and Arm 2 by using Wilcoxon's signed rank test. HbA1c: NR	Quality: Jadad: 2 Concealment of allocation: ND Applicability: IIB Funding source: hospital and industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Axelrod, 1994[75]	Sample size: 20 Age (mean/range): 57 / NR Race: Caucasian, Black % male: NR # sites: 1 Location: US	Design: RCT Duration: 12 wk	Inclusion: Age/Controlled diabetes/No weight change in previous 2 or 3 mo./Hb A1c < 9.5% or 10.5%/Hb=13 for men, HB=12 for women/Retinopathy Exclusion: Steroids use/NSAIDs use/Reliable adherence/Bleeding disorder/ASA use/Not moderate or high fish intake/Proliferative retinopathy/Intraocular hemorrhage	Covariates: Hypoglycemic treatment/Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160	1	Safflower oil 5 g/d X 6 wk
					2	Super EPA (fish oil) 5 g/d X 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Axelrod, 1994[75]	Total cholesterol (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: No significant effect (p=0.129) for fish oil (arm 2) using analysis of covariance. LDL (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: No significant effect for fish oil (arm 2) using analysis of covariance. HDL (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: No significant effect for fish oil (arm 2) using analysis of covariance. Triglycerides (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: Significant (p=0.027) reduction in triglycerides for fish oil using analysis of covariance. HgA1c (% at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: Significant (p=0.009) increase in HgA1c for fish oil using analysis of covariance. Fasting blood glucose (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates at follow-up not reported. Reported testing: No significant effect for fish oil (arm 2) using analysis of covariance.	Quality: Jadad: 4 Concealment of allocation:Yes Applicability: IB Funding source: private, non-industry, hospital

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Boberg, 1992[76]	Sample size: 14 Age (mean/range): 65 / 55-75 Race: NR % male: 86 # sites: 1 Location: Sweden	Design: RXT Duration: 16 wk X-over: week 8 Run-in: None Wash-out: None	Inclusion: Diet treatment=1 yr Exclusion: Lipid lowering drug use	Covariates: Hypoglycemic treatment/Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160	1	Olive oil 10 g/d X 8wk
					2	Max EPA (fish oil) 10 g/d X 8wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Boberg, 1992[76]	Total cholesterol (mg/dl at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between groups using analysis of covariance. LDL (mg/dl at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p<0.001) increase in LDL for for fish oil (arm 2) relative to olive oil (arm 1) using analysis of covariance. HDL (mg/dl at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: : No significant difference between groups using analysis of covariance. Triglycerides (mg/dl at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p< 0.001) reduction in triglycerides for fish oil (arm 2) relative to olive oil (arm 1) using analysis of covariance. HgA1c (% at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: : No significant difference between groups using analysis of covariance. Fasting blood glucose (mg/dl at week 8): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: : No significant difference between groups using analysis of covariance.	Quality: Jadad: 3 Concealment of allocation:NR Applicability: IIB Funding source: Government, private, non-industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Borkman, 1989[77]	Sample size: 10 Age (mean/range): 57 / 43-64 Race: NR % male: 70 # sites: 1 Location: Australia	Design: RXT Duration: 12 wk X-over: week 9 Run-in: 3 wk Washout: 3 wk	Inclusion: NR Exclusion: NR	Covariates: Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hypertension	1	Safflower oil 10 g/d X 3 wk
					2	Max EPA (fish oil) 10 g/d X 3 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Borkman, 1989[77]	Total cholesterol (mg/dl at week 6): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Testing between arms not reported. LDL (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Testing between arms not reported. HDL (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Testing between arms not reported. Triglycerides (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Testing between arms not reported. HgA1c: NR Fasting blood glucose (mg/dl at week 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Testing between arms not reported.	Quality: Jadad: 1 Concealment of allocation:NR Applicability: IB Funding source: Government, hospital

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Chan, 2002[58]	Sample size: 52 Age (mean/range): 53 / NR Race: NR % male: 100 # sites: 1 Location: Australia	Design: RCT Duration: 6 wk	Inclusion: Hyperlipidemia/No weight change in previous 2 or 3 mo Exclusion: Lipid lowering drug use/Baseline serum creatinine>0.40 mmol/l or >120 mmol/L/Not moderate or high fish intake/Diabetes/Thyroid abnormalities/Liver disease/Alcohol use	Covariates: Hypertension/Obesity: BMI=27, kg=72.7, lbs=160.	1	Placebo/control Dosage/duration not collected
					2	Atorvastatin Dosage/duration not collected
					3	Omacor 4 g for 6 wk
					4	Omacor plus Atorvastatin 4 g for 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Chan, 2002[58]	Total cholesterol (mg/dl at month 1.5) Arm 1 mean=223.94 Arm 3 mean=212.36 Mean difference=-11.58 (-36.35, 13.19) Arm 2 mean=139.00 Arm 4 mean=150.58 Mean difference=11.58 (-9.59, 32.76) Reported testing: Article reports significant Atorvastatin main effect (p=0.001) and nonsignificant Fish main effect based on general linear model. Triglyceride (mg/dl at month 1.5) Arm 1 mean=256.64 Arm 3 mean=132.74 Mean difference=-123.89 (-366.93, 119.14) Arm 2 mean=123.89 Arm 4 mean=106.20 Mean difference=-17.70 (-52.99, 17.59) Reported testing: Article reports significant Atorvastatin main effect (p=0.002) and Fish main effect (p=0.002) based on general linear model. HDL (mg/dl at month 1.5) Arm 1 mean=39.38 Arm 3 mean=38.61 Mean difference=-0.77 (-6.33, 4.78) Arm 2 mean=40.15 Arm 4 mean=48.26 Mean difference=8.11 (0.63, 15.59) Reported testing: Article reports significant Atorvastatin main effect (p=0.007) and Fish main effect (p=0.041) based on general linear model. LDL (mg/dl at month 1.5) Arm 1 mean=147.88 Arm 3 mean=142.09 Mean difference=-5.79 (-20.88, 9.29) Arm 2 mean=71.04 Arm 4 mean=83.01 Mean difference=11.97 (-4.51, 28.45) Reported testing: Article reports significant Atorvastatin main effect (p=0.001) and nonsignificant Fish main effect based on general linear model. Fasting blood glucose: NR HbA1c: NR	Quality: Jadad: 3 Concealment of allocation:NR Applicability: IIB Funding source: Government, industry,

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Connor, 1993[78]	Sample size: 16 Age (mean/range): 59 / 46-72 Race: NR % male: 81 # sites: 1 Location: US	Design: RXT Duration: 15 mo X-over: month 9 Run-in: 3 mo Washout: None	Inclusion: Hyperlipidemia Exclusion: NR	Covariates: Hypoglycemic treatment/Obesity: BMI=27, kg=72.7, lbs=160.	1	Olive oil 15 g/d X 6 mo
					2	Promega (fish oil) 15 g/d X 6 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Connor, 1993[78]	Total cholesterol (mg/dl at month 9): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using Wilcoxian signed rank test. LDL (mg/dl at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=0.0003) difference favoring olive oil (arm 1) using Wilcoxian signed rank test. HDL (mg/dl at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using Wilcoxian signed rank test. Triglycerides (mg/dl at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=0.0004) difference favoring fish oil (arm 2) using Wilcoxian signed rank test. HgA1c (% at month 9) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using Wilcoxian signed rank test. Fasting blood glucose (mg/dl at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using Wilcoxian signed rank test.	Quality: Jadad: 2 Concealment of allocation:NR Applicability: IIIB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Dunstan, 1998[59]	Sample size: 48 Age (mean/range): 53 / NR Race: NR % male: 76 # sites: 1 Location: Australia	Design: RCT Duration: 8 wk	Inclusion: Age/Nonsmoker/Hyperlipidemia/Sedentary Exclusion: Lipid lowering drug use/Not moderate or high fish intake/Proliferative retinopathy/Alcohol use/Liver disease/ReNRl disease/Neuropathy/Cardiovascular disease	Covariates: Hypoglycemic treatment/Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hb A1c	1	Low-fat and low-sodium diet X 8 wk
					2	Low-fat and low-sodium diet X 8 wk
					3	Fish Approximately 3.6 g/d of omega-3 fatty acids/d X 8 wk
					4	Fish Approximately 3.6 g/d of omega-3 fatty acids/d X 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source

Dunstan, 1998[59]	Total cholesterol (mg/dl at month 2) Arm 1 mean=204.63 Arm 3 mean=185.33 Mean difference=-19.31 (-46.67, 8.06) Arm 2 mean=173.75 Arm 4 mean=181.47 Mean difference=7.72 (-19.28, 34.73) Reported testing: Article reports no significant differences based on a generalized linear model or a multiple regression model. Triglyceride (mg/dl at month 2) Arm 1 mean=247.79 Arm 3 mean=132.74 Mean difference=-115.04 (-195.84, -34.24) Arm 2 mean=168.14 Arm 4 mean=115.04 Mean difference=-53.1 (-132.84, 26.65) Reported testing: Article reports significant results for a generalized linear model and a multiple regression model. HDL (mg/dl at month 2) Arm 1 mean=29.73 Arm 3 mean=34.36 Mean difference=4.63 (-3.90, 13.16) Arm 2 mean=30.50 Arm 4 mean=30.89 Mean difference=0.39 (-8.03, 8.80) Reported testing: Article reports no significant differences based on a generalized linear model or a multiple regression model. LDL (mg/dl at month 2) Arm 1 mean=127.41 Arm 3 mean=132.43 Mean difference=5.02 (-21.44, 31.48) Arm 3 mean=108.10 Arm 4 mean=127.41 Mean difference=19.31 (-6.81, 45.42) Reported testing: Article reports no significant differences based on a generalized linear model or a multiple regression model. Fasting blood glucose (mg/dl at month 2) Arm 1 mean=167.57 Arm 3 mean=176.58 Mean difference=9.01 (-33.00, 51.02) Arm 2 mean=165.77 Arm 4 mean=169.37 Mean difference=3.60 (-37.85, 45.06) Reported testing: Article reports significant results for a generalized linear model and a multiple regression model. HbA1c: NR	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Fasching, 1996[79]	Sample size: 10 Age (mean/range): 61 / NR Race: NR % male: 40 # sites: 1 Location: Australia	Design: RXT Duration: 20 wk X-over: week 18 Run-in: 8 wk Wash-out: 8 wk	Inclusion: Hyperlipidemia/Controlled diabetes/WHO diabetes criteria Exclusion: Lipid lowering drug use	Covariates: Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160.	1	Gemfibrozil 4 mmol/d x 2 wk
					2	EPAX 5000 (fish oil) 22 mol/d x 2 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Fasching, 1996[79]	Total cholesterol: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=.05) difference between groups, test not specified. LDL: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p<.02) difference between groups, test not specified. HDL: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between groups, test not specified. Triglycerides: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p<.05) difference between groups, test not specified. HgA1c: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between groups, test not specified. Fasting blood glucose: (at week 10): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between groups, test not specified.	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Government, hospital

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Goh, 1997[80]	Sample size: 28 Age (mean/range): 58 / NR Race: NR % male: NR # sites: 1 Location: Canada	Design: RXT Duration: 9 mo X-over: month 6 Run-in: 3 mo Wash-out: None	Inclusion: Controlled diabetes/Hb A1c < 9.5% or 10.5% Exclusion: Lipid lowering drug use	Covariates: Hb A1c .	1	Linseed oil Variable dose x 3 mo
					2	Fish oil Variable dose x 3 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Goh, 1997[80]	Total cholesterol (mg/dl at month 3): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms by ANOVA. LDL (mg/dl at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=0.0003) difference favoring olive oil (arm 1) using Wilcoxian signed rank test. HDL (mg/dl at month 3): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms by ANOVA. Triglycerides (mg/dl at month 3): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=0.05) difference favoring fish oil (arm 2) by ANOVA. HgA1c (% at month 3) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using Wilcoxian signed rank test. HgA1c: NR Fasting blood glucose: NR	Quality: Jadad: 2 Concealment of allocation: NR Applicability: NR Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Hendra, 1990[60]	Sample size: 80 Age (mean/range): 56 / NR Race: Caucasian, Black, Asian % male: 69 # sites: 1 Location: UK	Design: RCT Duration: 1.5 mo	Inclusion: Controlled diabetes/Hyperlipidemia Exclusion: PregNRncy/lactating/Cardiovascular disease	Covariates: Duration of diabetes/Hypertension/Hypoglycemic treatment/Obesity: BMI=27, kg=72.7, lbs=160	1	Placebo/control Dosage/duration not collected
					2	Max EPA (fish oil) 10 g for 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Hendra, 1990[60]	Total cholesterol (mg/dl at month 1.5) Arm 1 mean=239.38 Arm 2 mean=227.80 Mean difference=-11.58 (-30.89, 7.72) Reported testing: Article reports no significant differences (p=0.7) for changes between Arm 1 and Arm 2 with unpaired Student's t tests. Triglyceride (mg/dl at month 1.5) Arm 1 mean=194.69 Arm 2 mean=150.44 Mean difference=-44.25 (-89.80, 1.31) Reported testing: Article reports significant differences (p<0.001) for changes between Arm 1 and Arm 2 with unpaired Student's t tests. HDL (mg/dl at month 1.5) Arm 1 mean=46.33 Arm 2 mean=38.61 Mean difference=-7.72 (-14.68, -0.76) Reported testing: Article reports no significant differences (p=0.6) for changes between Arm 1 and Arm 2 with unpaired Student's t tests. LDL (mg/dl at month 1.5) Arm 1 mean=162.16 Arm 2 mean=158.30 Mean difference=-3.86 (-22.97, 15.25) Reported testing: Article reports no significant differences (p=0.085) for changes between Arm 1 and Arm 2 with unpaired Student's t tests. Fasting blood glucose (mg/dl at month 1.5) Arm 1 mean=203.60 Arm 2 mean=225.23 Mean difference=21.62 (-18.06, 61.30) Reported testing: Article reports no significant differences (p=0.17) for changes between Arm 1 and Arm 2 with unpaired Student's t tests. HbA1c: NR	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: industry, hospital

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Hermans [74]	Sample size: 20 Age (mean/range): 46 / NR Race: NR % male: NR # sites: 1 Location: Belgium	Design: RCT Duration: 2 mo	Inclusion: Diabetic nephropathy Exclusion: NR	Covariates: Hypoglycemic treatment/Hb A1c/Hypertension	1	Placebo/control NR Dosage NR x 2 mo
					2	Fish oil 9 g/d x 2 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Hermans [74]	Total cholesterol: NR LDL: NR HDL: NR Triglyceride: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. HgA1c: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. Fasting blood glucose: NR	Quality: Jadad: 2 Concealment of allocation: NR Applicability: NR Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Jensen, 1989[81]	Sample size: 18 Age (mean/range): 37 / 22-47 Race: NR % male: 78 # sites: 1 Location: Denmark	Design: RXT Duration: 28 wk X-over: week 20 Run-in: 4 wk Wash-out: 8 wk	Inclusion: Proteinuria/Retinopathy Exclusion: NR	Covariates: Duration of diabetes/Hypoglycemic treatment	1	Olive oil 21 ml/d x 8 wk
					2	Cod-liver oil (Eskisol) 21 ml/d x 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Jensen, 1989[81]	Total cholesterol: (at week 10) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Testing between groups was not significant; either Wilcoxon test for paired differences or paired Student's t-test used. LDL: (at week 10) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Significant (p<.05) difference between groups; either Wilcoxon test for paired differences or paired Student's t-test used. HDL: (at week 10) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Testing between groups was not significant; either Wilcoxon test for paired differences or paired Student's t-test used. Triglycerides: (at week 10) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Significant (p<.05) difference between groups favoring cod-liver oil; either Wilcoxon test for paired differences or paired Student's t-test used. Change in HgA1c(at week 10) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Statisticaltesting between groups was not reported	Quality Jadad: 2 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Luo, 1998[82]	Sample size: NR Age (mean/range): 54 / NR Race: NR % male: 10 # sites: 1 Location: Portugal	Design: RXT Duration: 6 mo X-over: month 2 Run-in: None Wash-out: 2 mo	Inclusion: Hb A1c < 9.5% or 10.5%/Fasting blood glucose Exclusion: ReNRI disease/Thyroid abnormalities/Liver disease/Lipid lowering drug use/GI disorders	Covariates: Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160/Hypoglycemic treatment	1	Sunflower oil 6g/d x 2 mo
					2	Fish oil 6 g/d x 2 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Luo, 1998[82]	Total cholesterol: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. LDL: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. HDL: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. Triglycerides: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Significant (p<.05) treatment effect for arm 2 (fish oil) by ANOVA. HgA1c: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. Fasting blood glucose: (at month 2) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA.	Quality: Jadad: 2 Concealment of allocation: Yes Applicability: IIB Funding source: Government, industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Maffettone, 1996[73]	Sample size: 16 Age (mean/range): 56 / NR Race: NR % male: 40 # sites: NR Location: Italy	Design: RCT Duration: 6 mo	Inclusion: Diabetes type II > 2 years/ elevated triglycerides/age 40-75 Exclusion: End organ failure/coagulopathy/anticoagulants	Covariates: NR	1	Placebo/control Dosage/duration not collected
					2	Fish oil 2 g for 6 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Maffettone, 1996[73]	Total cholesterol: NR Triglyceride: NR HDL (mg/dl at month 6) Arm 1 mean=36.68 Arm 2 mean=34.36 MD =-2.32 (-10.69, 6.06) Reported testing: Article reports no significant differences (p>0.05) for changes between Arm 1 and Arm 2. LDL (mg/dl at month 6) Arm 1 mean=127.41 Arm 2 mean=127.02 Mean difference=-0.39 (-47.32, 46.55) Reported testing: Article reports no significant differences (p>0.05) for changes between Arm 1 and Arm 2. Fasting blood glucose: NR HbA1c: NR	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: NR

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
McGrath, 1996[83]	Sample size: 23 Age (mean/range): 53 / 44-61 Race: NR % male: 87 # sites: 1 Location: UK	Design: RXT Duration: 18 wk X-over: week 6 Run-in: None Wash-out: 6 wk	Inclusion: NR Exclusion: Cardiovascular disease/Hypertension/ReNRl disease/Lipid lowering drug use/Antihypertensive meds/Cardiovascular drugs	Covariates: Obesity: BMI=27, kg=72.7, lbs=160/Hypoglycemic treatment/Duration of diabetes/Hb A1c	1	Olive oil 10g/d x 6 wk
					2	Max EPA (fish oil) 10 g/d x 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
McGrath, 1996[83]	Total cholesterol: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. LDL: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. HDL: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. Triglycerides: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. HgA1c: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA. Fasting blood glucose: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No treatment effect by ANOVA.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Meshcheriakova, 2001[66]	Sample size: 120 Age (mean/range): 55 / 39-65 Race: NR % male: NR # sites: 1 Location: Russia	Design: RCT Duration: 4 wk	Inclusion: Controlled diabetes/Hyperlipedemia/Age Exclusion: NR	Covariates: Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hb A1c	1	Low-fat and low-sodium diet
					2	Eiconol 8 g for 4 wk
					3	Linseed oil 18 g for 4 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Meshcheriakova, 2001[66]	Total cholesterol (mg/dl at week 4) Arm 1 mean=244.40 Arm 2 and Arm 3 (combined) mean=249.03 Mean difference=4.63 (-15.75, 25.01) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. LDL: NR HDL: NR Triglyceride (mg/dl at week 4) Arm 1 mean=283.19 Arm 2 and Arm 3 (combined) mean=247.79 Mean difference=-35.40 (-88.83, 18.03) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HgA1c: NR Fasting blood glucose: NR	Quality: Jadad: 1 Concealment of allocation: NR Applicability: NR Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Morgan, 1995[61]	Sample size: 40 Age (mean/range): 54 / NR Race: Caucasian, Black, Hispanic % male: 45 # sites: 1 Location: US	Design: RCT Duration: 3.0 mo	Inclusion: Hyperlipedemia/Controlled diabetes Exclusion: NR	Covariates: Hb A1c/Hypoglycemic treatment/Duration of diabetes	1	Placebo/control Dosage/duration not collected
					2	Placebo/control Dosage/duration not collected
					3	Fish oil 9 g for 12 wk
					4	Fish oil 18 g for 12 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Morgan, 1995[61]	Total cholesterol (mg/dl at month 3) Arm 1 mean=263.71 Arm 2 mean=250.58 Mean difference=-13.13 (-37.43, 11.18) Reported testing: Article reports no significant differences (p>0.05). Triglyceride (mg/dl at month 3) Arm 1 mean=760.17 Arm 2 mean=413.27 Mean difference=-346.90 (-656.00, -37.81) Reported testing: Article reports significant differences (p=0.0001) between Arm 1 and Arm 2. HDL (mg/dl at month 3) Arm 1 mean=35.91 Arm 2 mean=38.61 Mean difference=2.70 (-6.18, 11.58) Reported testing: Article reports no significant differences (p>0.05). LDL (mg/dl at month 3) Arm 1 mean=149.42 Arm 2 mean=157.53 Mean difference=8.11 (-19.46, 35.67) Reported testing: Article reports no significant differences (p>0.05). Fasting blood glucose (mg/dl at month 3) Arm 1 mean=223.42 Arm 2 mean=209.01 Mean difference=-14.41 (-52.95, 24.12) Reported testing: Article reports no significant differences (p>0.05). HbA1c (% at month 3) Arm 1 mean=7.80 Arm 2 mean=7.70 Mean difference=-0.10 (-1.25, 1.05) Reported testing: Article reports no significant differences (p>0.05).	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Hospital, industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Morgan,[67]	Sample size: 25 Age (mean/range): 54 / 41-64 Race: Caucasian, Black, Hispanic % male: 40 # sites: 1 Location: US	Design: RCT Duration: 5.3 mo	Inclusion: Age/Hyperlipidemia Exclusion: Cardiovascular disease/Liver disease/PregNRncy/lactating/ReNRl disease/Thyroid abnormalities/Alcohol use/Cardiovascular drugs/Hormone replacement treatment	Covariates: Hypoglycemic treatment/Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hyperlipidemia	1	Placebo/control Dosage/duration not collected
					2	Placebo/control Dosage/duration not collected
					3	Fish oil 18 g for 12 wk
					4	Fish oil 9 g for 12 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes, Results	Quality . Applicability Funding Source
Morgan,[67]	Total cholesterol (mg/dl at week 12) Arm 1 (Low dosage placebo) mean=282.00 Arm 3 (Low dosage fish oil) mean=245.00 Mean difference=-37.00 (-96.98, 22.98) Arm 2 (High dosage placebo) mean=249.00 Arm 4 (High dosage fish oil) mean=273.00 Mean difference=24.00 (-5.75, 53.75) Reported testing: Article reports no significant differences (p>0.05). Triglyceride (mg/dl at week 12) Arm 1 (Low dosage placebo) mean=311.00 Arm 2 (Low dosage fish oil) mean=195.00 Mean difference=-116.00 (-267.44, 35.44) Arm 1 (High dosage placebo) mean=204.00 Arm 2 (High dosage fish oil) mean=197.00 Mean difference=-7.00 (-110.19, 96.19) HDL (mg/dl at week 12) Arm 1 (Low dosage placebo) mean=23.00 Arm 3 (Low dosage fish oil) mean=32.00 Mean difference=9.00 (-3.49, 21.49) Arm 2 (High dosage placebo) mean=37.00 Arm 4 (High dosage fish oil) mean=46.00 Mean difference=9.00 (-13.03, 31.03) Reported testing: Article reports no significant differences (p>0.05). LDL (mg/dl at week 12) Arm 1 (Low dosage placebo) mean=157.00 Arm 3 (Low dosage fish oil) mean=165.00 Mean difference=8.00 (-52.53, 68.53) Arm 2 (High dosage placebo) mean=134.00 Arm 4 (High dosage fish oil) mean=157.00 Mean difference=23.00 (-31.39, 77.39) Reported testing: Article reports no significant differences (p>0.05). Fasting blood glucose (mg/dl at week 12) Arm 1 (Low dosage placebo) mean=252.00 Arm 2 (Low dosage fish oil) mean=211.00 Mean difference=-41.00 (-114.16, 32.16) Arm 1 (High dosage placebo) mean=226.00 Arm 2 (High dosage fish oil) mean=209.00 Mean difference=-17.00 (-89.43, 55.43) Reported testing: Article reports no significant differences (p>0.05). HbA1c (% at week 12) Arm 1 (Low dosage placebo) mean=8.80 Arm 2 (Low dosage fish oil) mean=7.50 Mean difference=-1.30 (-3.42, 0.82) Arm 1 (High dosage placebo) mean=7.30 Arm 2 (High dosage fish oil) mean=8.00 Mean difference=0.70 (-0.68, 2.08) Reported testing: Article reports no significant differences (p>0.05).	Quality: Jadad: 4 Concealment of allocation: Yes Applicability: IB Funding source: NR

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Patti, 1999[68]	Sample size: 1006 Age (mean/range): 57 / NR Race: NR % male: 44 # sites: 1 Location: Italy	Design: RCT Duration: 6.0 mo	Inclusion: Age/WHO diabetes criteria/Disease > 1 year/Controlled diabetes/No weight change in previous 2 or 3 mo/Hyperlipidemia/Diet treatment=1 yr/Postmenopausal women ± hormone replacement Exclusion: Lipid lowering drug use/Antiplatelet or anticoagulation/Liver disease/ReNRl disease/Bleeding disorder/Proliferative retinopathy/Intraocular hemorrhage	Covariates: Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160/Hypoglycemic treatment/Duration of diabetes	1	Placebo/control Dosage/duration not collected
					2	Fish oil Variable dose for 6 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Patti, 1999[68]	Total cholesterol (mg/dl at month 6) Arm 1 mean=239.77 Arm 2 mean=220.46 Mean difference=-19.31 (-57.98, 19.37) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Triglyceride (mg/dl at month 6) Arm 1 mean=277.88 Arm 2 mean=258.41 Mean difference=-19.47 (-89.24, 50.30) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HDL (mg/dl at month 6) Arm 1 mean=36.68 Arm 2 mean=34.36 Mean difference=-2.32 (-10.78, 6.14) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. LDL: NR Fasting blood glucose (mg/dl at month 6) Arm 1 mean=185.59 Arm 2 mean=196.40 Mean difference=10.81 (-28.67, 50.29) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HbA1c (% at month 6) Arm 1 mean=7.70 Arm 2 mean=8.30 Mean difference=0.60 (-0.79, 1.99) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2.	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Government, industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Pelikanova, 1993[62]	Sample size: 20 Age (mean/range): 52 / 40-60 Race: NR % male: 100 # sites: 1 Location: Czech Republic	Design: RCT Duration: 0.8 mo	Inclusion: Age/Hyperlipidemia/Controlled diabetes Exclusion: NR	Covariates: Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160/Malabsortion	1	Placebo/control Dosage/duration not collected
					2	Fish oil 15 ml for 3 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Pelikanova, 1993[62]	Total cholesterol (mg/dl at week 3) Arm 1 mean=236.68 Arm 2 mean=255.60 Mean difference=18.92 (-12.96, 50.80) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Triglyceride (mg/dl at week 3) Arm 1 mean=168.14 Arm 2 mean=131.86 Mean difference=-36.28 (-101.90, 29.33) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HDL: NR LDL: NR. Fasting blood glucose: NR HbA1c (% at week 3) Arm 1 mean=7.50 Arm 2 mean=8.40 Mean difference=0.90 (0.02, 1.78) Reported testing: Article reports no significant differences between Arm 1 and Arm 2.	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Petersen, 2002[63]	Sample size: 42 Age (mean/range): 63 / 33-85 Race: NR % male: 62 # sites: 1 Location: Denmark	Design: RCT Duration: 2.0 mo	Inclusion: Disease > 1 year/Hyperlipidemia/Diabetes onset at 30 years up/Not postmenopausal or hormone replacement Exclusion: Lipid lowering drug use/No fish or fish supplement/Alcohol use	Covariates: Hypoglycemic treatment/Duration of diabetes/Hb A1c/Hypertension	1	Placebo/control Dosage/duration not collected
					2	Futura 1000 (fish oil) 4 g for 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Petersen, 2002[63]	Total cholesterol (mg/dl at month 2) Arm 1 mean=209.65 Arm 2 mean=226.64 Mean difference=16.99 (-5.97, 39.95) Reported testing: Article reports no significant differences (p=0.162) between Arm 1 and Arm 2. Triglyceride (mg/dl at month 2) Arm 1 mean=240.71 Arm 2 mean=160.18 Mean difference=-80.53 (-175.69, 14.63) Reported testing: Article reports no significant differences (p=0.105) between Arm 1 and Arm 2. HDL (mg/dl at month 2) Arm 1 mean=42.86 Arm 2 mean=49.42 Mean difference=6.56 (0.13, 13.00) Reported testing: Article reports no significant differences (p=0.062) between Arm 1 and Arm 2. LDL (mg/dl at month 0.5) Arm 1 mean=110.81 Arm 2 mean=132.43 Mean difference=21.62 (2.79, 40.45) Reported testing: Article reports significant differences (p=0.031) between Arm 1 and Arm 2. Fasting blood glucose: (at month 0.5) Arm 1: point estimate not reported. Arm 2: point estimate not reported. Meta-analysis: Not included; point estimates not reported. Reported testing: Article reports 'no significant changes.' HgA1c: (at month 0.5) Arm 1: point estimate not reported. Arm 2: point estimate not reported. Meta-analysis: Not included; point estimates not reported. Reported testing: Article reports 'no significant changes.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: government, industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Puhakainen, 1995[86]	Sample size: 9 Age (mean/range): 53 / NR Race: NR % male: 44 # sites: 1 Location: Finland	Design: RXT Duration: 12 wk X-over: week 6 Run-in: None Wash-out: None	Inclusion: NR Exclusion: Cardiovascular disease	Covariates: Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160/Hypoglycemic treatment	1	Corn and olive oils 12 g/d x 6 wk
					2	Max EPA (fish oil) 12 g/d x 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Puhakainen, 1995[86]	Total cholesterol: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No difference between groups by paired Student's t test . LDL: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No difference between groups by paired Student's t test. HDL: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: No difference between groups by paired Student's t test. Triglycerides: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Significant ($p<.05$) difference between groups favoring fish oil by Student's t test. HgA1c: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Reported testing: No difference between groups by paired Student's t test. Fasting blood glucose: (at week 6) Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported before crossover. Reported testing: Reported testing: No difference between groups by paired Student's t test.	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Rivellese, 1996[69]	Sample size: 904 Age (mean/range): 57 / NR Race: NR % male: 44 # sites: 1 Location: Italy	Design: RCT Duration: 6 mo	Inclusion: WHO diabetes criteria/Controlled diabetes/Diet treatment=1 yr/No weight change in previous 2 or 3 mo/Hyperlipidemia/Age/Postmenopausal women ± hormone replacement/Disease > 1 year Exclusion: Intraocular hemorrhage/Liver disease/ReNRl disease/Bleeding disorder/Proliferative retinopathy/Antiplatelet or anticoagulation/Lipid lowering drug use	Covariates: Hypoglycemic treatment/Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160	1	Olive oil Variable dose x 6 mo
					2	Fish oil Variable dose x 6 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Rivellese, 1996[69]	Total cholesterol: (mmol/l at month 6) Arm 1= point estimate not reported Arm 2= 5.7 mmol/l Meta-analysis: Not included; point estimate for Arm 1 not reported. Reported testing: Testing between arms was not reported. LDL (mg/dl at month 6) Arm 1 mean=127.41 Arm 2 mean=127.02 Mean difference=-0.39 (-47.31, 46.54) Reported testing: Article reports no significant differences (p>0.05) for changes between Arm 1 and Arm 2. HDL: (mmol/l at month 6) Arm 1= 0.25 Arm 2= 0.19 Meta-analysis: Not included. Reported testing: No significant difference between groups using paired Student's t test. Triglycerides: Not reported Note: triglyceride contend of specific lipoproteins was reported, but not total serum triglycerides. HgA1c: (%at month 6) Arm 1 = 6.9 Arm 2 = 8.3 Meta-analysis: Not included. Reported testing: No difference between groups by paired Student's t test. Fasting blood glucose: (mmol/l at month 6) Arm 1 = 10.3 Arm 2 = 10.9 Meta-analysis: Not included. Reported testing: No difference between groups by paired Student's t test.	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Government, industry

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Sarkkinen, 1996[70]	Sample size: 31 Age (mean/range): 56 / NR Race: NR % male: 59 # sites: 1 Location: Finland	Design: RCT Duration: 2.0 mo	Inclusion: WHO diabetes criteria/WHO impaired glucose tolerance criteria Exclusion: NR	Covariates: NR	1	Sunflower oil Dosage/duration not collected
					2	Rapeseed (LEAR) oil Dosage/duration NR

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Sarkkinen, 1996[70]	Total cholesterol (mg/dl at month 2) Arm 1 mean=232.82 Arm 2 mean=215.06 Mean difference=-17.76 (-45.21, 9.69) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Triglyceride (mg/dl at month 2) Arm 1 mean=151.33 Arm 2 mean=128.32 Mean difference=-23.01 (-80.05, 34.03) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HDL (mg/dl at month 2) Arm 1 mean=49.03 Arm 2 mean=45.94 Mean difference=-3.09 (-9.84, 3.67) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. LDL (mg/dl at month 2) Arm 1 mean=151.74 Arm 2 mean=141.70 Mean difference=-10.04 (-37.38, 17.30) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Fasting blood glucose: (mg/dl at month 2) Arm 1 = point estimate not reported. Arm 2 = point estimate not reported. Meta-analysis: Not included; point estimates not reported. Reported testing: No significant difference between Arm 1 and Arm 2 using Students t test. HgA1c: NR	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Schectman, 1988[87]	Sample size: 13 Age (mean/range): 52 / 29-66 Race: NR % male: 69 # sites: 1 Location: US	Design: RXT Duration: 15 wk X-over: week 11 Run-in: 3 wk Wash-out: 4 wk	Inclusion: Hyperlipidemia/Diet treatment=1 yr/Controlled diabetes Exclusion: Liver disease/ReNRI disease/Thyroid abnormalities/Diabetes/Lipid lowering drug use/No fish or fish supplement	Covariates: Obesity: BMI=27, kg=72.7, lbs=160/Hyperlipidemia/Hypoglycemic treatment/Hypertension	1	Safflower oil 12g/d x 4 wk
					2	Max EPA (fish oil) 12 g/d x 4 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Schectman, 1988[87]	Total cholesterol: (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: A tendency towards an increase with fish oil by ANOVA (p<0.05). LDL: (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: A tendency towards an increase with fish oil by ANOVA (p<0.05). HDL: (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant treatment effect by ANOVA. Change in Triglycerides: (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: A tendency towards an increase with fish oil by ANOVA (p<0.05). Fasting blood glucose: (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: A tendency towards an increase with fish oil by ANOVA (p<0.05). HgA1c. (at week 7) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant treatment effect by ANOVA.	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Schwab, 1998[88]	Sample size: 31 Age (mean/range): 56 / 47-64 Race: NR % male: 59 # sites: 1 Location: Finland	Design: RCT Duration: 8 wk	Inclusion: WHO diabetes criteria/WHO impaired glucose tolerance criteria Exclusion: NR	Covariates: Obesity: BMI=27, kg=72.7, lbs=160/Hypertension	1	Sunflower oil Dosage NR x 8 wk
					2	Rapeseed (LEAR) oil Dosage NR x 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Schwab, 1998[88]	Total cholesterol: (at week 8) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant difference between groups by paired Student's t test. LDL: (at week 8) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant difference between groups by paired Student's t test. HDL: (at week 8) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant difference between groups by paired Student's t test. Change in Triglycerides: (at week 8) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates before cross over not reported. Reported testing: No significant difference between groups by paired Student's t test. Fasting blood glucose: NR HgA1c. NR	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IB Funding source: Government, non-industry, private

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Shimizu, 1995[56]	Sample size: 45 Age (mean/range): 63 / NR Race: NR % male: 49 # sites: 1 Location: Japan	Design: RCT Duration: 12 mo	Inclusion: Normal BUN/Normal serum creatinine Exclusion: NR	Covariates: Hypertension/Hypoglycemic treatment/Duration of diabetes	1	Placebo/control Dosage/duration not collected
					2	EPA-E 900 mg for 12 hr

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Shimizu, 1995[56]	Total cholesterol (mg/dl at month 12) Arm 1 mean=191.00 Arm 2 mean=203.40 Mean difference=12.40 (-2.30, 27.10) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Triglyceride (mg/dl at month 12) Arm 1 mean=162.00 Arm 2 mean=192.40 Mean difference=30.40 (-23.37, 84.17) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. HDL (mg/dl at month 12) Arm 1 mean=50.00 Arm 2 mean=55.80 Mean difference=5.80 (-2.70, 14.30) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. LDL: NR Fasting blood glucose: NR HbA1c (% at month 12) Arm 1 mean=7.76 Arm 2 mean=7.82 Mean difference=0.06(-8.44, 8.56) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2.	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IB Funding source: unclear

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Sirtori, 1997[89]	Sample size: 935 Age (mean/range): 59 / NR Race: NR % male: 62 # sites: 63 Location: Italy	Design: RCT Duration: 6 mo	Inclusion: Age/Hyperlipidemia/Disease > 1 year/Controlled diabetes Exclusion: ReNRl disease/Lipid lowering drug use/Cardiovascular disease/Reliable adherence/Alcohol use/Cardiovascular drugs/Insulin treatment/Obesity	Covariates: Obesity: BMI=27, kg=72.7, lbs=160 .	1	Olive oil Variable dose x 6 mo
					2	Esapent (fish oil) Variable dose x 6 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Sirtori, 1997[89]	Total cholesterol: (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: No difference between arms by ANOVA. LDL: (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: Significant (p<.048) difference between arms with higher LDL in fish oil arm by ANOVA. HDL: (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: No difference between arms by ANOVA. Change in Triglycerides: (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: Significant (p<.0001) difference between arms with lower triglyceride in fish oil arm by ANOVA. Fasting blood glucose: : (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: No difference between arms by ANOVA. HgA1c. : (at month 6) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: No difference between arms by ANOVA.	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Sirtori, 1998[64]	Sample size: 935 Age (mean/range): 59 / NR Race: NR % male: 62 # sites: 63 Location: Italy	Design: RCT Duration: 12 mo	Inclusion: Hyperlipidemia/Age/Disease > 1 year/Controlled diabetes Exclusion: Lipid lowering drug use/Reliable adherence/ReNRl disease/Alcohol use/Cardiovascular disease/Cardiovascular drugs/Insulin treatment/Obesity	Covariates: Obesity: BMI=27, kg=72.7, lbs=160	1	Olive oil Variable dose x 12 mo
					2	Esapent (fish oil) Variable dose for 12 mo

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Sirtori, 1998[64]	Total cholesterol (change from graph data mg/dl at month 6): Arm 1: +0.5 Arm 2: -1.0 Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: No significant difference between groups using repeated measures ANOVA. LDL(change mg/dl at month 6) : Arm 1: point estimate not reported Arm 2: +8.16 Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: Borderline significant (p=0.046) between fish oil (Arm 1) and olive oil (Arm 2) using repeated measures ANOVA. HDL (% change mg/dl at month 6): Arm 1: + 5% Arm 2: + 5% Meta-analysis: Not included; point estimates not reported. Reported testing: No significant difference between groups using repeated measures ANOVA. Triglycerides(change from graph data mg/dl at month 6): Arm 1: -20 Arm 2: -62 Meta-analysis: Not included; point estimates not reported; graphical data only. Reported testing: Significant (P<0.0001) difference between fish oil (Arm 1) and olive oil (Arm 2) using repeated measures ANOVA. Fasting blood glucose (mg/dl at month 6) Arm 1 mean=142.90 Arm 2 mean=147.20 Mean difference=4.30 (-2.82, 11.42) Reported testing: Article reports no significant differences (p>0.05) between Arm 1 and Arm 2. HbA1c (% at month 6) Arm 1 mean=6.88 Arm 2 mean=7.05 Mean difference=0.17 (-0.12, 0.46) Reported testing: Article reports no significant differences (p>0.05) between Arm 1 and Arm 2.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Comments: Meta-analysis performed on HgA1c and fasting blood glucose. Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Vandongen, 1988[90]	Sample size: 22 Age (mean/range): 32 / 20-41 Race: NR % male: 100 # sites: 1 Location: Australia	Design: CCT Duration: 9 wk	Inclusion: Hyperlipidemia/Age Exclusion: NR	Covariates: Duration of diabetes/Obesity: BMI=27, kg=72.7, lbs=160/Hypoglycemic treatment	1	Usual diet X 3 wk
					2	Max EPA (fish oil) 15 g/d x 3 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Vandongen, 1988[90]	Total cholesterol (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. HDL (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. LDL (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. Triglycerides (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. HgA1c (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported. Fasting blood glucose (at week 9): Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Testing between groups not reported.	Quality: Jadad: 0 Concealment of allocation: NR Applicability: IIB Funding source: government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Vessby, 1990[91]	Sample size: 14 Age (mean/range): NR / 39-72 Race: NR % male: 79 # sites: 1 Location: Sweden	Design: RXT Duration: 16 wk X-over: week 8 Run-in: None Wash-out: None	Inclusion: Diet treatment=1 yr/Controlled diabetes Exclusion: Lipid lowering drug use	Covariates: NR	1	Olive oil 10 g/d x 8 wk
					2	Max EPA (fish oil) 10 g/d x 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Vessby, 1990[91]	Total cholesterol (at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using analysis of variance. LDL(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using analysis of variance. HDL(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using analysis of variance. Triglycerides(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using analysis of variance. HgA1c(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: No significant difference between arms using analysis of variance. Fasting blood glucose(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-analysis: Not performed; point estimates before cross-over not reported. Reported testing: Significant (p=0.007) difference between fish oil (Arm 1) and olive oil (Arm 2) using analysis of variance.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: Government, non-industry, private

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Westerveld, 1993[71]	Sample size: 24 Age (mean/range): 57 / 37-71 Race: NR % male: 63 # sites: 1 Location: Netherlands	Design: RCT Duration: 8 wk	Inclusion: WHO diabetes criteria/Clinically stable/Diet treatment=1 yr Exclusion: Cardiovascular disease/Lipid lowering drug use/No fish or fish supplement/GI disorders/Liver disease/ReNRI disease/Bleeding disorder/Antiplatelet or anticoagulation	Covariates: Duration of diabetes/Hypoglycemic treatment/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160	1	Olive oil 1656 mg/d x 8 wk
					2	EPA-E 1800 mg/d x 8 wk
					3	EPA-E 900 mg/d x 8 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Westerveld, 1993[71]	Total cholesterol (at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Arm 3= point estim ate not reported Meta-analysis: Not performed; point estimates not reported. Reported testing: No significant difference between arms using repeated measures ANOVA. LDL (at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Arm 3= point estimate not reported Meta-analysis: Not performed; point estimates not reported. Reported testing: No significant difference between arms using repeated measures ANOVA. HDL(at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Arm 3= point estimate not reported Meta-analysis: Not performed; point estimates not reported. Reported testing: No significant difference between arms using repeated measures ANOVA. Triglyceride (at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Arm 3= point estimate not reported Meta-analysis: Not performed; point estimates not reported. Reported testing: No significant difference between arms using repeated measures ANOVA. HbA1c (% at month 2) Arm 1 mean=9.30 Arm 2 and Arm 3 (combined) mean=8.00 Mean difference=-1.30 (-3.55, 0.95) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2 and Arm 3. Fasting blood glucose (at week 8): Arm 1= point estimate not reported Arm 2= point estimate not reported Arm 3= point estimate not reported Meta-analysis: Not performed; point estimates not reported. Reported testing: No significant difference between arms using repeated measures ANOVA.	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Woodman, 2002[72]	Sample size: 51 Age (mean/range): 61 / NR Race: NR % male: 77 # sites: 1 Location: Australia	Design: RCT Duration: 1.5 mo	Inclusion: Hyperlipidemia/Age/Hb A1c < 9.5% or 10.5%/Controlled diabetes/Nonsmoker/Clinically stable/Fasting blood glucose/Not on insulin treatment Exclusion: NSAIDs use/Liver disease/ReNRI disease/Cardiovascular disease/Not moderate or high fish intake/Microproteinuria/Neuropathy/Smoking	Covariates: Duration of diabetes/Hb A1c/Obesity: BMI=27, kg=72.7, lbs=160/ 0	1	Placebo/control Dosage/duration not collected
					2	EPA 4 g for 6 wk
					3	DHA 4 g for 6 wk

Table C.1. Evidence table of clinical effect of omega-3 fatty acids in type II diabetes or metabolic syndrome (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Woodman, 2002[72]	Total cholesterol (mg/dl at week 6) Arm 1 mean=177.99 Arm 2 and Arm 3 (combined) mean=173.24 Mean difference=-4.75 (-22.48, 12.97) Reported testing: Article reports no significant EPA effect (p>0.05) and DHA effect (p>0.05) without adjusting baseline value by using the Bonferroni method. Triglyceride (mg/dl at week 6) Arm 1 mean=148.67 Arm 2 and Arm 3 (combined) mean=109.15 Mean difference=-39.52 (-68.98, -10.06) Reported testing: Article reports significant EPA effect (p<0.05) and DHA effect (p<0.05) without adjusting baseline value by using the Bonferroni method. HDL (mg/dl at week 6) Arm 1 mean=41.31 Arm 2 and Arm 3 (combined) mean=43.33 Mean difference=2.02 (-4.44, 8.48) Reported testing: Article reports no significant EPA effect (p>0.05) and DHA effect (p>0.05) without adjusting baseline value by using the Bonferroni method. LDL (mg/dl at week 6) Arm 1 mean=106.95 Arm 2 and Arm 3 (combined) mean=107.45 Mean difference=0.50 (-13.80, 14.79) Reported testing: Article reports no significant EPA effect (p>0.05) and DHA effect (p>0.05) without adjusting baseline value by using the Bonferroni method. Fasting blood glucose (mg/dl at week 6) Arm 1 mean=136.04 Arm 2 and Arm 3 (combined) mean=155.85 Mean difference=19.81 (2.25, 37.37) Reported testing: Article reports significant EPA effect (p=0.002) and DHA effect (p=0.002) after adjustment for baseline value by using the Bonferroni method. HbA1c (% at week 6) Arm 1 mean=7.04 Arm 2 and Arm 3 (combined) mean=7.27 Mean difference=0.23 (-0.28, 0.75) Reported testing: Article reports no significant EPA effect (p>0.05) and DHA effect (p>0.05) after adjustment for baseline value by using the Bonferroni method.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.2. Evidence table of clinical effect of omega-3 fatty acids in inflammatory bowel disease.

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Almallah YZ, 1998[44]	Sample size: 18 Age (mean/range): NA / 29-72 Race: NA % male: 50 # sites: NA Location: UK	Design: RCT Duration: 6 mo	Inclusion: Biopsy-proven ulcerative colitis/Distal disease Exclusion: Steroid treatment/Pregnancy/ Immune disorder	Covariates: Sulphasalazine or mesalazine (SASP)/Rectal steroids	1 2	Sunflower oil 15 ml/d x 6 mo Fish oil 15 ml/d x 6 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Almallah YZ, 1998[44]	Clinical score (change at month 6): Arm 1= -2 Arm 2 = -5 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Sigmoidoscopic score (change at month 6): Arm 1= -5 Arm 2 = -9 Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (p = 0.013) effect for fish oil (Arm 2) relative to sunflower oil (Arm 1) using Mann-Whitney U test. Histological score (change at month 6): Arm 1= -2 Arm 2 = -4 Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (p = 0.016) effect for fish oil (Arm 2) relative to sunflower oil (Arm 1) using Mann-Whitney U test. Induced remission(rate at month 6): Arm 1= point estimate not reported Arm 2 = 100% Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Relapse: NA Immunosupressive requirement (# of patients at month 6, prednisolone enemata/oral corticosteroids): Arm 1 = 4/3 Arm 2 = 2/0 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported.	Quality: Jadad: 2 Concealment of allocation: Yes Applicability: IB Funding source: Hospital

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Aslan A, 1992[46]	Sample size: 11 Age (mean/range): 63 / 31-74 Race: NR % male: 100 # sites: 1 Location: US	Design: RXT Duration: 3 mo X-over: month 3 Run-in: None Wash-out: 2 mo	Inclusion: Mild to moderate IBD with min 10 cm/Biopsy-proven ulcerative colitis Exclusion: NR	Covariates: Sulphasalazine or mesalazine (SASP)/Rectal steroids	1 2	Oleic, palmitic, and linoleic acids 15 cap/d x 3 mo Max EPA (fish oil) 15 cap/d x 3 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Aslan A, 1992[46]	Clinical score (change at month 3): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant ($p < 0.05$) effect for fish oil (Arm 2) relative to oleic, palmitic, and linoleic acids (Arm 1) using paired univariate Student's t test. Sigmoidoscopic score: NA Histological score (change at month 3): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using paired univariate Student's t test. Induced remission: NA Relapse: NA Immunosupressive requirement: NA	Quality: Jadad: 5 Concealment of allocation: NR Applicability: IIIB Funding source: NR

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Belluzzi A, 1996[54]	Sample size: 78 Age (mean/range): NA / 18-67 Race: NA % male: 50 # sites: NA Location: Italy	Design: RCT Duration: 12 mo	Inclusion: Remission of Crohn's disease/Elevated serum markers of inflammation Exclusion: Steroid treatment/Previous cytotoxic or immunosuppressive drug treatment/Pregnancy/lactating/Age between 18 and 75 years old/ Previous bowel resection of more than 1 m/ Previous sulphasalazine or mesalazine treatment	Covariates: Previous surgery	1 2	Miglyol 812 15 g/d x 12 mo Fish oil, enteric coated 15 g/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Belluzzi A, 1996[54]	Clinical score: NA Sigmoidoscopic score: NA Histological score: NA Induced remission: NA Relapse (# of relapse at month 12) Arm 1 =27 Arm 2 =11 risk ratio=0.41 (0.24, 0.70) Reported testing: Article reports significant difference (p<0.001) between Arm 1 and Arm 2. Immunosupressive requirement: NA	Quality: Jadad: 5 Concealment of allocation: NA Applicability: IB Funding source: Industry

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Greenfield SM, 1993[42]	Sample size: 43 Age (mean/range): 54 / NA Race: NA % male: 70 # sites: NA Location: UK	Design: RCT Duration: 9 mo	Inclusion: Ulcerative colitis, Disease > 1 year/Clinically stable/Prednisone or prednisolone treatment < 10 mg/day Exclusion: NA	Covariates: Sulphasalazine or mesalazine treatment (SASP)/Rectal steroids	1 2 3	Olive oil Variable dose x 6 mo Max EPA (fish oil) Variable dose x 6 mo Super evening primrose oil (Borage and evening primrose oils) Variable dose x 6 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Greenfield SM, 1993[42]	Clinical score: NA Sigmoidoscopic score (change at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Arm 3 = point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using Mann-Whitney U test. Histological score(change at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Arm 3 = point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using Mann-Whitney U test Induced remission: NA Relapse(rate at month 9): Arm 1= point estimate not reported Arm 2 = point estimate not reported Arm 3 = point estimate not reported Meta-anlysis: This study was excluded from the meta-analysis of relapse because data was not reported separately by arm/group. The data was reported as number of patients in remission at entry. Reported testing: No significant difference between groups using Mann-Whitney U test Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IB Funding source: NR

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Hawthorne A, 1992[95]	Sample size: 96 Age (mean/range): 47 / 17-77 Race: NA % male: 55 # sites: 2 Location: UK	Design: RCT Duration: 14 mo	Inclusion: Biopsy-proven ulcerative colitis/ two or more relapses in the previous 3 years Exclusion: Prednisolone > 20 mg/Likely to require surgery or deteriorating	Covariates: Sulphasalazine or mesalazine treatment (SASP)	1	Olive oil 20 ml/d x 12 mo
					2	Hi EPA (Fish oil) 20 ml/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Hawthorne A, 1992[95]	Clinical score: NA Sigmoidoscopic score: NA Histological score: NA Induced remission (rate at month 12): Arm 1= 63% Arm 2 = 54% Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant effect (p = 0.44) for fish oil (Arm 2) relative to olive oil (Arm 1) using log rank analysis and Kaplan Meier method. [I think it's just Kaplan Meier] Relapse(rate at month 12): Arm 1= 48% Arm 2 = 42% Meta-anlysis: This study was excluded from the meta-analysis of relapse because the population was the same as another study that was included in the MA.[41] Reported testing: No significant effect (p = 0.54) for fish oil (Arm 2) relative to olive oil (Arm 1) using log rank analysis and Kaplan Meier method. I think it's just Kaplan Meier] Immunosuppressive requirement: (median prednisolone dose, mg at month 1, month 2) Arm 1: 6/5 Arm 2: 1/0 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported.	Quality: Jadad: 3 Concealment of allocation: Yes Applicability: IIIB Funding source: Industry and Private, non-industry

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Hawthorne A[41]	Sample size: 96 Age (mean/range): 47 / 17-77 Race: NA % male: 55 # sites: 2 Location: UK	Design: RCT Duration: 12 mo	Inclusion: Biopsy-proven ulcerative colitis / two or more relapses in the previous 3 years Exclusion: Prednisolone > 20 mg/Likely to require surgery or deteriorating	Covariates: Sulphasalazine or mesalazine treatment (SASP)	1	Olive oil 20 ml/d x 12 mo
					2	Hi EPA (Fish oil) 20 ml/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Hawthorne A[41]	Clinical score: NA Sigmoidoscopic score: NA Histological score: NA Induced remission(rate at month 12): Arm 1: 70% Arm 2: 61% Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Relapse (# of relapse at month 12) Arm 1 =11 Arm 2 =15 risk ratio=1.32 (0.71, 2.46) Reported testing: Article reports no significant difference between Arm 1 and Arm 2 by survival analysis. Immunosuppressive requirement: NA	Quality: Jadad: 3 Concealment of allocation: Yes Applicability: IIIB Funding source: Industry and Private, non-industry

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Loeschke K, 1996[39]	Sample size: 64 Age (mean/range): 40 / NA Race: NA % male: 52 # sites: 2 Location: Germany	Design: RCT Duration: 24 mo	Inclusion: Biopsy-proven ulcerative colitis/ At least 1 relapse in the last 2 years/Gomes clinical score (IBD) below 8 Exclusion: Steroid treatment/Pregnancy/Cytotoxic or immunosuppressive drug treatment/Questionable adherence	Covariates: 5-ASA/Sulphasalazine or mesalazine treatment (SASP)	1 2	Corn oil 6 ml/d x 24 mo Fish oil 5 g/d x 24 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Loeschke K, 1996[39]	Clinical score(change from graph data at month 24): Arm 1: +0.7 Arm 2: + 0.2 Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using two-way analysis of variance. Sigmoidoscopic score: NA Histological score (at month 24): Arm 1= point estimate not reported Arm 2= point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using Mann-Whiney U test. Induced remission: NA Relapse (# of relapse at month 24) Arm 1 =18 Arm 2 =18 risk ratio=1.06 (0.69, 1.64) Reported testing: Article reports no significant difference between Arm 1 and Arm 2 by chi-square test. Immunosuppressive requirement: NA	Quality: Jadad: 5 Concealment of allocation: NA Applicability: IB Funding source: Industry

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Lorenz R, 1989[52]	Sample size: 39 Age (mean/range): 37 / 21-71 Race: NA % male: 41 # sites: 1 Location: Germany	Design: RXT Duration: 7 mo X-over: month 3 Run-in: None Wash-out: 1 mo	Inclusion: Biopsy-proven Crohn's disease or ulcerative colitis Exclusion: Pregnancy/Pending surgery, abscesses or severe bleeding/Questionable adherence/Prednisone>8 mg/day/Inactive disease	Covariates: Sulphasalazine or mesalazine treatment (SASP)/Flagyl	1 2	Olive oil 11 ml/d x 3 mo Max EPA (fish oil) 11 ml/d x 3 mo
Lorenz-Meyer H, 1996[55]	Sample size: 204 Age (mean/range): 31 / 17-65 Race: NA % male: 33 # sites: 23 Location: Germany	Design: RCT Duration: 12 mo	Inclusion: Biopsy-proven Crohn's disease/Active disease/Steroid treatment Exclusion: Questionable adherence/Pregnancy/Cytotoxic or immunosuppressive drug treatment/NSAID treatment/Sulphasalazine or mesalazine treatment/Total parenteral nutrition (TPN)/Short bowel syndrome/Steatorrhea	Covariates: Fistula	1 2 3	Corn oil 6 g/d x 12 mo Low-carbohydate diet Dosage NA x 12 mo Fish oil 6 g/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Lorenz R, 1989[52]	Clinical score(change from graph data at month 3): Arm 1= -12 Crohn's Disease Activity Index -2 Ulcerative Colitis Activity Index Arm 2 = -3 Crohn's Disease Activity Index -2 Ulcerative Colitis Activity Index Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using… Sigmoidoscopic score (change at month 3): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant ($p < 0.05$) effect for fish oil (Arm 2) relative to olive oil (Arm 1) using… Histological score: NA Induced remission: NA Relapse: NA Immunosuppressive requirement: NA	Quality: Jadad: 5 Concealment of allocation: Yes Applicability: IB Funding source: Unclear
Lorenz-Meyer H, 1996[55]	Clinical score: NA Sigmoidoscopic score: NA Histological score: NA Induced remission: NA Relapse (# of relapse at month 12) Arm 1 =36 Arm 3 =40 risk ratio=1.03 (0.77, 1.39) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 3. Immunosuppressive requirement: NA	Quality: Jadad: 3 Concealment of allocation: NA Applicability: IB Funding source: NA

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Mantzaris GJ, 1996[40]	Sample size: 50 Age (mean/range): 36 / 17-65 Race: NA % male: 48 # sites: NA Location: Greece	Design: RCT Duration: 12 mo	Inclusion: Remission of biopsy-proven ulcerative colitis/Mesalazine treatment Exclusion: NA	Covariates: Sulphasalazine or mesalazine treatment (SASP)	1 2	Olive oil 20 ml/d x 12 mo Max EPA (fish oil) 20 ml/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Mantzaris GJ, 1996[40]	Clinical score: NA Sigmoidoscopic score: NA Histological score: NA Induced remission: NA Relapse (# of relapse at month 12) Arm 1 =5 Arm 2 =6 risk ratio=0.98 (0.36, 2.70) Reported testing: Article reports no significant difference (p>0.1) between Arm 1 and Arm 2 by chi-square test. Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IB Comments: This study is included in the meta-analysis of relapse. Funding source: NA

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Middleton SJ, 2002[43]	Sample size: 63 Age (mean/range): 42 / 18-66 Race: NA % male: 50 # sites: 1 Location: UK	Design: RCT Duration: 12 mo	Inclusion: Age between 18 and 70 years old/Biopsy-proven ulcerative colitis in remission Exclusion: Serious liver disease/Malignant disease/Pregnancy/lactating/ Antiplatelet or anticoagulating treatment/Epilepsy/Lithium or phenothiazine/Serious renal disease	Covariates: Smoking/Sulphasalazine or mesalazine treatment (SASP)/5-ASA	1 2	Sunflower oil 6 cap/d x 12 mo GLA+ EPA+DHA 6 cap/d x 12 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Middleton SJ, 2002[43]	Clinical score: NA Sigmoidoscopic score (at month 12): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using proportional Cox hazard regression. Histological score: NA Induced remission: NA Relapse (rate at month 12, extrapolated from graph): Arm 1= 38% Arm 2 = 55% Meta-anlysis: Not included in MA; point estimates not reported. Reported testing: No significant difference between groups using proportional Cox hazard regression. Immunosuppressive requirement: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: NR

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Stenson WF, 1992[53]	Sample size: 24 Age (mean/range): 42 / 25-62 Race: NA % male: 56 # sites: 4 Location: US	Design: RXT Duration: 9 mo X-over: month 4 Run-in: None Wash-out: 1 mo	Inclusion: Ulcerative colitis Active disease Exclusion: NA	Covariates: Rectal steroids/Sulphasalazine or mesalazine treatment (SASP)	1 2	Vegetable oil 18 cap/d x 4 mo Max EPA (fish oil) 18 cap/d x 4 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Stenson WF, 1992[53]	Clinical score (change at month 4): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (P < 0.14) effect for fish oil (Arm 2) relative to vegetable oil (Arm 1) using rank-sign test. Sigmoidoscopic score (change at month 4): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Histological score(change at month 4): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Induced remission: NA Relapse: NA Immunosuppressive requirement (mean prednisolone dose 8 in mg at month 4) Arm 1: 12.9 Arm 2: 6.1 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported.	Quality: Jadad: 2 Concealment of allocation: NA Applicability: NA Funding source: Government and Private, non-industry

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Varghese TJ, 2000[94]	Sample size: 51 Age (mean/range): NA / NA Race: NA % male: 99 # sites: NA Location: UK	Design: RCT Duration: 6 mo	Inclusion: Ulcerative colitis and extensive disease Exclusion: Cytotoxic or immunosuppressive drug treatment	Covariates: NA	1 2	Sunflower oil Dosage NA x 12 mo Omega-3 EFAs 6 mg/d x 6 mo

Table C.2. Evidence table of clinical effect and association of omega-3 fatty acids with inflammatory bowel disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Varghese TJ, 2000[94]	Clinical score (change at month 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (p = 0.001) effect for Omega-3 EFAs (Arm 2) relative to sunflower oil (Arm 1). Sigmoidoscopic score (change at month 6): Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (p = 0.054) effect for Omega-3 EFAs (Arm 2) relative to sunflower oil (Arm 1). Histological score: NA Induced remission: NA Relapse: NA Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: NA Funding source: NA

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Adam O, 2003[26]	Sample size: NA Age (mean/range): 57 / NA Race: NA % male: 7 # sites: NA Location: Germany	Design: RXT Duration: 8 mo X-over: month 5 Run-in: None Wash-out: 2 mo	Inclusion: >= 6 tender joints/>= 3 swollen joints/ AND one or both : morning stiffness >= 30 min/ elevated ESR or CRP Exclusion: Prednisone > 10 mg/d/GI disorders/Alcohol use/Metabolic disease/Known allergies	Covariates: Diet	1	Western diet Corn oil capsules 1g/10 kg body weight/day X 3 mo
					2	Placebo/control Modified lacto- vegetarian diet Corn oil capsules 1g/10 kg body weight/day X 3 mo
					3	Western diet Menhaden oil 1g/10 kg body weight/day X 3 mo
					4	Modified lacto-vegetarian diet Menhaden oil 1g/10 kg body weight/day X 3 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Adam O, 2003[26]	Pain (cm on VAS at month 3) Arms 1, 2, 3, 4 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between placebo (arms 1 and 2) and fish oil (arms 3 and 4) not reported. Swollen joints (number at month 3): Arms 1, 2, 3, 4 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between placebo (arms 1 and 2) and fish oil (arms 3 and 4) not reported. Acute phase reactant: NA Patient global assessment (at month 3): Arms 1, 2, 3, 4 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between placebo (arms 1 and 2) and fish oil (arms 3 and 4) not reported. Radiographic damage: NA NSAID consumption (at month 3): Arms 1, 2, 3, 4 = point estimate not reported Meta-analysis: Not performed, too few studies to pool. Reported testing: Testing between placebo (arms 1 and 2) and fish oil (arms 3 and 4) not reported. Steroid consumption (at month 3): Arms 1, 2, 3, 4 = point estimate not reported Meta-analysis: : Not performed, too few studies to pool. Reported testing: Testing between placebo (arms 1 and 2) and fish oil (arms 3 and 4) not reported. DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: Government

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Alpigiani M, 1996[27]	Sample size: 32 Age (mean/range): 14 / NA Race: NA % male: 44 # sites: 1 Location: Italy	Design: Duration: 6 mo	Inclusion: Juvenile chronic arthritis/Age 4-13 Exclusion: NA	Covariates: NA	1	Diet
					2	Cod-liver oil (Eskisol) 5 g/d x 6 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	
Alpigiani M, 1996[27]	Pain: NA Swollen joints: NA Acute phase reactant: (change at month 6, CRP, mg%): Arm 1: -0.05 Arm 2: -0.28 Meta-analysis: Not included; point estimates not reported. Reported testing: Significant (p=.009) difference between arms by ANOVA. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IIB Funding source: NA

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Belch JF, 1988[28]	Sample size: 49 Age (mean/range): 49 / 28-74 Race: NA % male: 12 # sites: NA Location: UK	Design: RCT Duration: 15 mo	Inclusion: NSAIDs use/No DMARDs Exclusion: NA	Covariates: Evening primrose oil	1	Placebo: Liquid paraffin capsules 12/d x 12 months
					2	Fish oil (240 mg EPA) plus evening primrose oil (540 mg GLA) daily x 12 mo
					3	Evening primrose oil (540 mg GLA) daily x 12 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Belch JF, 1988[28]	Pain (cm on VAS at month 12) Arms 1, 2, 3 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: No difference between groups using Mann-Whitney U test. Swollen joints (number at month 3): Arms 1, 2, 3 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: No difference between groups using Mann-Whitney U test. Acute phase reactant: (CRP and ESR at month 12) Arms 1, 2, 3 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: No difference in CRP or ESR between groups using Mann-Whitney U test. Patient global assessment: NA Radiographic damage: NA NSAID consumption (at month 15): Arm 1: Reduced in 33% of subjects Arm 2: Reduced in 80% of subjects Arm 3: Reduced in 73% of subjects Meta-analysis: Not performed, too few studies to pool. Reported testing: Testing between groups not reported. Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IIB Comments: Meta-analysis not performed because of insufficient statistics; study only reported data in graph. Funding source: Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Cleland LG, 1988[16]	Sample size: 60 Age (mean/range): 51 / 22-74 Race: NA % male: 30 # sites: NA Location: Australia	Design: RCT Duration: 3 mo	Inclusion: NA Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Olive oil 18 g/d x 3 mo
					2	Max EPA (fish oil) 18 g/d x 3 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Cleland LG, 1988[16]	Pain (Analogue pain scale at month 3) Arm 1 =7.1 Arm 2 =7 effect size=-0.02(-0.60, 0.56) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Swollen joints (# of swollen joint at month 3) Arm 1 =3.5 Arm 2 =3.6 effect size=0.04(-0.54, 0.62) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Acute phase reactant: (ESR at month 12) Arms 1, 2 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: No significant change within group by Student's t test; testing between groups not reported. Patient global assessment: (at month 12) Arms 1, 2 = point estimate not reported Meta-analysis: Not included, point estimates not reported. Reported testing: No significant change within group; testing between groups not reported. Radiographic damage: NA NSAID consumption NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: Government; Private, non-industry; Hospital

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Geusens P, 1994[17]	Sample size: 90 Age (mean/range): 57 / NA Race: NA % male: 22 # sites: NA Location: Belgium	Design: RCT Duration: 12 mo	Inclusion: Active disease Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Olive oil capsules 6 g/d x 12 mo
					2	Fish oil 3 g x 12 mo plus olive oil 3 g/d x 12 mo
					3	Fish oil 6 g/d x 12 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Geusens P, 1994[17]	Pain (0-4 scale at month 3) Arm 1 =1.97 Arm 2 and Arm 3 (combined) =1.89 effect size=-0.04(-0.57, 0.50) Reported testing: Article reports no significant differences (p>0.05) of the changes between Arm 2 or Arm 3 and Arm 1. Swollen joint:s NA Acute phase reactant: NA Radiographic damage:NA NSAID consumption: consumption of NSAIDs and DMARDs combined reported, see below. Steroid consumption: NA DMARD consumption: consumption of NSAIDs and DMARDs combined reported, see below. Patient global assessment (0-10cm visual analog scale at month 3) Arm 1 =5.68 Arm 2 and Arm 3 (combined) =4.53 effect size=-1.38(-1.97, -0.79) Reported testing: Article reports significant differences (p<0.01) of the changes between Arm 3 and Arm1 by Mann-Whitney test. NSAID and/or DMARD consumption: (% with dose reduction at month 12) Arm 1 = 15 Arm 2 = 29 Arm 3 = 47 Meta-analysis: Not done, too few studies to pool. Reported testing: Significant (p<.05) difference between arms 3 (high dose fish oil) and arm 1 (placebo) using chi-square test.	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: ND

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Hansen G, 1996[29]	Sample size: 109 Age (mean/range): 57 / NA Race: NA % male: 26 # sites: NA Location: Denmark	Design: RCT Duration: 6.0 mo	Inclusion: Increased morning stiffness/Increased sed rate/>= 3 swollen joints Exclusion: Underweight/Severe disorders	Covariates: NSAIDs	1	Normal diet
					2	Fish 114 g for 6 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Hansen G, 1996[29]	Pain: (change on VAS at month 6) Arm 1 = 0.2 Arm 2 = -0.2 Meta-analysis: Not included, point estimates not reported. Reported testing: Significant (p=0.01) difference between arms using Wilcoxons unpaired rank test. Swollen joints: (change on 1-3 scale at month 6) Arm 1 = -1 Arm 2 = -3 Meta-analysis: Not included, point estimates not reported. Reported testing: Significant (p=0.01) difference between arms using Wilcoxons unpaired rank test. Acute phase reactant: (change, ESR, mm/hr at month 6) Arm 1 = 0 Arm 2 = 1 Meta-analysis: Not included, point estimates not reported. Reported testing: No significant difference between arms using Wilcoxons unpaired rank test. Patient global assessment: NA Radiographic damage: (Change, Larsen score at month 6) Arm 1 = 4 Arm 2 = 3 Meta-analysis: Not included, point estimates not reported. Reported testing: No significant difference between arms using Wilcoxons unpaired rank test. NSAID consumption: Arm 1 = point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not performed, too few studies to pool. Reported testing: Testing between groups not reported. Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IB Funding source: ND

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Kjeldsen-Kragh J, 1992[30]	Sample size: 79 Age (mean/range): 57 / 23-73 Race: NA % male: 24 # sites: 7 Location: Russia	Design: RCT Duration: 4.0 mo	Inclusion: >= 6 tender joints/>= 3 swollen joints/Increased sed rate/Increased morning stiffness/Prednisone or prednisolone = 10 mg/Functional class/Stable medication Exclusion: NA	Covariates: Naproxen	1	Corn oil 7g/d X 16 weeks Naproxen 750 mg/d x 10 weeks then reduction to 0 mg/d by week 13 continued through week 16.
					2	K-85 (fish oil) 750 mg for 16 wk Naproxen 750 mg/d X 16 weeks
					3	K-85 (fish oil) 750 mg for 16 wk Naproxen 750 mg/d x 10 weeks then reduction to 0mg/d by week 13 continued through week 16.

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Kjeldsen-Kragh J, 1992[30]	Pain: (VAS at week 16) Arms 1, 2, 3: point estimates not reported. Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between groups not reported. Swollen joints: (number at month 16) Arms 1, 2, 3: point estimates not reported. Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between groups not reported. Acute phase reactant: NA Patient global assessment: (at week 16) Arms 1, 2, 3: point estimates not reported. Meta-analysis: Not included, point estimates not reported. Reported testing: Testing between groups not reported. Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Kremer J, 1990[19]	Sample size: 64 Age (mean/range): 58 / 22-81 Race: NA % male: 33 # sites: 1 Location: US	Design: RCT Duration: 9 mo	Inclusion: >= 6 tender joints/Increased sed rate/Increased morning stiffness/Stable medication/>= 3 swollen joints Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Olive oil capsules 9/d X 24 weeks
					2	Fish oil capsules X 24 weeks (27 mg/kg/d EPA, 18 mg/kg/d DHA)
					3	Fish oilcapsules X 24 weeks (54 mg/kg/d EPA, 36 mg/kg/d DHA)

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Kremer J, 1990[19]	Pain (0-4 five point scale at week 12) Arm 1 =1.60 Arm 2 and Arm3 (combined) =1.51 effect size=-0.04(-0.69, 0.61) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2 and Arm 3. Swollen joints (# of swollen joint at week 12) Arm 1 =13.50 Arm 2 and Arm3 (combined) =10.96 effect size=-0.63(-1.30, 0.03) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2 and Arm 3. Acute phase reactant: (ESR at week 24 and at week 36) Arms 1,2,3 = point estimates not reported. Meta-analysis: Not included, point estimates not reported. Reported testing: No significant difference in any arm using Student's t-test; testing between groups not reported. Patient global assessment (0-4 five point scale at week 12) Arm 1 =1.8 Arm 2 and Arm3 (combined) =1.69 effect size=-0.13(-0.78, 0.52) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2 and Arm 3. Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: NA

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Kremer J, 1995[31]	Sample size: 66 Age (mean/range): 58 / NA Race: NA % male: 45 # sites: 3 Location: US	Design: RCT Duration: 6.5 mo	Inclusion: >= 6 tender joints/>= 3 swollen joints/Increased morning stiffness/Increased sed rate Exclusion: NA	Covariates: DMARDs/NSAIDs	1	Corn oil, 9 capsules/d X 26 or 30 wk. Diclofenac, 75 mg BID X first 18 or 22 wk
					2	Menhaden oil (130 mg/kg/d of omega-3) X 26 or 30 wk, then corn oil until week 48. Diclofenac, 75 mg BID X first 18 or 22 wk

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Kremer J, 1995[31]	Pain: (0-4 scale, mean change at week 18 or 22) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included because point estimates not reported. Reported testing: Not reported for this outcome. Tender joints: (number, change at week 18 or 22) Arm 1= point estimate not reported Arm 2 = -5.3 Meta-analysis: Not included because point estimate not reported for control group. Reported testing: Testing between groups not reported. Swollen joints: (number at week 18 or 22) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included because point estimates not reported. Reported testing: Not reported for this outcome. Acute phase reactant: NA Patient global assessment: (mean change at week 18 or 22) Arm 1= point estimate not reported Arm 2 = -0.38 Meta-analysis: Not included because point estimate not reported for control group. Reported testing: Testing between groups not reported. Radiographic damage: NA NSAID consumption: Defined in study protocol Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: NR

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Kremer J, 1985[18]	Sample size: 52 Age (mean/range): 56 / NA Race: NA % male: 32 # sites: NA Location: US	Design: RCT Duration: 3 mo	Inclusion: Increased sed rate/>= 6 tender joints/>= 3 swollen joints/Increased morning stiffness Exclusion: Reliable adherence	Covariates: NSAIDs/DMARDs	1	Parafin placebo capsules 10/day X 12 weeks Diet with polyunsaturated fat: saturated fat ratio=1:4.
					2	Max EPA (fish oil) capsules 10/d X 12 wk Diet with polyunsaturated fat: saturated fat ratio=1.4:1.

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Kremer J, 1985[18]	Pain (1-5 five point scale at week 12) Arm 1 =2.8 Arm 2 =2.5 effect size=-0.13(-0.78, 0.51) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Swollen joints (# of swollen joint at week 12) Arm 1 =13.5 Arm 2 =13.4 effect size=-0.02(-0.66, 0.63) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Acute phase reactant Arm 1 =34.9 Arm 2 =24.2 effect size=-0.44(-1.10, 0.21) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Patient global assessment (1-5 five point scale at week 12) Arm 1 =2.9 Arm 2 =2.7 effect size=-0.24(-0.89, 0.41) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IB Funding source: NA

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Lau CS, 1995[38]	Sample size: 45 Age (mean/range): NA / 27-69 Race: NA % male: 29 # sites: 1 Location: UK	Design: RCT Duration: 6 mo	Inclusion: NSAIDs use/Clinically stable/No DMARDs Exclusion: NA	Covariates: NSAIDs	1	Air-filled placebo capsules 10/day X 6 mo
					2	Max EPA (fish oil) 10/day X 6 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Lau CS, 1995[38]	Pain: (at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: No statistically significant change within or between groups by ANOVA. Swollen joints: (at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: No statistically significant change within or between groups by ANOVA. Acute phase reactant: (ESR at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: No statistically significant change within or between groups by ANOVA. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 2 Concealment of allocation: NR Applicability: IB Funding source: ND

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Lau CS, 1993[32]	Sample size: 64 Age (mean/range): 51 / 26-73 Race: NA % male: 30 # sites: 1 Location: Scotland	Design: RCT Duration: 15 mo	Inclusion: NSAIDs use/Clinically stable/No DMARDs Exclusion: NA	Covariates: NSAIDs	1	Air-filled placebo capsules 10/day X 12 mo
					2	Max EPA (fish oil) capsules 10/day X 12 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Lau CS, 1993[32]	Pain: (VAS at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: No statistically significant change between groups by Wilcoxon rank sum test. Swollen joints: NA Acute phase reactant: (ESR at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not included; point estimates not reported. Reported testing: No statistically significant change within or between groups by ANOVA. Patient global assessment: NA Radiographic damage: NA NSAID consumption: (% requiring at month 15) Arm 1 = 86 Arm 2 = 45 Meta-analysis: Not performed, too few studies to pool. Reported testing: No statistically significant change within or between groups by ANOVA. Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IIB Funding source: Industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Magaro M, 1988[21]	Sample size: 20 Age (mean/range): NA / 25-45 Race: NA % male: NA # sites: NA Location: Italy	Design: RCT Duration: 1.5 mo	Inclusion: Increased sed rate/>= 6 tender joints/>= 3 swollen joints/Increased morning stiffness/NSAIDs use/No DMARDs Exclusion: Diabetes/Obesity	Covariates: NSAIDs	1	Usual diet
					2	Max EPA (fish oil) 9 g/d x 45 days Usual diet

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Magaro M, 1988[21]	Patient assess pain (cm at day 45) Arm 1 =4.20 Arm 2 =4.80 effect size=0.41 (-0.48, 1.29) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Swollen joints: NA Acute phase reactant (mm/1st hour at day 45) Arm 1 =66.00 Arm 2 =59.50 effect size=-0.16 (-1.04, 0.72) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 1 Concealment of allocation: NR Applicability: IIB Funding source: ND

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Magalish T, 2002[20]	Sample size: 112 Age (mean/range): NA / 17-77 Race: NA % male: 26 # sites: 2 Location: Russia	Design: CCT Duration: 10 d	Inclusion: Age Exclusion: NA	Covariates: Duration of diabetes	1	Phonopheresis with hydrocortisone cream q/d X 10 d
					2	Phonopheresis with omega-3 fatty acids q/d 10 d

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Magalish T, 2002[20]	Pain: (unspecified measure at day 10) Arm 1 = 0.7 Arm 2 = 0.6 Meta-analysis: Not included; measure not defined. Reported testing: Testing between groups not reported. Swollen joints (# of swollen joint at month 0.3) Arm 1 =0.7 Arm 2 =0.6 effect size=-0.02(-0.66, 0.63) Reported testing: Unable to translate. Acute phase reactant: NA Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 0 Concealment of allocation: NR Applicability: IIB Funding source: NR

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Nielsen G, 1992[22]	Sample size: 57 Age (mean/range): NA / 33-78 Race: NA % male: NA # sites: 3 Location: Denmark	Design: RCT Duration: 3.0 mo	Inclusion: Increased sed rate/>= 6 tender joints/>= 3 swollen joints/Increased morning stiffness Exclusion: No current change in meds	Covariates: NSAIDs/DMARDs	1	Control capsules (n-6 fatty acids) 6/day X 12 weeks
					2	Pikasol (fish oil) capsules 6/d X 12 weeks

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Nielsen G, 1992[22]	Pain (Visual pain score at week 12) Arm 1 =136 Arm 2 =104 effect size=-0.85 (-1.42, -0.27) Reported testing: Article reports significant differences (p=0.002) between Arm 1 and Arm 2. Swollen joints (0-2 three point index scale at wee 12) Arm 1 =8 Arm 2 =8 effect size=0.00 (-0.55, 0.55) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Acute phase reactant (mm/hour at week 12) Arm 1 =33 Arm 2 =34 effect size=0.06 (-0.49, 0.61) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Patient global assessment: NA Radiographic damage: NA NSAID consumption: (at week 12) Arms 1, 2 = point estimate not reported Meta-analysis: Not performed, too few studies to pool. Reported testing: No difference within group, testing between groups not reported. Steroid consumption: (at week 12) Arms 1, 2 = point estimate not reported Meta-analysis: Not performed, too few studies to pool. Reported testing: No difference within group, testing between groups not reported. DMARD consumption(at week 12) Arms 1, 2 = point estimate not reported Meta-analysis: Not performed, too few studies to pool. Reported testing: No difference within group, testing between groups not reported.	Quality: Jadad: 4 Concealment of allocation: NR Applicability: NR Comments: Meta-analysis performed on patient assessment of pain, acute phase reactant, and swollen joints. Funding source: Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Nordstrom D, 1995[23]	Sample size: 22 Age (mean/range): 52 / 34-72 Race: NA % male: NA # sites: 1 Location: Finland	Design: RCT Duration: 3 mo	Inclusion: NA Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Safflower oil 30 g/day X 3 mo
					2	Flaxseed oil 30 g/day X 3 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Nordstrom D, 1995[23]	Pain (Visual analogue scale at month 3) Arm 1 =4.60 Arm 2 =4.00 effect size=-0.21 (-1.04, 0.63) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Swollen Joints (Kaarela'sjoint score index at month 3) Arm 1 =9.50 Arm 2 =9.10 effect size=-0.06 (-0.90, 0.77) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Acute phase reactant (mm/hour at month 3) Arm 1 =32.50 Arm 2 =35.70 effect size=0.13 (-0.71, 0.96) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Patient global assessment (five-scale at month 3) Arm 1 =2.70 Arm 2 =2.90 effect size=0.26 (-0.58, 1.10) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: NR Funding source: Government; Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Skoldstam L, 1992[25]	Sample size: 46 Age (mean/range): 57 / 28-73 Race: NA % male: 26 # sites: NA Location: Sweden	Design: RCT Duration: 6 mo	Inclusion: Clinically stable/Stable medication/Increased sed rate/Increased morning stiffness/>= 6 tender joints/>= 3 swollen joints Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Control oil (maize, olive and peppermint oil) capsules 10 g/day X 6 mo
					2	Max EPA (fish oil) 10 g/day X 6 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Skoldstam L, 1992[25]	Pain (0-3 VAS at month 3) Arm 1 mean=1.28 Arm 2 mean=136 effect size=0.11 (-0.49, 0.71) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Swollen joints: NA Acute phase reactant (mm/hour at month 3) Arm 1 =39 Arm 2 =40 effect size=0.04 (-0.55, 0.64) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Patient global assessment (0-3 scale at month 3) Arm 1 =1.11 Arm 2 =1.20 effect size=0.04 (-0.56, 0.63) Reported testing: Article did not report statistical results comparing Arm 1 and Arm 2. Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: IB Funding source: Government

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Tulleken J, 1990[24]	Sample size: 28 Age (mean/range): 55 / 29-68 Race: NA % male: 11 # sites: NA Location: Italy	Design: RCT Duration: 3 mo	Inclusion: Stable medication Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Coconut oil capsules 4 TID X 3 mo
					2	Fish oil capsules 4 TID (6 g/day) X 3 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Tulleken J, 1990[24]	Pain (10 cm VAS at month 3) Arm 1 =3.8 Arm 2 =2.4 effect size=-0.72 (-1.50, 0.06) Reported testing: Article reports no significant differences (p>0.05) between Arm 1 and Arm 2. Swollen joints ((# of swollen joint at month 3) Arm 1 =4 Arm 2 =3 effect size=-0.26(-1.02, 0.50) Reported testing: Article reports no significant differences (p>0.05) between Arm 1 and Arm 2. Acute phase reactant (mm/hour at month 3) Arm 1 =53 Arm 2 =21 effect size=-1.82 (-2.71, -0.92) Reported testing: Article reports no significant differences (p>0.05) between Arm 1 and Arm 2. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 4 Concealment of allocation: Yes Applicability: IIB Comments: Meta-analysis performed on patient assessment of pain, swollen joints, and acute phase reactant. Funding source: Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage Duration
Tulleken J, 1988[34]	Sample size: NA Age (mean/range): NA / NA Race: NA % male: NA # sites: NA Location: Netherlands	Design: RXT Duration: 24 X-over: week 13 Run-in: NR Wash-out: NR	Inclusion: Active RA Exclusion: NR	Covariates: NSAIDs/DMARDs	1	Coconut oil capsules 12/day X 3 mo
					2	Fish oil capsules 12/day X 3 mo

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Tulleken J, 1988[34]	Pain: NA Swollen joints: (at month 3) Arms 1, 2 = point estimates not reported Meta-analysis: Not included; point estimates not reported. Reported testing: Significant difference between arms favoring fish oil, test not stated. Acute phase reactant: (CRP, mg/dl, at month 3) Arms 1, 2 = point estimates not reported before cross-over Meta-analysis: Not included; point estimates not reported. Reported testing: No significant difference between arms , test not stated. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 2 Concealment of allocation: NR Applicability: NR Funding source: ND

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage Duration
van der Tempel H, 1990[33]	Sample size: NA Age (mean/range): 53 / NA Race: NA % male: 44 # sites: NA Location: Netherlands	Design: RXT Duration: 36 wk X-over: week 13 Run-in: 12 wk Wash-out: None	Inclusion: NR Exclusion: NR	Covariates: NSAIDs/DMARDs	1	Coconut oil capsules 12/day X 12 wk
					2	Fish oil capsules 12/day X 12 wk

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis.

First Author, Year	Outcomes Results	Quality Applicability Funding Source
van der Tempel H, 1990[33]	Pain:(VAS, cm at week 12) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported before cross-over. Reported testing: No significant differences between arms using t-test. Swollen joints: (at week 12) Arms 1, 2 = point estimates not reported. Meta-analysis: Not included; point estimates not reported before cross-over. Reported testing: Significant differences between favoring fish oil using t-test. Acute phase reactant: (CRP, mg/dl, at month 3) Arms 1, 2 = point estimates not reported before cross-over Meta-analysis: Not included; point estimates not reported. Reported testing: No significant differences between arms using t-test. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IB Comments: Meta-analysis not performed because data was not reported by arm separately. Funding source: Private, non-industry

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Volker D, 2000[35]	Sample size: 50 Age (mean/range): 57 / NA Race: NA % male: NA # sites: NA Location: Australia	Design: RCT Duration: 15 wk	Inclusion: Stable medication/Active disease/Diet<10g n-6 fatty acids Exclusion: NA	Covariates: NSAIDs/DMARDs	1	Corn (50%)/olive oil (50%) soft gel capsules 40 mg/kg body weight/day x 15 wk
					2	Pikasol (fish oil) capsules 40 mg/kg body weight/day x15 wk

Table C.3. Evidence table of clinical effect of omega-3 fatty acids in rheumatoid arthritis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Volker D, 2000[35]	Pain: (percent change at week 15) Arm 1 = -8.6 Arm 2 = -10.0 Meta-analysis: Not included; data reported as percent change. Reported testing: No significant differnce between goups by MANOVA. Swollen joints: (percent change at week 15) Arm 1 = -16.6 Arm 2 = -36.7 Meta-analysis: Not included; data reported as percent change. Reported testing: No significant differnce between goups by MANOVA. Acute phase reactant: (ESR, percent change at week 15) Arm 1 = -31.9 Arm 2 = -6.2 Meta-analysis: Not included; data reported as percent change. Reported testing: No significant differnce between goups by MANOVA. Patient global assessment: NA Radiographic damage: NA NSAID consumption: NA Steroid consumption: NA DMARD consumption: NA	Quality: Jadad: 3 Concealment of allocation: NR Applicability: NR Funding source: Industry, private non-industry

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease.

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Bennett WM, 1989[100]	Sample size: 37 Age (mean/range) 39 / NA Race NA % male : 57 # sites: NA Location: Australia	Design: RCT Duration: 24 mo	Inclusion Biopsy-proven Ig A nephropathy Exclusion: Baseline serum creatinine>0.40 mmol/l or = 0.12 mmol/l without active disease	Covariates: Renal/Proteinuria/ Nephrotic Renal impairment: scr > 0.12 mm/l	1	No treatment x 24 mo
					2	Max EPA (fish oil) 10 g/d x 24 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Bennett WM, 1989[100]	Serum creatinine (change mmol/l at month 24): Arm 1= Subjects with baseline > 0.12 mmol/l = 0.22; Subjects with baseline <0.12 mmol/l, but with active disease = 0.01 Arm 2 = Subjects with baseline >0.12 mmol/l = 0.19; Subjects with baseline <0.12 mmol/l, but with active disease = 0.07 ± .06 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Creatinine clearance (change ml/min at month 24): Arm 1= -21 Arm 2 = -23 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. ESRD (rate at month 24): Arm 1= 10% Arm 2 = 12% Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Graft thrombosis: NA Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IIB Funding source: NA

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Clark WFP, 1993[99]	Sample size: 21 Age (mean/range) 39 / 22-66 Race: NA % male: 19 # sites: NA Location: Canada	Design: RXT Duration: 13 mo X-over: month 5 Run-in: None Wash-out: 3 mo	Inclusion: Lupus nephritis Exclusion: NA	Covariates: NSAIDs/DMARDs	1 2	Olive oil 15 cap/d x 12 mo Max EPA (fish oil) 15 cap/d x 12 mo
De Fijter CW, 1995[103]	Sample size: NA Age (mean/range) NA / NA Race: NA % male: NA # sites: NA Location: Netherlands	Design: RXT Duration: 27 mo X-over: month 12 Run-in: None Wash-out: 3 mo	Inclusion: Dialysis/Start of erythropoietin/ Exclusion: NA	Covariates: Hypertension	1 2	Corn oil 3 g/d x 5 mo EPA-B (fish oil) 3 g/d x 5 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Clark WFP, 1993[99]	Serum creatinine (µmol/L at month 12): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-analysis: Not done; too few studies to pool. Reported testing: No significant (p = 0.60) effect for fish oil (Arm 2) relative to olive oil (Arm 1). Creatinine clearance (ml/min/1.73 m^2 at at month 12): Arm 1= 78 Arm 2 = 75 Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant difference between groups. ESRD: NA Graft thrombosis: NA Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 3 Concealment of allocation: NA Applicability: IIIB Funding source: Private, non industry
De Fijter CW, 1995[103]	Serum creatinine: NA Creatinine clearance: NA ESRD: NA Graft thrombosis (rate at month 5): Arm 1= 0% Arm 2 = 0% Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 3 Concealment of allocation: NA Applicability: NA Funding source: NA

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Donadio JV, 1994[98]	Sample size: 106 Age (mean/range): 37 / NA Race: Caucasian % male: 74 # sites: 21 Location: US	Design: RCT Duration: 60 mo	Inclusion: Biopsy-proven Ig A nephropathy /Proteinuria/Serum creatinine increased by 25%/Creatinine <3.0 mg/dl/Expected survival of 2 or more years Exclusion: SLE/ Chronic liver disease/Pregnancy/lactating/ Antiglomerular basement membrane glomerulonephritis	Covariates: Renal/Proteinuria/Nephrotic	1	Olive oil 12 g/d x 24 mo
					2	Max EPA (fish oil) 12 g/d x 12 mo Menhaden oil (fish oil) 12 g/d x 12 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Donadio JV, 1994[98]	Serum creatinine (Annual median change mg/dl at month 24): Arm 1= 0.14 Arm 2 = 0.03 Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (P = 0.001) effect for fish oil (Arm 2) relative to olive oil (Arm 1) using rank-sum test. Creatinine clearance(Annual median change ml/min/1.73 m^2 at at month 24): Arm 1= -7.1 Arm 2 = -0.3 Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant (P = 0.009) effect for fish oil (Arm 2) relative to olive oil (Arm 1) using rank-sum test. ESRD (rate at month 60): Arm 1= 28% Arm 2 = 7% Meta-anlysis: Not done; too few studies to pool. Reported testing: Significant effect for fish oil (Arm 2) relative to olive oil (Arm 1) using rank-sum test and Kaplan-Meier analysis. Graft thrombosis: NA Mortality(rate at month 60): Arm 1= 1% Arm 2 = 2% Meta-anlysis: Meta-analysis not performed on renal studies due to insufficient statistics. Reported testing: No significant effect for fish oil (Arm 2) relative to olive oil (Arm 1) using rank-sum test and Kaplan-Meier analysis. Immunosuppressive requirement: NA	Quality: Jadad: 4 Concealment of allocation: NR Applicability: IIB Funding source: Hospital and Industry

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Donadio JV, 2001[104]	Sample size: 73 Age (mean/range): 46 / NA Race: Caucasian % male: 83 # sites: 14 Location: US	Design: RCT Duration: 60 mo	Inclusion: Biopsy-proven Ig A nephropathy /Age/Serum creatinine 1.5-4.9 mg/dl Exclusion: NA	Covariates: Previous meds tx/ Hypertension	1 2	Omacor 4 g/d x 24 mo Omacor 8 g/d x 24 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Donadio JV, 2001[104]	Serum creatinine (annual median change, mg/dl at month 60): Arm 1= 0.08 Arm 2 = 0.10 Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant (P = 0.51) effect for high dose Omacor (Arm 2) relative to low dose Omacor(Arm 1) using rank-sum test. Creatinine clearance: NA ESRD ((rate at month 36): Arm 1= 27% Arm 2 = 24% Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant (P = 0.56) effect for high dose Omacor (Arm 2) relative to low dose Omacor(Arm 1) using rank-sum test. Graft thrombosis: NA Mortality (rate at month 36): Arm 1= 0% Arm 2 = 0% Meta-anlysis: Not done; too few studies to pool. Reported testing: No significant effect for high dose Omacor (Arm 2) relative to low dose Omacor(Arm 1) using rank-sum test. Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IIB Funding source: Hospital and Industry

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Gentile MG, 1993[106]	Sample size: NA Age (mean/range): 45 / 15-60 Race: NA % male: 45 # sites: 1 Location: Italy	Design: RXT Duration: 9 mo X-over: month 4 Run-in: 2 mo Wash-out: None	Inclusion: Biopsy-proven glomerular disease/Proteinuria/ Hyperlipidemia Exclusion: Steroid treatment/Cytotoxic treatment/NSAID treatment/Lipid lowering drug treatment	Covariates: soy diet	1 2	Soy diet alone Dosage NA x 2 mo Soy diet Dosage NA x 2 mo Fish oil 5 g/d x 2 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Gentile MG, 1993[106]	Serum creatinine (mg/dl at month 2): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Creatinine clearance(ml/min atb month 2): Arm 1= point estimate before cross-over not reported Arm 2 = point estimate before cross-over not reported Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. ESRD: NA Graft thrombosis: NA Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IB Funding source: Government

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Pettersson EE, 1994[101]	Sample size: 34 Age (mean/range): 41 / 22-68 Race: NA % male: 78 # sites: NA Location: Sweden	Design: RCT Duration: 6 mo	Inclusion : Biopsy-proven Ig A nephropathy /Proteinuria Exclusion: SLE/Steroid treatment /Cytotoxic or immunosuppressive drug treatment/NSAID treatment /Diabetes/Malignant disease/Heart failure/Rapidly progressive renal insufficiency/Uncontrolled hypertension	Covariates: Proteinuria/ nephrotic	1 2	Corn oil 6g/d x 6 mo K-85 (fish oil) 6g/d x 6 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability) Funding Source
Pettersson EE, 1994[101]	Serum creatinine(change µmol/l at month 6): Arm 1= 1 Arm 2 = 8 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Creatinine clearance (change ml/min at month 6): Arm 1= 0 Arm 2 = 12 Meta-anlysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. ESRD: NA Graft thrombosis: NA Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 4 Concealment of allocation: NA Applicability: IIB Funding source: NA

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Covariates	Arm	Interventions Dosage/Duration
Schmitz PG, 2002[102]	Sample size: 24 Age (mean/range): 53 / NA Race: Black % male: 46 # sites: 1 Location: US	Design: RCT Duration: 12 mo	Inclusion: Initiation of hemodialysis with PTFE graft/Hemodialysis with new placement of PTFE graft Exclusion: Pregnancy/lactating/Surgical revision of graft/History of GI bleeding/Chronic anticoagulation treatment/ Malignant hypertension/Terminal of life-threatening diseases	Covariates: Hyperlipidemia/ Hypertension/ Diabetes/Venous output resistance	1 2	Corn oil 4g/d x 12 mo Fish oil 4g/d x 12 mo

Table C.4. Evidence table of clinical effect of omega-3 fatty acids in renal disease (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Schmitz PG, 2002[102]	Serum creatinine: NA Creatinine clearance: NA ESRD:NA Graft thrombosis(rate at 12 mo): Arm 1= 75% Arm 2 = 25% Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between arms not reported. Patency (rate at 12 mo): Arm 1= 15% Arm 2 = 76% Meta-analysis: Not done; too few studies to pool. Reported testing: Significant ($p < .03$) effect for fish oil (Arm 2) relative to corn oil (Arm 1) using Mantel-Cox test. Mortality: NA Immunosuppressive requirement: NA	Quality: Jadad: 4 Concealment of allocation: NA Applicability: IIB Funding source: Private, non-industry and Government

Table C.5. Evidence table of clinical effects of omega-3 fatty acids in systemic lupus erythematosus.

First Author, Year	Study Characteristics	Study design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Clark WF, 1993[99]	Sample size: 26 Age (mean/range): 39 / 22-66 Race: NA % male: 19 \# sites: NA Location: Canada	Design: RXT Duration: 24 mo X-over: month 13 Run-in: None Wash-out: 10 wk	Inclusion: Lupus nephritis Exclusion: NA	Covariates: NSAIDs/DMARDs	1 2	Olive oil capsules 15/d x 12 mo Max EPA (fish oil) 15/d x 12 mo
Walton AJ, 1991[107]	Sample size: 27 Age (mean/range): NA / 21-68 Race: NA % male: 7 \# sites: 1 Location: UK	Design: RXT Duration: 34 wk X-over: week 22 Run-in: 2 wk Wash-out: 8 wk	Inclusion: Established SLE	Covariates: NA	1 2	Olive oil 20g/d x 12 wk Max EPA (fish oil) 20g/d x 12 wk

Table C.5. Evidence table of clinical effects of omega-3 fatty acids in systemic lupus erythematosus (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Clark WF, 1993[99]	Disease activity: (SLEDAI score at month 12) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not done; too few studies to pool. **Reported testing: No change in SLEDAI scores for either arm, statistical test used and comparison between arms for this outcome not explicitly stated.** Disease activity: (anti-ds-DNA Ab level at month 12) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not done; too few studies to pool. Reported testing: No treatment (p=0.71), time (p=0.25), order (p=0.35) or carry-over effect (p=0.92); statistical test used not stated. Damage: NA Patient perception: NA	Quality: Jadad: 3 Concealment of allocation: NA Applicability: IIIB Funding source: Private, non-industry
Walton AJ, 1991[107]	Disease Activity: (Unspecified individualized responses defined a priori and based on change in clinical and laboratory parameters at month 6) Arm 1: 4/17 useful/ideal status 13/17 static/worse status Arm 2: 14/17 useful/ideal status 3/17 static/worse status Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Damage: NA Patient perception: NA	Quality: Jadad: 3 Concealment of allocation: Yes Applicability: IIB Funding source: government; private, non-industry

Table C.5. Evidence table of clinical effects of omega-3 fatty acids in systemic lupus erythematosus (continued).

First Author, Year	Study Characteristics	Study design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Westberg G, 1990[108]	Sample size: 20 Age (mean/range): 44 / 31-64 Race: NA % male: 12 # sites: 2 Location: Australia	Design: RXT Duration: 21 mo X-over: month 12 Run-in: 3 mo Wash-out: 3 mo	Inclusion: Stable medication Exclusion: Inactive disease	Covariates: DMARDs, steroid use	1 2	Placebo/control Dosage/duration not collected Max EPA (fish oil) Variable dose for 6 mo

Table C.5. Evidence table of clinical effects of omega-3 fatty acids in systemic lupus erythematosus (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Westberg G, 1990[108]	Disease activity: (Author's own instrument, at 6 mo) Arm 1= point estimates not reported. Arm 2 = point estimates not reported. Meta-analysis: Not done; too few studies to pool. Reported testing: No significant difference between groups using Student's t-test. Disease activity: (anti-DNA Ab level at month 6) Arm 1= point estimate not reported Arm 2 = point estimate not reported Meta-analysis: Not done; too few studies to pool. Reported testing No significant difference between groups using Student's t-test. Damage: NA Patient Perception: NA	Quality: Jadad: 5 Concealment of allocation Yes Applicability: IIB Funding source: NA

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis.

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Bassey EJ, 2000[109] Study A	Sample size: 64 Age (mean/range): 35 / 25-40 Race: NA % male: 0 # sites: 1 Location: UK	Design: RCT Duration: 12 mo	Inclusion: Age/Pre-menopausal Exclusion: Health problems/BMI>36, <18/BMD outside 2SD of norms/Confounding drug therapy/Pregnancy/Lactating/ Dietary supplements/Irregular menses	Covariates: Weight/Age/Dietary Calcium	1 2	Calcium 1g/d x 12 mo Efacal (Ca, Primrose oil, Fish oil) Ca 1 g/d x 12 mo Evening prim rose oil 4 g/d x 12 mo Fish oil 440 g/d x 12 mo
Bassey EJ, 2000[109] Study B	Sample Size: 57 Age (mean/range): 57/50-65 race: NA % male: 0 # sites: 1 Location: UK	Design: RCT Duration: 12 mo	Inclusion: Age/Postmenopausal Exclusion: Health problems/ BMI >36, <18/BMD outside 2SD of norms/Confounding drug therapy/Dietary supplements/ within 1 yr of menopause/Hormone levels outside of normal postmenopausal range/hormone replacement therapy	Covariates: Weight/Age/Dietary Calcium	1 2	Calcium 1g/d x 12 mo Efacal (Ca, Primrose oil, Fish oil) Ca 1 g/d x 12 mo Evening primrose oil 4 g/d x 12 mo Fish oil 440 g/d x 12 mo

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Bassey EJ, 2000[109] Study A	Bone mineral density: (change at month 12, g/cm^2) Arm 1= 0.011 Arm 2 = 0.008 Meta-analysis: Not done; too few studies to pool. Reported testing: Significant (p<.001) difference between groups using paired Student's t-test. Fractures: NA	Quality: Jadad: 2 Concealment of allocation: Yes Applicability: IA Funding source: Industry
Bassey EJ, 2000[109] Study B	Bone mineral density: (change at month 12, g/cm^2) Arm 1= -0.013 Arm 2 = -0.008 Meta-analysis: Not done; too few studies to pool. Reported testing: Significant (p<.001) difference between groups using paired Student's t-test. Fractures: NA	Quality: Jadad: 2 Concealment of allocation: Yes Applicability: IA Funding source: Industry

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Kruger MC, 1998[110]	Sample size: 66 starting Age (mean/range): 80 / NA Race: NA % male: 0 # sites: NA Location: South Africa	Design: RCT Duration: 18 mo	Inclusion: Osteoporosis confirmation by BMD Exclusion: Metabolic bone disease/ Diabetes/Renal failure	Covariates: Weight/Age	1	Coconut oil 6 g/d X 18 mo
					2	Fish oil 6 g/d X 18 mo
					2	EPA 2g x 12 mo plus HMGCoA reductace inhibitor

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Kruger MC, 1998[110]	Bone mineral density: (lumbar spine, g/cm ^{2} at month 18) Arm 1= 0.979 Arm 2 = 1.053 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Bone mineral density: (femoral neck, g/cm ^{2} at month 18) Arm 1= 0.709 Arm 2 = 0.774 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Fractures: (cumulative number at month 18) Arm 1= 0 Arm 2 = 0 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported.	Quality: Jadad: 2 Concealment of allocation: NA Applicability: IIIB Funding source: Industry

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Terano T, 2001[111]	Sample size: 33 Age (mean/range): 58 / NA Race: NA % male: 0 # sites: NA Location: Japan	Design: RCT Duration: 12 mo	Inclusion: Hyperlipidemia Exclusion: NA	Covariates: Hyperlipidemia/Age/ Weight	1	HMGCoA reductase inhibitor

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Terano T, 2001[111]	Bone mineral density: (speed of sound, %, at month 12) Arm 1= 98.6 Arm 2 = 99.3 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Bone mineral density: (transmission index, %, at month 12) Arm 1= 99.4 Arm 2 = 101 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Bone mineral density: (osteosono assessment index, %, at month 12) Arm 1= 99.4 Arm 2 = 99.3 Meta-analysis: Not done; too few studies to pool. Reported testing: Testing between groups not reported. Fractures: NA	Quality: Jadad: 1 Concealment of allocation: NR Applicability: Not described Funding source: NR

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Study Characteristics	Study Design Duration	Eligibility Criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Tsuchida K, 1999 [112]	Sample size: 995 Age (mean/range): 45 / 40-49 Race: Asian % male: 0 # sites: 18 Location: Japan	Design: Cohort Duration: NA	Inclusion: Age Exclusion: Medical treatment/Ovalectomy	Covariates: Weight/Age/Dietary Calcium/Menstrual cycle	1 2 3 4 5 6	Fish -0-1 portions/week Fish 2-5 portions/week Fish 6-7 portions/week Soybean 0-1 portions/week Soybean 2-5 portions/week Soybean 6-7 portions/week

Table C.6. Evidence table of clinical effect of omega-3 fatty acids in bone mineral density/osteoporosis (continued).

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Tsuchida K, 1999 [112]	Bone mineral density: There was no association between fish intake and BMD of the 2nd metacarpal bone. Soybean intake was associated with a significant (p=.03 by ANOVA) gradient in BMD of 2nd metacarpal independent of age, height, weight and weekly calcium intake. Those with 2 or more portions were significantly higher than 0-1 portions. Fractures: NA	Quality Jadad: NA Concealment of allocation: NA Applicability: IA Funding source: NR