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Effects of Omega-3 Fatty Acids on Eye Health

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The information in this report is intended to help health care decisionmakers, patients and clinicians, health system leaders, and policymakers make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report as they would any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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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 was requested and funded by the Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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

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

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Context: In the United States, blindness or low vision affects 3.3 million people over the age of 40, or one in 28 people in that age group. With the number of people aged 50 years or older expected to increase in upcoming decades, this number is expected to increase to 5.5 million Americans or 76 million people worldwide by the year 2020. The most important cause of low vision worldwide is cataracts; in developed countries, age related macular degeneration is the most common cause of low vision. The brain and eye are highly enriched with omega-3 fatty acids, which accumulate in these tissues during late fetal and early neonatal life. Some studies in preterm and term human infants have suggested that a dietary supply of omega-3 fatty acids is essential for optimal visual development. Several basic science studies support the hypothesis that omega-3 fatty acids may be useful therapeutic agents for pathologies of the retina and lens.

Objectives: The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise and synthesize the evidence for the effects of omega-3 fatty acids on eye health. Questions assessed the possible primary or secondary preventive influence of the intake of omega-3 fatty acids on important eye health-related outcomes. These included age-related macular degeneration (ARMD), diabetic retinopathy, retinitis pigmentosa, cataracts, and occlusions of either retinal veins or retinal arteries. Adverse effects associated with omega-3 fatty acid supplementation in interventional studies of eye health were also sought.

Data Sources: A comprehensive search was undertaken in six databases (MEDLINE®, PreMEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, CAB Health, and Dissertation Abstracts). Searches were not restricted by language of publication, publication type, or study design except with the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search terms related to omega-3 fatty acids and eye health. Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts.

Study Selection: Studies were considered relevant if they described live human populations of any age, involved any type of study design, and investigated the intake of any foods or extracts, known to contain omega-3 fatty acids, for their possible primary or secondary preventive influence on eye health. Ineligible were studies, which included populations exclusively exhibiting a possible or requisite subset of the symptoms or signs of eye disease/visual impairment (e.g., blurred vision). A review-pertinent diagnosis, as well as at least one review-relevant clinical ocular outcome, was required.

Data Extraction: Two levels of screening for relevance, and two reviewers per level, were employed (bibliographic records, then full articles). Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format. Disagreements were resolved by forced consensus and, if necessary, third party intervention. A Technical Expert Panel (TEP) consisting of six members was convened to provide advisory support to the project. They contributed to refining the questions and highlighting key variables requiring consideration in the review. Each included study was assessed for its quality as well as its applicability to the North American population.

Data Synthesis: Sixteen studies, described in 16 published journal articles, were found to investigate nine of 23 potential questions. Question-specific qualitative syntheses of the evidence were derived. Greater interpretative emphasis was placed on evidence from randomized controlled trials (RCTs) and other designs that were both prospective and controlled. Too little, or flawed, available evidence precluded meta-analysis for each question.

Conclusions: Based on the studies identified by this review, clinical research has only scratched the surface with respect to understanding the possible utility of the intake of omega-3 fatty acids as a primary or secondary prevention in eye health. Moreover, seen from the point of view of clinical research's typical, linear arc—which moves from basic science to observational research to RCTs, and culminating in the systematic review/meta-analysis of the observations obtained by these primary studies—there is a paucity of solid observational research with which to construct an experimental framework affording the meaningful conduct of RCTs. For example, there is little understanding of the exact sources, types and doses of omega-3 fatty acids, or even the possible duration of their use, which might usefully serve as definitions of a prevention-centered "intervention" for any of the eye diseases/visual impairments examined in our review. Perhaps only with respect to the question of preventing the development/progression of advanced ARMD is there some suggestive evidence, which is underscored by it being a strong public health problem, to allow researchers to consider conducting an RCT. At the same time, a single study reporting adverse event data likely does not permit laying to rest all possible concerns regarding the short- or long-term safety of omega-3 fatty acid interventions. It is therefore our view that much more research will need to be conducted before anything conclusive can be asserted with respect to the effects of omega-3 fatty acids on eye health. It is also our understanding that sorting out the possible benefits of the intake of omega-3 fatty acids in eye health might profit from taking into consideration the impact of the concurrent intake of omega-6 fatty acids and, by definition, the omega-6/omega-3 fatty acid intake ratio.

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Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 117

Effects of Omega-3 Fatty Acids on Eye Health

Summary

Authors: Hodge W, Barnes D, Schachter HM, Pan Y, Lowcock EC, Zhang L, Sampson M, Morrison A, Tran K, Miguelez M, Lewin G

Introduction

The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise, and synthesize the human evidence for the effects of omega-3 fatty acids on eye health. The review was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It was undertaken as part of a consortium involving three Evidence-based Practice Centers (EPCs), which investigated the value of omega-3 fatty acid supplementation across eleven health/disease areas. The three EPCs are Southern California-RAND, Tufts-New England Medical Center, and the University of Ottawa. To ensure consistency of approach, the three EPCs collaborated on selected methodologic elements, including literature search strategies, rating of evidence, and data table design.

Visual health is a broad topic, yet we focused on eye health conditions that have a large public health impact in North America. Impact was defined in various ways. Our definition encompassed conditions that either demonstrate high prevalence (e.g., diabetic retinopathy, age-related macular degeneration [ARMD], and retinal vascular occlusions), produce many potential years of vision loss in that they affect the young (e.g., retinitis pigmentosa [RP]), or constitute a challenge to health services in no small part because they are costly to treat (e.g., cataracts).

The brain and eye are highly enriched with omega-3 fatty acids, which accumulate in these tissues during late fetal and early neonatal life.[1] Very high levels of docosahexaenoic acid (DHA) are present in the retina, specifically in the disk membranes of the outer segments of photoreceptor cells. DHA accounts for over half the total fatty acyl groups present in the phospholipids of rod outer segment membranes, a proportion higher than is found in any other tissues.[2] Its specific role, however, is not well understood. The role of DHA may be related to its biophysical effects on the cell membrane. DHA influences the biophysical properties of membranes via its high polyunsaturation, and may help to create a membrane that accommodates the dynamic behavior of rhodopsin during the photoreceptive process.[3-5] In addition, DHA may modulate the activity of membrane bound enzymes and receptors, and the kinetics of membrane transport systems, as well as being a precursor for the synthesis of other biologically active molecules.

A number of studies in preterm and term human infants have suggested that a dietary supply of omega-3 fatty acids may be essential for optimal visual development.[6-8] Finally, animal data suggest that retinal degeneration in rats might be prevented by dietary intake of DHA,[9] and DHA administered before ischemia may

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reduce pressure-induced retinal damage in monkeys.[10] It is against this backdrop that the key questions were investigated. Our project's overarching goal was to systematically review the human evidence to help develop a research agenda.

Key Questions

The key questions are organized by type of eye disease or visual impairment.

Degenerative diseases of the retina—macular degeneration:

- What is the evidence for efficacy of omega-3 fatty acids in preventing ARMD and slowing the progression of ARMD?
- What is the evidence that omega-3 fatty acids decrease the rate of progression to advanced forms of macular degeneration in all patients, diabetics, and patients with cataracts?
- What is the evidence that omega-3 fatty acids decrease the rate of progression of advanced forms of macular degeneration in all patients, diabetics, and patients with cataracts?

Degenerative diseases of the retina—retinitis pigmentosa:

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of RP (i.e., an inherited retinal dystrophy)?

Vascular diseases of the retina—retinal vein or retinal artery occlusions:

- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal vein occlusion and retinal artery occlusion?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal vein occlusion and retinal artery occlusion?

Vascular diseases of the retina in diabetics:

- What is the evidence for efficacy of omega-3 fatty acids in preventing proliferative retinopathy in diabetics?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of proliferative retinopathy in diabetics?
- What is the evidence for efficacy of omega-3 fatty acids in preventing clinically significant macular edema in patients with diabetic retinopathy?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of clinically significant macular edema in patients with diabetic retinopathy?

Cataracts:

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related cataracts?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in all patients, diabetics, and patients with ARMD?
- What is the evidence that omega-3 fatty acids decrease the rate of cataract surgery in aging populations?

Adverse events:

- What is the evidence for the risk of short- and long-term adverse events related to the intake of omega-3 fatty acids?

Methods

A Technical Expert Panel was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Several electronic databases were searched: MEDLINE® (1966–November Week 2 2003 and updated to February Week 1 2004), PreMEDLINE® (May 4, 2004), EMBASE (1980 to 2003 Week 48 and updated to 2004 Week 7), the Cochrane Library including the Cochrane Central Register of Controlled Trials (3rd Quarter 2003), and CAB Health (1973–Dec 2003). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search elements included: scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid (EPA); omega-3 fatty acids; MaxEPA®); and, relevant population terms (e.g., macular degeneration). Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts. A

final set of 507 unique references was identified and posted to an Internet-based software system for review.

Studies were considered relevant if they described live human populations of any age, investigated the use of any source, type, dose, or method to deliver omega-3 fatty acids as primary or secondary prevention for any of the above-noted eye health conditions in any of the populations or subpopulations of interest (e.g., diabetics), and investigated at least one pertinent clinical outcome (e.g., prevalence, incidence; change in clinical status; need for cataract surgery). No restrictions were placed on the requisite levels of evidence (i.e., study designs) given the expected dearth of studies. As markers of omega-3 fatty acid metabolism, the following fatty acid compositions or concentrations, from any source (e.g., red blood cell membranes, plasma phospholipids), were considered relevant: EPA, DHA, arachidonic acid (AA)/EPA, AA/DHA, and AA/EPA+DHA.

Two initial levels of screening for relevance, and two reviewers per level, were employed (directed at bibliographic records, then full articles). Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[11] Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Abstraction

Following a calibration exercise, two reviewers independently abstracted the contents of included studies using an electronic Data Abstraction form developed especially for this review. A third reviewer then verified the data. Data abstracted included characteristics of the following:

- Report (e.g., publication status, language of publication, year of publication).
- Study (e.g., sample size, research design, number of study arms/groups).
- Population (e.g., age; diagnosis, including severity, duration, and comorbidity).
- Intervention/exposure (e.g., omega-3 fatty acid types, sources, doses, and intervention/exposure length), and comparator(s).
- Cointerventions (e.g., concurrent treatments/medications, omega-6 fatty acid use).
- Withdrawals and dropouts, including reasons.
- Clinical outcomes.
- Fatty acid content of biomarkers.
- Adverse events (e.g., side effects).

Data Synthesis

A summary table provided a question-specific overview of included studies' relevant data presented in greater detail in evidence tables. A question-specific summary matrix situated each study in terms of its quality (i.e., internal validity) and applicability ratings (i.e., generalizability to the North American population). Question-specific qualitative syntheses of the evidence were derived. While no restrictions were placed on study designs, greater interpretative weight was given to prospective and controlled designs. Given the paucity of relevant studies addressing any given question, as well as the variability in the research designs, definitions of the study populations, exposures/interventions or clinical outcomes employed to investigate it, meta-analysis was deemed impossible or inappropriate with respect to each of the questions.

Results

Sixteen unique studies were identified, which addressed nine of the 23 questions posed by our project. Only two studies were randomized clinical trials (RCTs).[12,13] The vast majority of investigations employed either a before-after or observational study design. The paucity of interventional studies involving omega-3 fatty acids delivered as supplementation made it difficult to ascertain the rates or types of harm. The single, placebo-controlled RCT systematically reporting harm data revealed few minor, mainly gastrointestinal, effects associated with low-dose DHA supplementation.[13]

The most-frequently investigated question concerned the primary prevention of ARMD.[14-19] Designs included a single prospective cohort study,[16] two case-control studies,[14,15] one retrospective population-based cohort study,[19] and two single population cross-sectional studies.[17,18] There are sufficient between and within study conflicts (e.g., results of univariate vs. multivariate analyses) in the results to preclude drawing any inference that is conclusive with respect to the value of the intake of omega-3 fatty acids to prevent ARMD. If it can be assumed that the study designs likely best suited to address this question should be both controlled and prospective, none of the included studies would qualify. The only prospective study included a large sample and appropriately conducted multivariate analysis, and controlled for key confounders.[14] These investigators observed that the consumption of canned

tuna fish or more than four fish servings per week each played a protective role against ARMD. However, their results also indicated that several types of oily fish well known to have high concentrations of DHA and EPA (i.e., sardines, mackerel) failed to show a similar, protective effect. These discordant observations will require an explanation before anything conclusive can be asserted based on this study alone. Moreover, their study design did not *a priori* employ a separate, unexposed cohort as a control. The remaining studies cannot resolve the divergent primary prevention results described by this study, even though each of the former failed to demonstrate a statistically significant association between exposure and outcome.[14,15,17-19] Foremost among reasons is the use of research designs that constitute less than ideal strategies to investigate this question. These studies also varied in their definitions of the exposure, clinical outcome, and/or confounders, which together make it impossible to draw a definitive conclusion regarding the potential of the intake of omega-3 fatty acids to prevent the onset of either early or late ARMD.

The nature of the RCT design and the "cocktail-like" exposure employed by Scorolli et al. made it impossible to isolate the specific impact of omega-3 fatty acids on slowing the progression of ARMD.[12] A small sample size, the uncommonness and dubious clinical relevance of the visual recovery outcome, low study quality, and little or no applicability to the North American population suggest that there are, at present, no data with which to meaningfully address this research question.

Seddon et al.'s single prospective cohort study found that fish intake did not affect the progression to advanced ARMD overall, or in a high linoleic acid (LA) consumption group, but did protect against the progression to advanced ARMD in the low (below median consumption) LA consumption group.[20] This parallels what was observed exclusively via a significant test for trend in the Seddon et al. study described earlier with reference to its investigation of the influence of the intake of omega-3 fatty acids on preventing the onset of advanced ARMD.[15] However, the results from neither study can be used as yet to provide a conclusive answer to their respective research questions. Both require replication and a plausible explanation.

The four studies examining whether the intake of omega-3 fatty acids slows the progression of RP do not provide a conclusive answer to this question.[13,21,22] Hoffman et al.'s good quality RCT constituted the most rigorous test and revealed conflicting results.[13] That said, rod and cone functional loss showed effect modification by age, with rod loss significantly reduced in the prepuberty group supplemented with DHA compared with placebo, and cone loss significantly reduced in the post-puberty group supplemented with DHA compared with placebo. The observation that certain analyses failed to reveal statistically significant between-group differences could be explained by this having been an underpowered trial.[13]

By virtue of its research design, which did not permit the isolation of the specific impact of omega-3 fatty acids on slowing the progression of RP, results from Dagnelie et al.'s Internet-based comparative before-after study cannot be used to meaningfully address this question.[21] In Hoffman et al.'s two very small noncomparative before-after studies of short duration, electroretinogram results did not reveal statistically significant changes following supplementation.[22] Thus, until Hoffman et al.'s RCT[13] is replicated with a much larger sample size, little that is conclusive can be said about the potential value of the intake of omega-3 fatty acids in slowing the progression of RP.

Sorokin et al.'s noncomparative before-after study received a low study quality score and failed to resolve the questions of whether the intake of omega-3 fatty acids can slow the progression of either proliferative retinopathy or clinically significant macular edema in patients with diabetic retinopathy.[23] This study did not constitute the best test of either of these possibilities, however. The most relevant clinical outcome by North American standards entailed fundus assessments, yet few details were reported. Covariates were not measured, and the univariate analysis of the data was flawed. Thus, the results of this study are inconclusive with respect to these two possible benefits of the intake of omega-3 fatty acids in diabetic retinopathy.

Although both the Arnarsson et al.[24] and Cumming et al.[25] studies are well known population-based risk factor studies, in neither of them was the association between the intake of foods or oils containing omega-3 fatty acids and age-related cataract prevalence the primary question. That said, no statistically significant associations were observed. Cross-sectional designs constitute very limited evaluations of this question.

Suzuki et al.'s noncomparative before-after study did not assess cataract status as its clinical outcome, preferring instead to examine visual acuity.[26] Thus, with improvements in visual acuity unlikely to have been produced by reduced cataract formation, this study does not directly address the question of whether the intake of omega-3 fatty acids can slow the rate of progression of age-related cataracts.

A paucity of data prevented us from examining the possible influence on efficacy, association, or safety evidence of various covariates, which included both population (e.g., age at onset or diagnosis, smoking, alcohol consumption) and intervention/exposure factors (e.g., source, type, dose, and method to deliver omega-3 fatty acids; intake of omega-6 fatty acids).

Discussion

Based on the studies identified by this review, it is apparent that clinical research has only scratched the surface with respect to understanding the possible utility of the intake of omega-3 fatty acids as a primary or secondary prevention in eye health. Moreover, seen from the point of view of clinical research's typical, linear arc—which moves from basic science to observational research to RCTs, and culminating in the systematic review/meta-analysis of the observations obtained by these primary studies—there is a paucity of solid observational research with which to construct an experimental framework affording the meaningful conduct of RCTs. For example, there is little understanding of the exact sources, types, and doses of omega-3 fatty acids, or even the possible duration of their use, which might usefully serve as definitions of a prevention-centered "intervention" for any of the eye diseases/visual impairments examined in our review. Moreover, a single study reporting adverse event data likely does not permit laying to rest all possible concerns regarding the short- or long-term safety of such an intervention.

It is therefore our view that much more research will need to be conducted before anything conclusive can be asserted with respect to the effects of omega-3 fatty acids on eye health. It is also our understanding that sorting out the possible benefits of the intake of omega-3 fatty acids in eye health might profit from taking into consideration the impact of the concurrent intake of omega-6 fatty acids and, by definition, the omega-6/omega-3 fatty acid intake ratio. Finally, any notable causal or correlational relationships observed between the omega-6/omega-3 fatty acid intake ratio and the development or progression of eye disease/visual impairment may then be "explained" by future studies, which focus on observing patterns of omega-6/omega-3 fatty acid content in peripheral, or even brain, biomarkers.

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 University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021. It is expected to be available in July 2005. 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. 117, *Effects of Omega-3 Fatty Acids on Eye Health*. 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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Evidence Report

Chapter 1. Introduction

This evidence report by the University of Ottawa's Evidence-Based Practice Center (EPC) concerning the effects of omega-3 fatty acids on eye health is one among several that address topics related to omega-3 fatty acids that were requested and funded by the Office of Dietary Supplements (ODS), National Institutes of Health (NIH), through the EPC program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-New England Medical Center (Tufts-NEMC) EPC, the Southern California-RAND (SC-RAND) EPC, and the University of Ottawa EPC (UO-EPC)—each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

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

The focus of this report is on eye health outcomes in humans (i.e., eye disease/visual impairment). In this chapter, the metabolism, physiological functions, and sources of omega-3 fatty acids are briefly discussed. This constitutes background material, placing in context the data presented in the evidence report. As well, the description of the U.S. population's intake of omega-3 fatty acids is provided in response to a general question posed within the task order (i.e., project). This introductory material is then complemented by a brief review of the epidemiology and issues (e.g., risk factors) related to the types of eye disease/visual impairment of interest to the review. This brief overview is designed to orient the reader rather than to serve as a comprehensive description.

Chapter 2 describes the methods used to identify, review and synthesize the results from studies concerning omega-3 fatty acids in eye health. Chapter 3 presents the findings of studies meeting eligibility criteria, with discussion points—including recommendations for future research—completing the report in Chapter 4.

Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. It encompasses saturated fatty acids (SFAs), which are usually solid at room temperature, and unsaturated fatty acids (UFAs), which are liquid at room temperature. UFAs can be further divided into monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs). PUFAs can be classified, on the basis of their chemical structure, into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The omega-3 or *n-3* notation means that the first double bond in this family of PUFAs is 3 carbons from the methyl end of the molecule. The same principle

applies to the omega-6 or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (i.e., 9 kcal/g or 37 kJ/g).

Of all fats found in food, two—alpha-linolenic acid (chemical abbreviation: ALA; 18:3 n-3) and linoleic acid (LA; 18:2 n-6)—cannot be synthesized in the human body, yet these are necessary for proper physiological functioning. These two fats are thus called "essential fatty acids" (EFAs). The EFAs can be converted in the liver to long-chain PUFAs (LC PUFAs), which have a higher number of carbon atoms and double bonds. These LC PUFAs retain the omega type (n-3 or n-6) of the parent essential fatty acids.

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

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

As shown in Figure 1, eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3) can act as competitors for the same metabolic pathways as arachidonic acid (AA; 20:4 n-6). In human studies, the analyses of fatty-acid compositions in both blood phospholipids and adipose tissue have shown a similar competitive relationship between omega-3 LC PUFAs and AA. General scientific agreement supports an increased consumption of omega-3 fatty acids and reduced intake of omega-6 fatty acids to promote good health. However, for omega-3 fatty acid intake, the specific quantitative recommendations vary widely among countries not only in terms of different units—ratio, grams, total energy intake—but also in quantity.[3] Furthermore, there remain numerous questions relating to the inherent complexities concerning omega-3 and omega-6 fatty acid metabolism, in particular the relationships between the two fatty acids. For example, it remains unclear to what extent ALA is converted to EPA and DHA in humans, and to what extent the high intake of omega-6 fatty acids compromises any benefits of omega-3 fatty acid consumption. Without the resolution of these two fundamental questions, it remains difficult to study the importance of the omega-6/omega-3 fatty acid ratio.

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

Omega-3 and omega-6 fatty acids share the same pools of enzymes and go through the same oxidation pathways while being metabolized (Figure 1). Once ingested, the parent of the omega-3 fatty acids, ALA, and the parent of the omega-6 fatty acids, LA, can be elongated and desaturated into LC PUFAs. LA is converted into gamma-linolenic acid (GLA; 18:3 n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the long-chain omega-6 fatty acid, AA, while ALA can be converted, to a lesser extent, to the long-chain omega-3 fatty acids, EPA and DHA. However, the conversion from parent fatty acids into LC PUFAs occurs slowly in humans, and conversion rates are not well understood. Because of

the slow rate of conversion, and the importance of LC PUFAs to many physiological processes, humans must augment their level of LC PUFAs by consuming foods rich in these important compounds. Meat is the primary food source of AA, and fish is the primary food source of EPA.

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

As shown in Figure 1, the long-chain omega-6 fatty acid, AA, is the precursor of a group of eicosanoids including series-2 prostaglandins (PG_2) and series-4 leukotrienes (LT_4). The omega-3 fatty acid, EPA, is the precursor to a group of eicosanoids including series-3 prostaglandins (PG_3) and series-5 leukotrienes (LT_5). The series-2 prostaglandins and series-4 leukotrienes derived from AA are involved in intense actions (such as accelerating platelet aggregation, and enhancing vasoconstriction and the synthesis of mediators of inflammation) in response to physiological stressors. The series-3 prostaglandins and series-5 leukotrienes derived from EPA are less physiologically potent than those derived from AA. More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate excessive series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins, which are derived from the omega-3 fatty acid, EPA, may protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus and asthma.[4] In addition, animal studies have demonstrated that omega-3 LC PUFAs, such as EPA and DHA, engage in multiple cytoprotective activities that may contribute to antiarrhythmic mechanisms.[5] Arrhythmias are thought to be the cause of "sudden death" in heart disease.

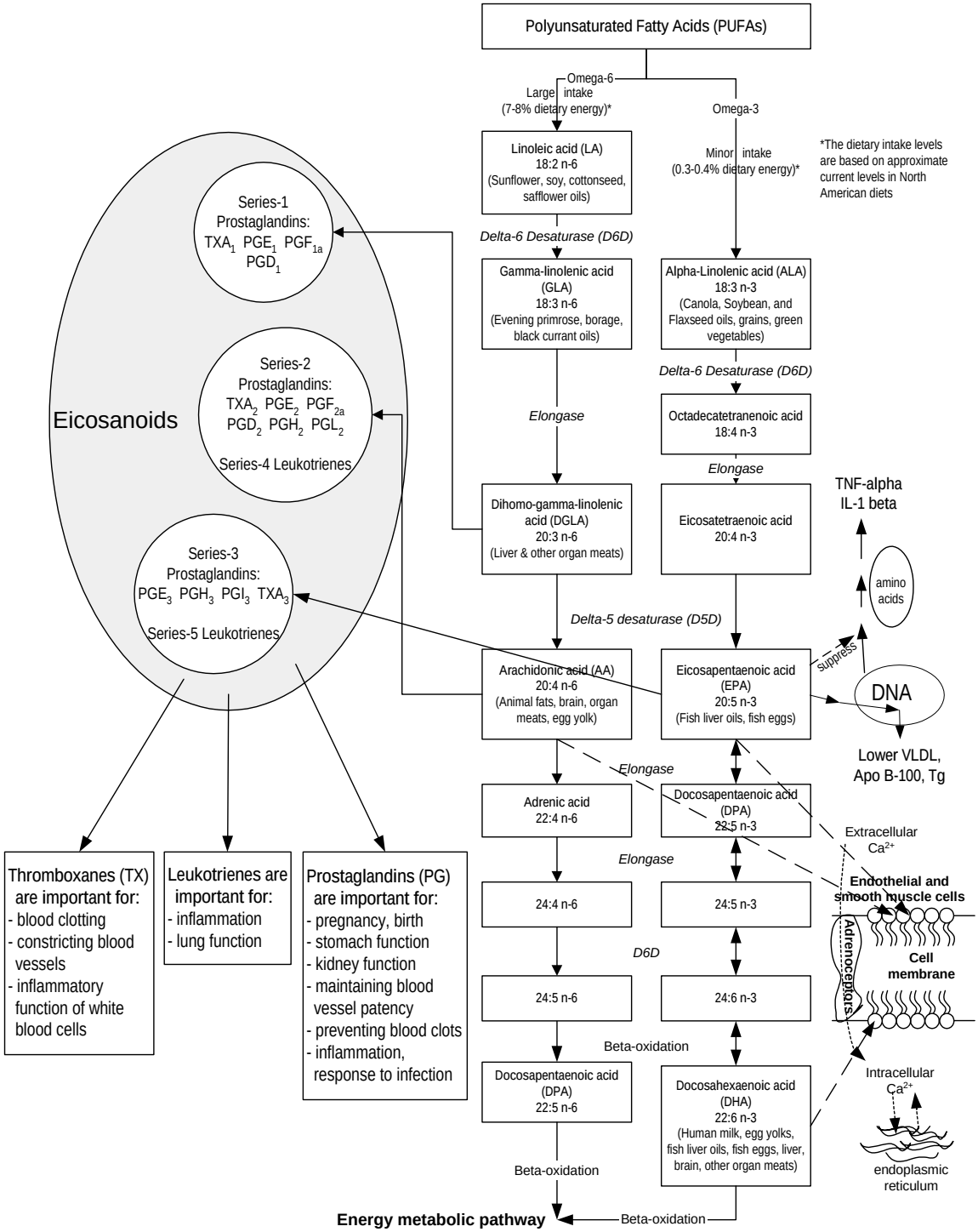
In addition to affecting eicosanoid production as described above, EPA also affects lipoprotein metabolism and decreases the production of other compounds—including cytokines, interleukin 1 (IL-1), and tumor necrosis factor (TNF-)—which have pro-inflammatory effects. These compounds exert pro-inflammatory cellular actions that include stimulating the production of collagenase and increasing the expression of adhesion molecules necessary for leukocyte extravasation.[6] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs remains unknown, although suppression of eicosanoid production by omega-3 fatty acids may be involved. EPA can also be converted into the longer chain omega-3 form of docosapentaenoic acid (DPA, 22:5 n-3), and then further elongated and oxygenated into DHA. EPA and DHA are frequently referred to as VLN-3FA—very long chain n-3 fatty acids. DHA, which is thought to be important for brain development and functioning, is present in significant amounts in a variety of food products, including fish, fish liver oils, fish eggs, and organ meats. Similarly, AA can convert into an omega-6 form of DPA.

Studies have reported that omega-3 fatty acids decrease triglycerides (TG) and very low density lipoprotein (VLDL) in hypertriglyceridemic subjects, concomitant with an increase in high density lipoprotein (HDL). However, they appear to increase or have no effect on low density lipoprotein (LDL). Omega-3 fatty acids apparently lower TG by inhibiting VLDL and apolipoprotein B-100 synthesis, and decreasing post-prandial lipemia.[7] Omega-3 fatty acids, in

conjunction with transcription factors (small proteins that bind to the regulatory domains of genes), target the genes governing cellular TG production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for TG production.[8]

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

Figure 1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acids in regulating health/disease markers



U.S. Population Intake of Omega-3 Fatty Acids

The major source of omega-3 fatty acids is dietary intake of fish, fish oil, vegetable oils (principally canola and soybean), some nuts such as walnuts, and, dietary supplements. Two population-based surveys, the third National Health and Nutrition Examination (NHANES III) 1988-94, and the Continuing Survey of Food Intakes by Individuals 1994-98 (CSFII), are the main sources of dietary intake data for the U.S. population. NHANES III collected information on the U.S. population aged ≥2 months. Mexican Americans and non-Hispanic African-Americans, children ≤5 years old, and adults ≥ 60 years old were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall.

The CSFII 1994-96, popularly known as the "What We Eat in America" survey, addressed the requirements of the National Nutrition Monitoring and Related Research Act of 1990 (Public Law 101-445) for continuous monitoring of the dietary status of the American population. The CSFII 1994-96 utilized an improved data-collection method for 24-hour recall known as the multiple-pass approach. Given the large variation in intake from day-to-day, multiple 24-hour recalls are considered to be best suited for most nutrition monitoring and will produce stable estimates of mean nutrient intake from groups of individuals.[9] In 1998, the Supplemental Children's Survey, a survey of food and nutrient intake by children under the age of 10 years, was conducted as a supplement to the CSFII 1994-96. The CSFII 1994-96, 1998 surveyed 20,607 people of all ages with over-sampling of low-income population (<130% of the poverty threshold). Dietary intake data from individuals of all ages were collected over two nonconsecutive days via two one-day dietary recalls.

Table 1 reports the NHANES III survey mean intake ± the standard error of the mean (SEM), in addition to the median and range for each omega-3 fatty acid. Distributions of EPA, DPA, and DHA were very skewed; therefore, the means and standard errors of the means should be used and interpreted with caution. Table 2 reports the CSFII survey mean and median intakes for each omega-3 fatty acid, along with SEMs, as reported in the Dietary Reference Intakes from the Institute of Medicine.[2]

Table 1: Estimates of the mean±standard error of the mean (SEM) intake of linoleic acid (LA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the US population, based on analyses of a single 24-hour dietary recall of NHANES III data

	Grams/day		% Kcal/day	
	Mean±SEM	**Median (range)[1]**	**Mean±SEM**	**Median (range)[1]**
LA (18:2 n-6)	14.1±0.2	9.9 (0 - 168)	5.79±0.05	5.30 (0 - 39.4)
ALA (18:3 n-3)	1.33±0.02	0.90 (0 - 17)	0.55±0.004	0.48 (0 - 4.98)
EPA (20:5 n-3)	0.04±0.003	0.00 (0 - 4.1)	0.02±0.001	0.00 (0 - 0.61)
DHA (22:6 n-3)	0.07±0.004	0.00 (0 - 7.8)	0.03±0.002	0.00 (0 - 2.86)

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

Table 2: Mean, range, median, and standard error of the mean (SEM) of usual daily intakes of linoleic acid (LA), total omega-3 fatty acids (n-3 FA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in the US population, based on CSFII data (1994-1996, 1998)

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

Dietary Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be found in many different sources of food, including fish, shellfish, some nuts, and various plant oils. Selected from the USDA website, Table 3 lists the amount of omega-3 fatty acids in some commonly consumed fish, shellfish, nuts, and edible oils.[10]

Table 3: The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils that contain at least 5 g omega-3 fatty acids per 100 g

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

Trace = <0.1; - = 0 or no data; Sp. = species; [a]Except as indicated; [b]Lox.; [c]Solids with bone and liquid; [d]Drained solids with bone; [e]Drained solids.

Eye Health: An Increasingly Important Public Health Issue

Eye health is becoming an increasingly important public health concern due primarily to the rapid aging of populations in most countries. Worldwide, it is estimated that 45 million people are blind or visually impaired, and an additional 145 million people have low vision.[11] Over 80% of these individuals are living in underdeveloped countries. In the US, blindness or low vision affects 3.3 million people over the age of 40, or one in 28 people in that age group.[12] With the number of people aged 50 years or older expected to increase in upcoming decades, this number is expected to increase to 5.5 million Americans or 76 million people worldwide by the year 2020.[12]

Low vision, or visual impairment, describes individuals whose eyesight cannot be corrected with eyeglasses, contact lenses, medication or surgery.[13] The World Health Organization (WHO) defines low vision as visual acuity between 20/70 and 20/400 with the best possible correction, or a visual field of 20 degrees or less. Blindness is defined as visual acuity worse than 20/400, with correction, or a visual field of 10 degrees or less. In the US, a person is said to be "legally blind" if they have a visual acuity of 20/2000 or worse with correction, or a visual field of 20 degrees or less.[13]

The specific cause of the visual impairment, particularly blindness, varies by race and/or ethnicity.[12] Of the approximately one million Americans over the age of 40 who are blind, macular degeneration is its leading cause in the White population, whereas cataracts and glaucoma account for more than 60% of the cases in the Black population. Cataracts are the leading cause of low vision among White, Black and Hispanic persons. Both men and women appear to be equally affected by blindness and visual impairment.[12]

Diabetic eye disease—a group of eye diseases afflicting individuals with diabetes—is also a common cause of visual impairment. Diabetic retinopathy, the most common of these diseases, affects an estimated 5.3 million Americans over the age of 18 and is the leading cause of new cases of blindness in the US, accounting for an estimated 8,000 new cases of blindness each year.[14] It is the most important cause of visual impairment and blindness in the working age population. Individuals with diabetes are also 60% more likely to develop cataracts during their lifetime than people without diabetes. In addition, cataracts develop at a younger age and progress faster in individuals with diabetes.[15]

Children are less likely to be affected by visual impairment. Data reported by the Lighthouse National Center for Vision and Child Development, based on statistics from the 1994 National Health Interview Survey, indicate that approximately 1% of American children under the age of 18, or over 600,000 children, are visually impaired, indicating that they are blind in one or both eyes, or have difficulty seeing even with corrective lens. The majority of cases of childhood visual impairment are due to developmental or congenital abnormalities.[16]

Economic Burden of Visual Impairment

The Centers for Disease Control and Prevention have estimated that for all persons born in the year 2000 with a visual impairment, the lifetime cost to the patient, health care system and society, will total $2.5 billion (in 2003 US dollars).[17] Direct costs, which include doctor visits,

prescription drugs, inpatient hospital stays, as well as nonmedical expenses such as home modifications and special education, make up approximately 22% of the cost. Indirect costs, which account for 77% of the cost, include lost wages due to lost work or premature death. These estimates do not, however, include additional expenses such as hospital outpatient or emergency department visits; hence, the actual economic burden of vision impairment is substantial.

Vascular Diseases of the Retina

Retinal vascular diseases include those eye diseases that affect the blood vessels of the retina and consequently damage the inner to mid retinal tissue. The most common retinal vascular diseases include diabetic eye diseases and vascular occlusions.

Retinal Vessel Occlusion

Retinal vessel occlusions occur when the retinal arteries (retinal artery occlusion) or retinal veins (retinal vein occlusion) become occluded, decreasing the oxygen supply to the retina. The blockage is usually caused by a blood clot, fat deposit, or fragment of atherosclerotic plaque, and is usually associated with an underlying disorder such as hypertension, diabetes or atherosclerosis. Both retinal vein occlusion and retinal artery occlusion result in a sudden, painless loss of vision in the involved eye. Clinical examination of the eye reveals diffuse ischemia marked by a pale whitening (artery occlusion) or a swelling or edema of the retina with marked tortuosity in vascularity (vein occlusion).

Next to diabetic retinopathy, retinal vein occlusion is the second most common retinal vascular disease. Occlusion of a retinal vein results in variable vision loss depending on its extent and location. There is also an increased risk for developing glaucoma with large occlusions. Treatments for retinal vein occlusions include acetylsalicylic acid and/or laser therapy.

Like retinal vein occlusion, the degree of vision loss in retinal artery occlusion depends on the extent and location of the occlusion. Treatments for retinal artery occlusions, which tend to produce very unsatisfactory results, include inhalation of carbon monoxide/oxygen mixtures to displace the clot, paracentesis, eye pressure lowering agents and, depending on the cause, systemic anticoagulation.

Diabetic Retinopathy

Diabetic retinopathy is the most common eye complication from diabetes (both type I and type II diabetes) and is a leading cause of blindness in the diabetic population. There are an estimated 10.2 million adults 40 years or older in the US with diabetes, the majority of whom will experience some degree of diabetic retinopathy during the course of their disease.[18]

Diabetic retinopathy occurs when the blood vessels of the retina become damaged. In its earliest stages, the blood vessels may form tiny blebs that often result in microaneurysms that appear as red dots on clinical examination. This mild form of diabetic retinopathy is referred to as nonproliferative retinopathy and is very common in individuals with diabetes. It usually has

no effect on vision and, even if detected, it is left untreated. In some instances, however, the weakened capillary walls may become more permeable, losing their ability to control the passage of substances between the blood and the retina, including serum, blood cells, proteins, fats and other large molecules. When this process occurs in the macula, "clinically significant macular edema" results, which is the most common cause of visual loss in diabetic patients. Macular edema can occur at any stage of diabetic retinopathy, although it is more likely to occur in later stages of the disease. Klein et al. found that, over a 10-year period, the incidence of macular edema was 20% in individuals diagnosed with diabetes before the age of 30 and 25% in individuals diagnosed after the age of 30.[19]

In some individuals, diabetic retinopathy progresses to the more advanced form called proliferative retinopathy. This occurs when multiple areas of the retina have lost their blood supply. In response, angiogenic factors are released by the retinal cells to stimulate the development of new blood vessels. These new blood vessels tend to be weak, however, and can result in the leakage of blood into the vitreous humor. Like all hemorrhagic processes, remodeling and scar tissue can result, leading to a severe form of retinal detachment—tractional retinal detachments. Individuals with tractional retinal detachments involving the macula have a very poor prognosis.

Degenerative Retinal Diseases

Macular Degeneration

Macular degeneration is a group of diseases characterized by the progressive deterioration of the macula, leading to loss of central vision while peripheral vision is maintained. Age-related macular degeneration is the most common form and is the leading cause of visual loss in adults over the age of 55. Macular degeneration rarely affects younger individuals; however, early-onset forms of macular degeneration do exist, the majority of which are inherited.

Stargardt disease is the most common form of inherited juvenile macular degeneration, with an estimated incidence of 1 in 10,000.[20] It usually begins to damage the macula of both eyes between the ages of 6 and 20, although symptoms may not be immediately apparent. The disease is usually diagnosed when children begin to complain about dark or hazy spots in the center of their field of vision. It may also take longer for their eyes to adjust from light to dark environments. Clinical examination reveals the presence of a macular lesion surrounded by yellow-white flecks. Progression of the disease is variable; however, once a visual acuity of 20/40 is reached, there is often a rapid progression of the disease. By the age of 50, approximately 50% of individuals with Stargardt's disease will have visual acuities of 20/200 or worse. Generally, night vision is not affected but there may be noticeable loss of color vision in late stages of the disease. Recently, the gene responsible for Stargardt's disease, the ABCR gene, has been isolated.[20] Mutations in the gene result in a dysfunctional protein necessary for energy transport to and from photoreceptor cells in the retina.

Increasing age is the most important risk factor for developing age-related macular degeneration. One commonly believed pathogenic mechanism involves age-related changes to the retinal pigment epithelium; as people age, the retinal pigment epithelium, the outermost layer of the retina, begins to slowly deteriorate. The retinal pigment epithelium is a critical

passageway for nutrients and wastes between the retina and the underlying layer of choroidal blood vessels. When the retinal pigment epithelium begins to deteriorate, the nutritional and waste-removing cycles involving the retina and the underlying layer of blood vessels, which nourish the cones and rods of the retina, is interrupted. This leads to damage to the light-sensitive cells of the macula. Studies have demonstrated that genetic and environmental factors such as smoking and nutrition contribute to the disease.[14,21] Women are more likely than men to develop the disease and since they tend to live longer, women are more likely to suffer from severe vision loss due to the disease.

There are two types of macular degeneration, wet and dry. Dry macular degeneration is the most common, accounting for 85% to 90% of cases of macular degeneration.[21] Dry macular degeneration is associated with the formation of drusen—small yellow spots of acellular debris that form under the basement membrane of the retinal pigment epithelium as a result of interruption of the waste-removing cycles between the retinal and the underlying blood vessels. Almost all individuals over the age of 50 have small drusen in one or both eyes. However, for individuals with large and multiple drusen, symptoms may include decreased central visual quality (resulting in a need for increasingly bright illumination for reading or close-up work), blurry vision, or a blind spot in a person's central vision. The treatment for dry age-related macular degeneration is multivitamins rich in antioxidants.[22]

Although age-related macular degeneration always begins as the dry form, it may progress to the wet form. Wet macular degeneration is less common but accounts for nearly 90% of the severe vision loss experienced by individuals with macular degeneration. It occurs when new choroidal blood vessels, formed to improve the blood supply to the oxygen-deprived retina, rupture and cause bleeding and damage to the surrounding tissue. Loss of vision is usually rapid and severe. Laser treatment may be effective at slowing the rate of vision loss by sealing off the newly-formed leaky vessels.

Retinitis Pigmentosa

Retinitis pigmentosa is a group of inherited eye diseases that cause degeneration of the photoreceptor cells of the retina. In most forms of retinitis pigmentosa, the rod cells are the first to be affected. Early degeneration of rod cells results in night blindness. Symptoms are most often recognized in children, adolescents and young adults. As the disease progresses throughout an individual's life, and more rod cells degenerate, patients lose their peripheral vision and in advanced cases, their central vision.

Cataracts

Cataracts are a clouding of the lens of the eye that is severe enough to impair vision. Generally, increasing age is the single greatest risk factor for developing cataracts, with as many as 70% of Americans over the age of 75 having cataracts. Cataracts are caused by changes in the protein fibres that make up the lens of the eye. As a person ages, the protein fibres degenerate, causing the lens to become less flexible, thicker, and subsequently less transparent. Surgery to remove the clouded lens and replace it with a clear lens implant is currently an effective treatment option for cataracts. Cataract surgery is one of the most frequently performed

surgeries in the US at this time, and hence is one of the most important economic and health service issues in all Western health care systems.

In addition to the contribution from ageing, damage from free radicals, smoking and exposure to UV light may also contribute to the development of cataracts. Cataract development has also been associated with cardiovascular disease, diabetes and renal and gastrointestinal disease.[23,24] For example, individuals with diabetes are 60% more likely to develop a cataract. In addition, a number of epidemiological studies have implicated a role for nutrition in the development of cataracts.[14,25,26]

Omega-3 Fatty Acids and the Eye

The brain and eye are highly enriched with omega-3 fatty acids, which accumulate in these tissues during late fetal and early neonatal life.[27] A number of studies in preterm and term human infants have suggested that a dietary supply of omega-3 fatty acids is essential for optimal visual development.[28-30] This evidence is systematically reviewed in our UO-EPC evidence report titled "Effects of Omega-3 Fatty Acids on Child and Maternal Health."

Very high levels of DHA are present in the retina, specifically in the disk membranes of the outer segments of photoreceptor cells. DHA accounts for over half the total fatty acyl groups present in the phospholipids of rod outer segment membranes, a proportion higher than is found in any other tissues.[31] Rod outer segments are unique specialized structures composed of stacks of membranous discs that contain photosensitive proteins which detect and respond to light, thereby initiating the visual process. Rod outer segment membranes are constantly being renewed; however, DHA turnover in the retina is surprisingly slow.[32,33] Furthermore, high levels of DHA appear to be maintained in the retina despite reductions in dietary intakes of omega-3 fatty acids.[34]

The high DHA content, and its specific and consistent tissue distribution, suggests that DHA has an important functional role in the retina.[35] Its specific role, however, is not well understood. The role of DHA may be related to its biophysical effects on the cell membrane. DHA influences the biophysical properties of membranes via its high polyunsaturation, and may help to create a membrane that accommodates the dynamic behavior of rhodopsin during the photoreceptive process.[36-38] In addition, DHA may modulate the activity of membrane bound enzymes and receptors, and the kinetics of membrane transport systems, as well as being a precursor for the synthesis of other biologically active molecules. A recent study suggests that DHA plays a role in modulating G-protein coupled signaling pathways that are involved in visual transduction.[38]

The lipid composition of cell membranes is affected by dietary factors, and the synthesis of phospholipids and their modification via polar head and acyl group turnover are metabolically regulated.[39] Thus, it is possible that with certain extrinsic (metabolic) and intrinsic (dietary) conditions, a reduction in DHA in the outer segment membranes could occur that would be expected to alter their physical and functional properties. A number of studies have shown that, in animals, dietary deprivation of DHA results in abnormal electroretinograms and visual impairment which is accompanied by lower retinal levels of DHA-phospholipids.[40,41] In the eye, omega-3 LC PUFAs are stored mainly in phospholipids. Moreover, animal data suggest that

retinal degeneration in rats might be prevented by dietary intake of DHA,[42] and DHA administered before ischemia may reduce pressure-induced retinal damage in monkeys.[43]

In addition to its role in the development of vision and retinal functioning, it has been suggested that DHA may also be beneficial in eye diseases that are associated with atherosclerosis of the blood vessels that supply the retina.[44] Analogous to DHA's effect on coronary artery atherosclerosis, DHA may prevent and treat atherosclerosis of the blood vessels of the eye by inhibiting the development of plaques and blood clots.[45] Pathogenic factors and processes activate fatty acid cleavage enzymes and make them available as a substrate pool for important biological chemicals such as cyclooxygenase, lipoxygenase, aspirin, and endocannabinoid synthetic enzymes.

In the human biosystem, an optimal balance between omega-3 and omega-6 fatty acids is likely essential for normal neuronal function, and it has been suggested that the current imbalance in the omega-6 to omega-3 fatty acid ratio in the North American diet may contribute to some degree to the observed increases in disorders of all kinds.[46-58] Moreover, different countries and regions vary in terms of the omega-6/omega-3 fatty acid content of their background diet.[46-58] However, the present review was not conducted to evaluate this hypothesis. Rather, consistent with the rationale for the two-year project investigating the possible health benefits of omega-3 fatty acids, its objective was to systematically review the evidence concerning the influence of omega-3 fatty acids on the onset and progression of specific visual impairments, to aid in the development of a research agenda. Thus, while there appears to be no known biological rationale for a role of omega-3 fatty acids in cataract formation, following consultation with our expert panel, we nevertheless agreed to investigate certain questions concerning this topic that had been posed by the funders of this project.

Chapter 2. Methods

Overview

The UO-EPC's evidence report on omega-3 fatty acids in eye health is based on a systematic review of the scientific-medical literature to identify, and synthesize the results from, studies addressing key questions. Together with content experts, UO-EPC staff identified specific issues integral to the review. A Technical Expert Panel (TEP) helped refine the research questions as well as highlighted key variables requiring consideration in the evidence synthesis. Evidence tables presenting key study-related characteristics were developed and are found in the Appendices. In-text summary tables were derived from the evidence tables. The methodological quality and generalizability of the included studies were appraised, and individual study results were summarized.

Key Questions Addressed In This Report

The purpose of this evidence report was to synthesize information from relevant studies to address the following questions, organized by type of eye disease/visual impairment and identified by type of question (in parentheses):

Degenerative Diseases of the Retina—Macular Degeneration:

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related macular degeneration?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of age-related macular degeneration?
- What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration in diabetics?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration in patients with cataracts?
- What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration?

- What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration in diabetics?

- What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration in patients with cataracts?

Degenerative Diseases of the Retina—Retinitis Pigmentosa:

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinitis pigmentosa (i.e., an inherited retinal dystrophy)?

Vascular Diseases of the Retina—Retinal Vein or Retinal Artery Occlusions:

- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal vein occlusion?

- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal artery occlusion?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal vein occlusion?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal artery occlusion?

Vascular Diseases of the Retina in Diabetics:

- What is the evidence for efficacy of omega-3 fatty acids in preventing proliferative retinopathy in diabetics?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of proliferative retinopathy in diabetics?

- What is the evidence for efficacy of omega-3 fatty acids in preventing clinically significant macular edema in patients with diabetic retinopathy?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of clinically significant macular edema in patients with diabetic retinopathy?

Cataracts:

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related cataracts?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in diabetics?

- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in patients with age-related macular degeneration?

- What is the evidence that omega-3 fatty acids decrease the rate of cataract surgery in ageing populations?

Adverse Events:

- What is the evidence for the risk of short- and longterm adverse events related to the intake of omega-3 fatty acids?

The overarching goal was to identify and systematically review whatever evidence exists within the eligibility boundaries established for this review in consultation with our TEP and in light of the topics being addressed by SC-RAND and Tufts-NEMC EPCs. These boundaries are delineated in the Eligibility Criteria section (below). More details concerning the questions are provided in conjunction with the description of the Analytic Framework (below). We were also guided collectively by ODS, our TEP and our UO-EPC review team content experts to examine, where data permitted, the possible influence on efficacy, association or safety evidence of the following potential covariates:

- intervention/exposure length;

- type(s) of omega-3 fatty acid (e.g., ALA, EPA, DHA);

- source of the omega-3 fatty acids (e.g., marine, plant, nut), including the specific source (e.g., mackerel as an oily fish);

- delivery format (e.g., whole food servings, capsules, pourable or spreadable oils);

- dose/serving size, including the precision/control of its delivery (e.g., per-day specific, minimum, maximum or range of numbers of capsules, whole food servings or bottle-pourable liters);

- type of processing used to purify the intervention/exposure and/or to maintain the experimental blind (e.g., ethyl esterification; adding an anti-oxidant to stabilize/preserve oils; adding flavor to oils; [vacuum] deodorization);

- amount/dose of omega-6 fatty acid intake either added as a separate cointervention or identified as being present in the background diet, thereby establishing a specific, minimum, maximum or range of allowable or mandated on-study omega-6/omega-3 fatty acid intake;

- the identity of the manufacturer and/or certain characteristics of their product(s) (i.e., purity; presence of other potentially active agents that have not been added intentionally: e.g., methylmercury content);

- the prestudy/baseline or on-study omega-3 or omega-6/omega-3 fatty acid content of blood lipid biomarkers;

- absolute or relative omega-3 fatty acid content of the prestudy/baseline diet;

- omega-6/omega-3 fatty acid content in the prestudy/baseline diet, with the study population's country of origin as a possible surrogate measure of the omega-6/omega-3 fatty acid content of the background diet; and,

- any study subpopulations (e.g., minority; ethnic; genetic, including diabetics).

Furthermore, where data permitted, the following factors with the potential to influence eye health outcomes were also investigated (see Appendix C:* Data Abstraction form for more detail):

- primary diagnosis of eye disease/visual impairment, including which eye(s);

- stage/severity and prognosis (e.g., wet vs dry age-related macular degeneration);

- current age, age at onset, age at diagnosis (duration) and etiology;

- concurrent conditions, or general health status (e.g., diabetes, high blood pressure, myopia);

- history/current surgeries, therapies and medication for primary diagnosis, including responses;

- history/current lutein, beta carotene, antioxidant, other supplement or complementary/alternative medicine (CAM) use (e.g., vitamins, minerals);

- additional medication/treatments (e.g., insulin);

- key sociodemographic factors (e.g., marital status, education, income, employment status) and race/ethnicity;

- other notable characteristics/conditions (e.g., pregnant; blue eyes; oral contraceptive use; steroid use);

- exposure to sunlight; and,

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

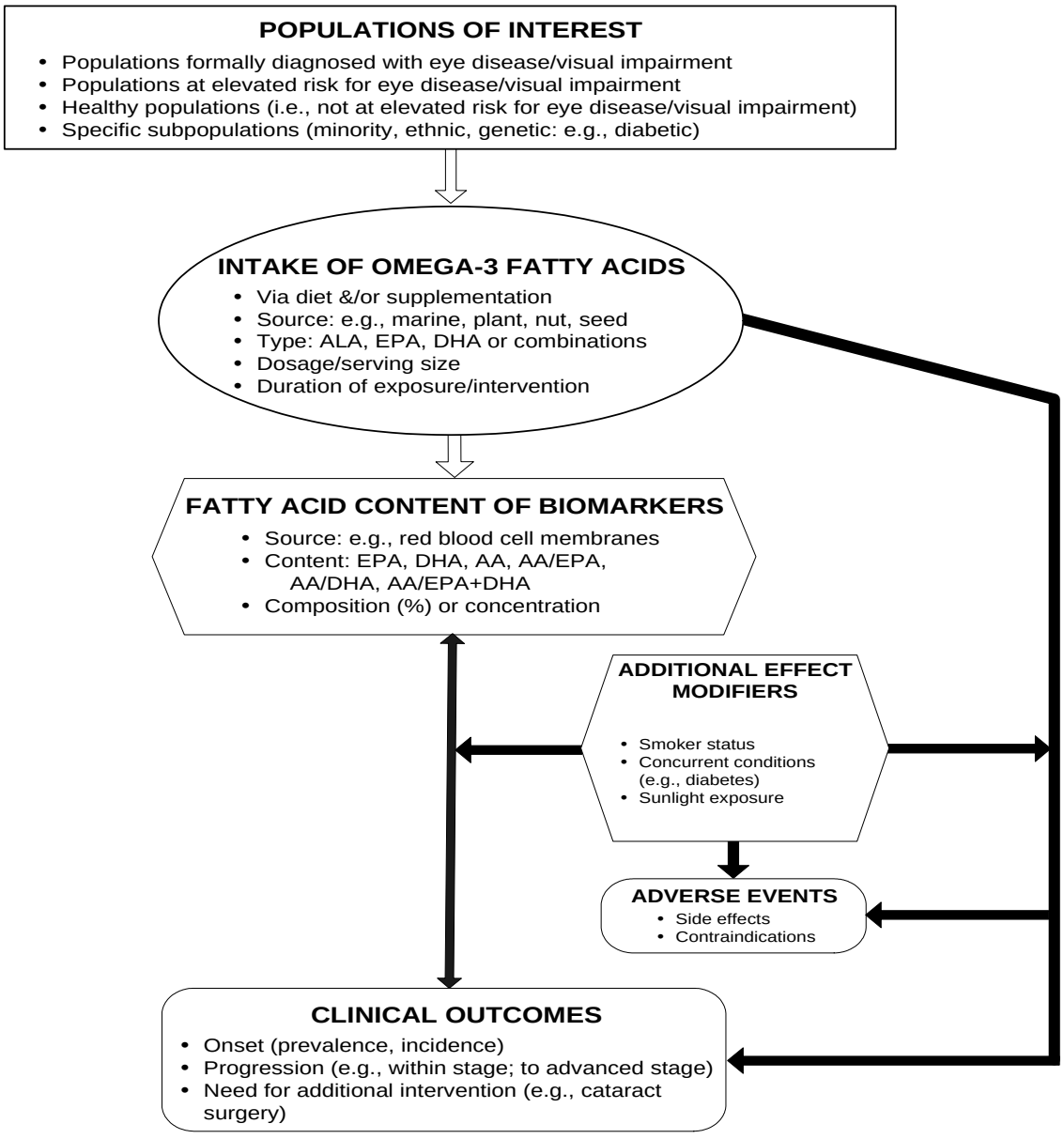
- past/current smoker status, alcohol consumption and illicit drug use.

Current smoker status and alcohol consumption may be important covariates in that they have often been observed to influence various kinds of health status as well as essential fatty acid status, with levels of the latter potentially affecting the former.[59,60]

Analytic Framework

An analytic framework was developed to make explicit the review's specific links relating the populations and settings of interest (i.e., the study participants and the eye diseases/visual impairments of interest), the focal exposure or intervention (i.e., omega-3 fatty acids ingested as supplementation and/or from food sources), potential effect-modifying factors, key eye health outcomes, and the possible role played by the omega-3 or omega-6/omega-3 fatty acid content of biomarkers in mediating the intake-outcome relationship (Figure 2). The possibilities of adverse events (e.g., side effects) and contraindications are recognized. In short, the framework outlines the various lines of logic defining the review's research questions. However, not all linkages were investigated.

Figure 2. Analytic Framework for omega-3 fatty acids in eye health. Populations of interest in rectangles. Exposure in oval. Outcomes in rounded rectangles. Covariates in hexagons. Solid connecting arrows indicate associations and effects reviewed in this report.



One criterion established in this review is that each researchable question had to be clinically relevant. That is, each question had to involve the investigation of at least one relevant clinical outcome. Likewise, to be eligible for inclusion in the review, each study had to entail an investigation of at least one pertinent clinical outcome. Considering the purpose of the two-year

task order is to afford a clinically-relevant research agenda, this decision was judged to be appropriate by both our TEP and our review team.

Each of the clinically-relevant research questions entailed the investigation of the potentially beneficial influence of omega-3 fatty acid intake, via diet and/or supplementation, on eye health-related clinical outcomes in at least one of the following populations of interest:

- those with a current eye disease/visual impairment diagnosis (Population 1);
- those at elevated risk to develop eye disease/visual impairment (Population 2);
- "healthy" individuals who have not been identified as being at elevated risk to develop eye disease/visual impairment (Population 3); or,
- specific subpopulations (e.g., minority, ethnic, genetic) thereof, including those individuals with diabetes (Population 4).

The questions primarily concerned primary or secondary prevention. Primary prevention studies could enroll participants from Populations 2 or 3, each with or without representation from a relevant subpopulation (i.e., Population 4). Secondary prevention studies could involve individuals drawn from Population 1, also with or without representation from a relevant subpopulation (i.e., Population 4).

The possible impact of predefined covariates on efficacy or association data was assessed where data were available (e.g., omega-3 fatty acid source, dose/serving size, exposure/intervention length, and type [e.g., ALA, DHA, EPA, or combinations thereof]; omega-6/omega-3 fatty acid content of the background diet; age; sex). These data are highlighted in question-specific sections titled "Impact of Covariates and Confounders," which identify those variables in included studies that were observed, by virtue of (failed or no) attempts to control for them either experimentally or analytically, to (in)consistently (fail to) influence clinical outcomes.

Given that each included study had to entail an investigation of at least one pertinent clinical outcome, excluded were studies whose sole focus was to examine the impact of omega-3 fatty acid interventions or exposures on the omega-3 or omega-6/omega-3 fatty acid content of biomarkers, even if the study populations were individuals with eye disease/visual impairment. Data concerning the omega-3 or omega-6/omega-3 fatty acid content of biomarkers were eligible for systematic review only if they were collected in a study evaluating the relationship between the intake of omega-3 fatty acids and pertinent clinical outcomes. This evidence could be important since levels of omega-3 or omega-6/omega-3 fatty acid content in human biomarkers (i.e., composition or concentration) might be found to influence (i.e., predispose; protect) the onset, progression or outcome of eye disease/visual impairment; and, reliable associations between biomarker and clinical effects in interventional studies could suggest a mechanism by which omega-3 fatty acid interventions/exposures bring about improved clinical outcomes. Outcomes of interest included the onset (prevalence, incidence), progression (e.g., change in clinical status, indicating progression to an advanced stage) or outcome (e.g., need for cataract surgery) of eye disease/visual impairment.

Study Identification

Search Strategy

The search strategy for this project was designed to be comprehensive and achieve the highest possible recall of relevant clinical studies. The electronic search strategy was developed by an information specialist in consultation with a clinical content expert in eye health, and reviewed by a second information specialist. The eye search concept was combined with the core omega-3 fatty acids search strategy established in collaboration with the project librarians, biochemists, nutritionists, and clinicians from the three EPCs involved in the 2-year, Health Benefits of Omega-3 Fatty Acids project. Consultation among these sources provided the biochemical names and abbreviations of omega-3 fatty acids, names of commercial omega-3 fatty acids products, and food sources of omega-3 fatty acids.

The following electronic databases were searched: Medline (1966 - November Week 2 2003 and updated to February Week 1 2004), Premedline (May 4 2004), Embase (1980 to 2003 Week 48 and updated to 2004 Week 7), the Cochrane Library including the Cochrane Central Register of Controlled Trials (3rd Quarter 2003), and CAB Health (1973-Dec 2003). All databases were searched via the Ovid interface using Search Strategy 1 (Appendix A*), except CAB Health, which was searched through SilverPlatter using Search Strategy 2 (Appendix A*). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH term "dietary fats," which was limited by study design to increase its specificity. A total of 721 bibliographic records were downloaded, with duplicate records identified and removed using citation management software (Reference Manager®).

Reference lists of included studies, book chapters, and narrative or systematic reviews retrieved after having passed the first level of relevance screening, were manually searched to identify additional unique references. Through contact with content experts, attempts were made to identify both published and unpublished studies. On behalf of the three EPCs investigating the evidence concerning the health benefits of omega-3 fatty acids, a letter was written to industry representatives to obtain additional evidence (Appendix B*). A member of our TEP, Dr. John Paul SanGiovanni, provided access to numerous publications as well as reference lists from past and in press publications to aid this endeavor. These efforts identified an additional 25 records that were added to the collection for review. A final set of 507 unique references was identified.

Eligibility Criteria

Published and unpublished studies, written in any language, were eligible for inclusion. Excluding grey literature from systematic reviews of interventions can lead to the overestimation of effect sizes.[61] Substantial bias in the results of a systematic review pertaining to a complementary/alternative medical (CAM) intervention can ensue from the exclusion of data

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

from reports written in languages other than English.[62] AHRQ and ODS consider omega-3 fatty acids to be a CAM exposure.

Data from live human study populations or subpopulations (e.g., genetic, minority, ethnic: e.g., for diabetic retinopathy) of any age were required to maximize generalizability. Study populations had to have been assessed using standard methods (e.g., electroretinograms) and diagnostic criteria to establish eye disease/visual impairment. The specific types of population required to address each of the research questions are described with reference to the analytic framework, and those details are not repeated here. Consultation with our TEP finalized the eye diseases/visual impairments of interest based on a list provided initially by ODS.

Studies had to specifically investigate foods or supplements known to contain omega-3 fatty acids of any type (e.g., EPA, ALA), from any source (e.g., fish, walnuts, seed oil), any serving size or dose, delivered in any fashion (e.g., capsules, liquid, PUFA-rich diet) and for any length of time. Studies investigating "PUFAs" or " LC PUFAs," or even types of diet one might presume would contain marine or land sources of omega-3 fatty acids (e.g., "Mediterranean diet") at minimum had to highlight at least one source of the omega-3 fatty acid content (e.g., oily fish servings). No restrictions were placed on the types or doses of pre- or on-study cointerventions (e.g., medication, omega-6 fatty acid intake, other dietary supplements).

Given the expectation that the relevant literature would be quite small, no restrictions were placed on the levels of evidence required for inclusion in the review. Nevertheless, it was assumed that, for questions of intervention efficacy or effectiveness, randomized controlled trial (RCT) evidence would carry greater interpretative weight since this research design is the gold standard method to investigate these questions.[63] RCTs exhibit a greater inherent potential to deal with potentially serious biasing influences (e.g., selection bias; confounding) although a poorly designed or conducted RCT can produce results whose interpretability is no less complicated by the presence of confounding influences, for example, than observations derived from a well-constructed and conducted study employing a design with a lesser intrinsic capacity to control for these biases (e.g., non-RCT; prospective cohort study). For example, not all RCTs succeed, either through an explicit experimental plan or the process of randomization per se, to equally distribute known confounding influences (e.g., background diet; energy/caloric intake from the intervention; types and doses of as-needed medication) across study arms in intervention studies. Here, controlled studies of an observational nature were considered to carry greater interpretative weight than uncontrolled observational ones even though poorly designed or conducted controlled studies (e.g., inappropriate selection of controls in a case-control study) may likewise fail to produce fewer complications for interpretability than well-designed uncontrolled ones. Finally, greater interpretative weight was associated with results obtained from prospective designs.

Pertinent clinical outcomes are described in relation to the analytic framework. As markers of omega-3 fatty acid metabolism, the following fatty acid compositions or concentrations, from any source (e.g., red blood cell [RBC] membranes, plasma phospholipids), were considered relevant: EPA, DHA, AA/EPA, AA/DHA, and AA/EPA+DHA.

Study Selection Process

The present review employed specific electronic functionality in the form of an internet-based software system, housed on a secure web site. It brings appreciable efficiencies to the

systematic review process and the management of a systematic review team. Electronic yields of literature searches are posted to the system for review. Reviewers then submit all of their results of relevance screening, data appraisal or data abstraction directly to the system. The software system automatically conducts an internal comparison of multiple reviewers' responses to screening questions, to determine the eligibility/relevance of a bibliographic record or a full report. As well, the software captures responses to specific requests to abstract pre-specified data (e.g., mean age of study participants; the assessment of a study's internal validity) from pertinent reports. One large advantage associated with using this software is that review team members are able to complete their work from wherever they have Internet access.

Following a calibration exercise, which involved screening five sample records using an electronic form developed and tested especially for this review (Appendix C*), two reviewers independently screened the title, abstract, and key words from each bibliographic record for relevance by liberally applying the eligibility criteria. A record was retained if it appeared to contain pertinent study information. If the reviewers did not agree in finding at least one unequivocal reason for excluding it, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format (Appendix D*).[64] The screening process also aimed to determine whether a record might also or instead pertain to any of the other topics being systematically reviewed by the three EPCs in year 2 of the omega-3 fatty acids project.

Print or electronic copies of the full reports for those citations having passed level one screening were then retrieved. After completing a calibration exercise, which involved evaluating five sample reports using the same eligibility criteria (Appendix C*), the rest of the reports were independently assessed by two reviewers. Reports were not masked given the equivocal evidence regarding the benefits of this practice.[65] To be considered relevant at this second level of screening, all eligibility criteria had to be met.

Disagreements arising at screening level 2 were resolved by forced consensus and, if necessary, third party intervention. Excluded studies are noted as to the reason for their ineligibility in a listing found at the end of this report.

Data Abstraction

Following a calibration exercise involving two studies, two reviewers independently abstracted the contents of included studies using an electronic Data Abstraction form developed especially for this review (Appendix C*). A third reviewer then verified those data. Data abstracted included the characteristics of the:

- report (e.g., publication status, language of publication, year of publication);
- study (e.g., sample size; research design; number of study arms/groups, cohorts, or phases; funding source);

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

- population (e.g., age; percent males; diagnosis description, including severity, duration, and comorbid conditions);
- intervention/exposure (e.g., omega-3 fatty acid types, sources, doses, and intervention/exposure length), and comparator(s);
- cointerventions (e.g., concurrent medications, omega-6 fatty acid use);
- withdrawals and dropouts, including reasons;
- clinical outcomes;
- fatty acid content of biomarkers; and,
- adverse events (e.g., side effects).

Summarizing the Evidence

Overview

The evidence is presented in three ways. Evidence tables in the Appendices offer a detailed description of the included studies (e.g., study design, population characteristics [e.g., diagnosis], intervention/exposure characteristics [e.g., omega-3 fatty acid types and doses], and "cointerventions" [e.g., background diet, concurrent medication]), with a study represented only once. These tables are organized by research design (Table 1: RCTs; Table 2: quasi-experimental studies [i.e., comparative and noncomparative before-after studies]; Table 3: observational studies [e.g., case-control studies examining the possible association of the intake of omega-3 fatty acids with the onset of eye disease/visual impairment]), with studies arranged alphabetically within each of the three table/design categories.

Question-specific summary tables embedded in the text describe each study addressing a given question in abbreviated fashion, highlighting some key characteristics, including sample size (as measure of the "weight" of the evidence and possible precision of the results), dose and type of omega-3 fatty acids, and comparators' (i.e., comparison groups') specifications. This affords a comparison of all studies addressing a given question. A study can appear in more than one summary table since it can address more than one research question. Also question-specific is each summary matrix, which situates each study in terms of its study quality and its applicability (see below).

Study Quality

Study quality refers to the internal validity, or methodological soundness, of a study. A systematic review can be faced with great variability in the quality of its included studies. Our

approach is not to use a minimal level of quality as an inclusion criterion since this precludes assessing the possible impact of study quality on study results.

A study with low quality can make it difficult to clearly and meaningfully interpret its results, for example, to unequivocally attribute a significant observed benefit exclusively to an intervention/exposure (as opposed to other factors). Since definitions, or standards, of study quality can depend on the type of research design, different constructs were selected to evaluate, from study reports, the quality of RCTs and studies employing other types of research design. One assessor with many years of experience evaluated study quality for all types of design. Time did not permit studies' dual assessment.

Four fundamental quality constructs from two instruments were used to rate the internal validity of RCTs. These tools were chosen collectively by the three EPCs involved in the 2-year task order because they have been validated. The Jadad items[66] assess the reporting of randomization, double blinding, and, withdrawals and dropouts (Appendix C*). Total scores range from 0 to 5, with a score less than 3 indicating low quality. The reporting of the concealment of a trial's allocation to treatment[67] yields three grades (A = adequate; B = unclear; C = inadequate) (Appendix C*).

The assessment of the quality of studies using designs other than RCTs is complicated by the dearth of validated instruments and the variety of such designs (e.g., non-randomized controlled trials; uncontrolled studies). Nevertheless, a recent systematic review by Deeks et al. identified a number of "best tools" for use with these designs.[68] Among them were a published instrument developed by Downs and Black[69] and an unpublished one derived by experts in Newcastle and Ottawa (NOS).[70] The former validated both design-specific and design-neutral items.

Where case-control and cohort studies were included in the review, the validated NOS was employed. Items applicable to other designs such as non-RCTs, cross-sectional designs, cross-sectional surveys and others were taken from the Downs and Black instrument; or, if the required constructs were not operationalized in this instrument, they were developed as modifications of existing Downs and Black items (e.g., for multiple-group cross-sectional designs) or NOS items (e.g., single prospective cohort studies), borrowed from Jadad's assessment tool (e.g., description of withdrawals/dropouts), or developed outright (Appendix C*).

It should be noted that the items defining the case-control and cohort study assessment tools from the NOS were each used as a whole, although specific guidelines as to which design-specific total scores indicate low or sound quality are unavailable. Likewise, no guidelines exist to mark low or sound study quality based on any subset of Downs and Black's 27-item instrument. As already asserted, a Jadad total quality score of less than 3 indicates low quality. To permit the entry of these quality data into a summary matrix, cutpoints for each type of design were set somewhat arbitrarily to establish three levels of internal validity (see Summary Matrix). The aforementioned items/instruments and their related cutpoints were used in our recently completed evidence report on the Effects of Omega-3 Fatty Acids on Mental Health.

It was decided by our review team that, given the limitations of space, especially in print-based study reports, and the amount of detail that would likely be required to provide all of the details we needed to fully establish that only appropriate methods had been used to extract, prepare, store and analyze lipid content, it was reasonable to appraise these methods by focusing

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

instead on identifying extant descriptions of inappropriate methods. On occasion, the inappropriateness of methods had to be determined by reference to certain protocols.

Pilot-tested exclusively for their ease of use within the data abstraction form were questions designed to informally assess the successful control of study confounding from variables identified by content experts as potential threats to the internal validity of studies pertinent to the review. In their view, these variables required experimental or statistical control to permit an uncomplicated interpretation of study results (Appendix C*). Two important categories of threat in controlled designs come from having study groups vary in terms of key prestudy or baseline characteristics (e.g., background diet; psychotropic medication; severity of a disorder), or from having certain on-study changes (e.g., unexpected stressors; changes in medication type or dose) unrelated to the exposure or intervention, occur unequally across study groups to produce confounding. Even RCTs are not immune to being affected by these threats to internal validity.

For example, if in a placebo-controlled RCT test of the supplemental prevention efficacy of omega-3 fatty acids, only certain treatment group members' background diets changed appreciably from what was observed at baseline (e.g., decreased fish intake and thus an increased omega-6/omega-3 ratio in the background diet), at which point the two study groups' baseline diets had been deemed comparable, then this on-study inequality could influence study outcomes. Because of this change in background diet, one study group might all of a sudden be receiving a different ratio of omega-6/omega-3 fatty acid intake than what had been set in the study protocol. This would amount to a change in the planned, on-study between-group difference in omega-6/omega-3 fatty acid intake; and, it is this intake ratio which could have the greatest influence on clinical outcomes. In general, contraventions of planned on-study between-group equivalences (e.g., caloric/energy intake; background diet; medication types and doses; severity of disorder; current smoker status; alcohol consumption) or of planned, on-study between-group differences (e.g., amount of omega-3 fatty acid intake) related to events other than the intervention/exposure (e.g., life stressors, which can influence patterns of eating as well as health in general), that is, in variables with the potential to affect eye health outcomes (and biomarker levels), could either "mask" or incorrectly "reveal" clinical benefits depending on the groups in which these unexpected changes occurred. Then, unless statistical adjustments are made, such a scenario could complicate the meaningful interpretation of outcomes.

These informal assessment items were modified to assess single group studies since on-study changes involving the same key variables can also complicate the interpretation of their study results. However, no quality scores were derived from the data abstractors' responses to these questions pertaining to controlled or uncontrolled studies.

Study Applicability

As specified in the scope of work for this series of evidence reports on the health benefits of omega-3 fatty acids, the primary focus is on the US population. Given the geographical location of the UO-EPC, however, the definition of study applicability was expanded slightly to include Canada as part of a larger North American context. This study's reference point became the "typical" North American.

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Also known as external validity, or generalizability, the construct of applicability refers to the degree to which a given study's sample population is sufficiently representative of the population to which one wishes to generalize its results. In the present review, two schemes operationally defined applicability (Appendix C*). One assessed studies involving at least one target population identified with an eye disease/visual impairment, with the other evaluating studies involving a target "undiagnosed" population with or without a known elevated risk for an eye disease/visual impairment.

With regards to the highest level of applicability (Level I) in the first scheme, the broadest definition of the population of interest is the otherwise "healthy" North American (or similar individual) identified with an eye disease/visual impairment, diagnosed using a standard North American strategy and methodology/nomenclature, possibly receiving "typical" North American medications/treatments for their eye disease/visual impairment, is drawn from a somewhat broad socio-demographic spectrum (i.e., gender, race), and eats a diet "typical" of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio of at least 15: see below for references). For Level I applicability in the second scheme, the broadest definition of the population of interest is the otherwise "healthy" North American (or similar) individual, presenting with or without a known elevated risk for onset of an eye disease/visual impairment, representing a somewhat broad socio-demographic spectrum (i.e., gender, race), and eating a diet "typical" of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio of at least 15).

Together, these Level I definitions represent the respective reference points, with applicability decreasing as the definition of the sample study population narrows in terms of the factors represented in the two schemes. With respect to these schemes applied to studies with either diagnosed or undiagnosed participants, we identified what is likely the most important source of population variability: the background diet of participants leading up to the study, if not also during the study. This rationale is based on the observations that 1) countries (e.g., Japan), regions (e.g., coastal areas) and cultures (e.g., Inuit) can vary considerably in terms of their background diet and thus, their typical intake of omega-6/omega-3 fatty acid content, 2) omega-3 and omega-6 fatty acid contents within the human biosystem compete for enzymes to yield key metabolites with specific effects in the human biosystem and for placement in cell membranes from which to likely have these possible influences (e.g., clinical improvement or prevention) (see Chapter 1), and 3) it is the impact of omega-3 fatty acids on eye health that is being investigated in the present review. For example, the typical North American diet contains an omega-6/omega-3 fatty acid intake ratio of at least 15, while urban India and Japan's corresponding values are 38-50 and 4, respectively.[46-58]

That said, a high background omega-6/omega-3 fatty acid intake ratio, potentially reflected in a corresponding differential in these contents in cell membranes, may make it harder for omega-3 fatty acid supplementation to make a noticeable clinical difference,[71] although already having considerable omega-3 fatty acid content in the background diet and in cell membranes because of a low omega-6/omega-3 fatty acid intake ratio may make it difficult for the typically small amounts of omega-3 fatty acid supplementation in studies to make a clinical difference (see Discussion). Irrespective of which of these hypotheses may be confirmed elsewhere, the fact that study populations can vary in terms of their typical omega-6/omega-3 fatty acid intake

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strongly suggests that this potential confounding influence on study outcomes needs to be represented in the applicability schemes whereby the North American value is the reference point.

UK populations represent somewhat of a special case in that, while they can exhibit socio-demographic pictures similarly broad to the ones seen in North American study populations, their somewhat different lifestyle and background diet recommends an applicability value of "II." However, if participants were drawn from a narrower UK population, then a "III" would be assigned. One experienced assessor evaluated study applicability.

Summary Matrix

For a given research question, and where possible (e.g., more than one study addressing the question), a summary matrix situates the pertinent studies in terms of their respective study quality (internal validity) and applicability (external validity) values. The Jadad total quality score defined RCTs' internal validity in summary matrices. A three-level format was derived from the range of possible RCT quality scores (A = Jadad total score of 4 or 5; B = Jadad total score of 3; C = Jadad total score of 0, 1 or 2). Given that allocation concealment scores have in the past tended to vary less widely than Jadad total scores, allocation concealment values were entered as superscripts in the summary matrices.[71] A similar approach was taken for the studies employing other research designs. The following cutpoints were established, albeit without benefit of a validational exercise:

- (quasi-experimental) comparative before-after study: A = total quality score of 8-11; B = 5-7; C = 1-4;
- (quasi-experimental) noncomparative before-after study: A = total quality score of 8-11; B = 5-7; C = 1-4;
- case control study (NOS): A = 8-10; B = 4-7; C = 1-3;
- single prospective cohort study (Modified NOS): A = 8-10; B = 4-7; C = 1-3;
- single population cross-sectional study: A = 7-9; B = 4-6; C = 1-3; and,
- retrospective single population (e.g., population-based) cohort study: A = 7-9; B = 4-6; C = 1-3.

Our recently completed evidence report on the Effects of Omega-3 Fatty Acids on Mental Health employed this approach. The three-level applicability format was established by the 3 EPCs involved in the 2-year project for practical reasons, to permit the incorporation of quality scores within a summary matrix. Studies assigned an "X" (i.e., insufficient information to establish applicability) were excluded from summary matrices.

Qualitative Data Synthesis

An overarching qualitative synthesis describes the progress of each citation, then report, through the stages of the systematic review. It also highlights certain report and study design characteristics of included studies (e.g., distributions of research design by research question). Then, for each question, a separate qualitative synthesis is derived for included evidence, organized by broad categories of research design (i.e., RCTs vs quasi-experimental designs vs observational studies). A brief study-by-study overview typically introduces the synthesis, followed by a narrative summary of the key defining features of relevant studies (e.g., inclusion/exclusion criteria), including their populations (e.g., diagnosis-related information), intervention/exposures (e.g., types of omega-3 fatty acid), cointerventions (e.g., medication), outcomes, study quality, applicability and results. Whether or not data can be organized according to these subheadings depends on the number of studies addressing a given question and the amount or variety of detail available in the study reports.

Juxtaposing, in turn, all pertinent studies' parameters for a given research question has two key consequences. It allows us to identify the "gaps" in knowledge deemed crucial by content experts to understand the clinical phenomenon (e.g., efficacy of omega-3 fatty acids). That is, data regarding possible confounders may be lacking, making it difficult to interpret study results with unfettered confidence. These gaps point to those variables requiring measurement and experimental or statistical control in future research. Second, it affords an understanding of the definition and extent of the included studies' clinical homogeneity (i.e., population, intervention, cointervention, outcome), which can then inform decisions regarding the appropriateness of meta-analysis. Where strong clinical heterogeneity is observed, it may be important to forego meta-analysis because the "population" to which any point estimate, and measure of precision, might be extrapolated may not exist per se; it, too, is synthetic (e.g., the "average" person with cataracts). Subject to scrutiny in the evaluation of cross-study clinical homogeneity is the ability of each study to control for confounding influences and yield results that can be interpreted without serious reservation. The existence of statistical heterogeneity also plays a role in the decision to do without a quantitative synthesis. Whether or not meta-analysis is considered appropriate, an attempt is made to make sense of the possible influence of covariates and confounders within the context of the qualitative synthesis.

Where eligibility criteria permit, evidence from research designs with a lesser inherent potential to control for biasing influences are used to see whether, collectively, they confirm the picture of efficacy, or association, derived from designs with a greater inherent potential to achieve this goal (see Eligibility Criteria). For the purposes of interpreting results, greater emphasis is placed on the latter, with "greater emphasis" meaning that we assign greater interpretative, not numerical or statistical, weight to these intrinsically stronger designs. Factors other than study design also taken into account in interpreting results include study quality, the number of studies, and whether studies were sufficiently powered.

Quantitative Data Synthesis

Given the paucity of relevant studies addressing any given question, as well as the variability in the research designs, definitions of the study populations, exposures/interventions or clinical

outcomes employed to investigate it, meta-analysis was deemed impossible or inappropriate with respect to each of the questions.

Chapter 3. Results

Results of Literature Search

Regardless of its source, the progress of each bibliographic record through the stages of the systematic review is illustrated in the modified QUOROM flow chart (Appendix D*). Ideally, a record included an abstract and key words, in addition to a citation. When a citation was discovered, for example through a manual search of a reference list, its complete bibliographic record was sought (e.g., Pubmed) and then entered into the first level of relevance screening.

Of 507 records entered into the initial screening for relevance, 395 were excluded. Reflecting the specific eligibility criteria, the reasons for exclusion were: a) not a first publication of empirical evidence (e.g., a review; n = 93); b) not involving human participants (n = 206); c) no omega-3 fatty acid focus (i.e., intervention/exposure; n = 80); and, d) not related to predefined eye health outcomes (n = 16). All reports having passed this level of screening were then retrieved and subjected to a more detailed relevance assessment.

A second relevance screening then excluded 96 reports for the following reasons: a) not a first publication of empirical evidence (e.g., a review; n = 39); b) not involving human participants (n = 8); c) no omega-3 fatty acid focus (i.e., intervention/exposure; n = 39); and, d) not related to predefined eye health outcomes (n = 10).

In total, 16 reports, describing 16 unique studies, were deemed relevant for the systematic review, with two different studies presented in one report[72] and one study described in two reports.[73,74] To avoid confusion in the text, evidence tables, summary tables and figures, the report by Hoffman et al.[73] is used to refer to the single study described by two reports.[73,74] One report[73] described efficacy data, whereas the second[74] presented safety data. Another report by Hoffman and colleagues,[72] which outlined two different studies, yielded two evidence tables (Appendix E*). As stated earlier, the listing of studies excluded as a result of the appraisal of full reports is presented at the end of this document.

Report and Study Design Characteristics of Included Studies

Sixteen unique studies, described in 16 published journal reports, met eligibility criteria and were included in the systematic review. Any study that may have at best indirectly or superficially addressed a research question is identified in the appropriate section of this Chapter.

Each of the included studies was described by at least one published report. All but two reports were written in English, with one requiring translation from Russian (Sorokin et al.)[75] and the other from French (Scorolli et al.).[76]

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Three categories of research design (two RCTs, five quasi-experimental designs, and nine observational studies), including seven different design types overall, are represented in the review. These consisted of two parallel arm RCTs,[73,76] one comparative before-after design,[77] four noncomparative before-after studies,[72,75,78] two single prospective cohort studies,[60,79] one retrospective population-based cohort study,[80] two case control studies,[81,82] and four single population cross-sectional studies.[83-86] It should be recalled that the Hoffman et al. report[72] described two noncomparative before-after studies.

The question examining the role of omega-3 fatty acids in preventing age-related macular degeneration (ARMD) was addressed by two case-control studies,[81,82] one single prospective cohort,[79] one retrospective population based cohort,[80] and two single population cross-sectional designs.[83,84] One RCT investigated the role of omega-3 fatty acids in slowing the progression *of* ARMD,[76] while a single prospective cohort study examined their influence on slowing the progression *to* advanced ARMD.[60] One RCT,[73] one comparative before-after study,[77] and two noncomparative before-after studies[72] assessed the impact of omega-3 fatty acids on slowing the progression of RP. One noncomparative before-after study[75] included outcomes permitting it to be classified as evaluating, in diabetics, the omega-3 fatty acids' potential to prevent proliferative retinopathy and slow the progression of clinically significant macular edema. Two single population cross-sectional studies observed whether omega-3 fatty acids prevent age-related cataracts.[85,86] Finally, a noncomparative before-after design investigated the impact of omega-3 fatty acids on slowing the rate of progression of age-related cataracts.[78]

Of the 16 relevant studies, eight concerned primary prevention of either ARMD[79-84] or age-related cataracts.[85,86] The remainder focused on secondary prevention.[60,72,73,75-78] A single interventional study solicited reports of adverse events from study participants, and described these results.[73,87]

The remainder of this chapter is organized by eye disease/visual impairment. If a question is not represented in the report, there was no evidence that met eligibility criteria. Safety data are presented last. We begin with ARMD.

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Preventing Age-related Macular Degeneration?

As observed in Summary Tables 1 to 3 (below), derived from Evidence Table 3 (Appendix E[*]), six observational studies met eligibility criteria in investigating omega-3 fatty acids' possible value in preventing ARMD. These investigations concerning primary prevention were published between 1995 and 2002.

Overview of Relevant Studies

Cho et al. evaluated the association between total fat intake and the development of age-related ARMD in a single prospective cohort study that was part of the Nurses' Health Study and

[*]Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

the Health Professionals Follow Up Study (n=72,489) (Summary Table 1).[79] Participants were followed for 10 to 12 years in the US. Intake of omega-3 fatty acids and total fish intake, as a source of omega-3 fatty acids, were assessed using a food frequency questionnaire completed at various times during the followup. The primary outcome was self-reported ARMD, with a visual loss of 20/30 or worse.

Summary Table 1: Association between omega-3 fatty acid intake and onset of age-related macular degeneration (observational study)

Author, Year, Location: Length & Design	Study groups[1]		Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)		
Cho, 2001, US: 10-12 y single prospective cohort study[79]	By 1994, women (n=71,486) & men (n=41,474) ≥50 y of age		Total quality: 5 [Grade: B]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; ARMD = age-related macular degeneration

Seddon et al. conducted an analysis of the dietary intake/maculopathy data from the Eye Disease Case Control Study.[82] A total of 853 patients were enrolled, of which 349 were cases. The cases and controls were selected between 1986 and 1990 from five large ophthalmology centers in the US. Enrolled at the same time as cases, controls (n=504) were selected from the same study base. The outcome of interest was advanced ARMD, which was confirmed photographically and by review of medical records. A food frequency questionnaire yielded data reflecting total fat intake as well as intake by type of fat.

Summary Table 2: Association between omega-3 fatty acid intake and onset of age-related macular degeneration (observational studies)

Author, Year, Location: Length & Design	Study groups[1]		Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)		
Seddon, 2001, US: case-control study[82]	Advanced ARMD cases (n=349)	Controls (n= 504)	Total quality: 8 [Grade: A]	II
Ouchi, 2002, Japan: case-control study[81]	Advanced ARMD cases (n=11)	Healthy controls (n=10)	Total quality: 0 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; ARMD = age-related macular degeneration

Ouchi et al. conducted a very small case control study in Japan.[81] Cases (n=11) exhibited advanced (i.e., exudative) ARMD in that they all showed signs of choroidal neovascularization. Where "healthy" controls (n=10) were drawn from was not described. Fish intake frequency was evaluated to estimate, by proxy, omega-3 fatty acid intake. At the same time, the investigators performed a cross-sectional analysis of fatty acid fractions (e.g., EPA, DHA) in the red blood cells (RBCs) and plasma of cases and controls. The assessment of the diet-ARMD relationship was secondary to their focus on possible between-group differences in biomarkers data.

Mares-Perlman et al.'s retrospective population-based cohort (n=2,152; ages 45-84 years) study investigated the relationship of dietary fat intake and both early and late forms of ARMD as part of the Beaver Dam Eye Study.[80] A total of 2,152 persons (90%) participated, with 1,968 participants providing both gradable fundus photographs and dietary intake data. Fundus photographs were taken from 1988 through 1990, while dietary history data were collected from 1978 through 1980. Fish intake was used as evidence for omega-3 fatty acid intake. Dietary intake data pertained to the year prior to the interview (n=2,152) and 10 years prior to the interview (n=2,003).

Summary Table 3: Association between omega-3 fatty acid intake and onset of age-related macular degeneration (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Internal validity	Applicability
Mares-Perlman, 1995, US: retrospective population-based cohort study[80]	n=1,968 participants with exposure & clinical outcome data; 344 total ARMD diagnoses, including n=314 with early ARMD (i.e., soft distinct drusen [n=196]; retinal pigment epithelial degeneration [n=142]; increased retinal pigment [n=236]) & n=30 with late ARMD (i.e., geographic atrophy [n=9] vs exudative ARMD [n=21])		Total quality: 6 [Grade: B]	I
Smith, 2000, Australia: single population cross-sectional study[83]	n=2,900 with exposure & clinical outcome data; n=228 total ARMD diagnoses, including n=182 with early ARMD (i.e., soft indistinct or reticular drusen vs retinal pigmentary abnormalities) & n=46 with late ARMD (i.e., neovascular vs atrophic)		Total quality: 5 [Grade: B]	III
Heuberger, 2001, US: single population cross-sectional study[84]	n=7,883 with exposure & clinical outcome data; pts ages 40-79 y included in analyses for early ARMD (n=644) & pts ages >60 y included in analyses for late ARMD (n=53)		Total quality: 5 [Grade: B]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; ARMD = age-related macular degeneration

Smith et al.'s (single population) cross-sectional study assessed the association between the dietary intake of fat and ARMD in a survey of vision and common eye diseases in Australia (n=3,654), as part of the Blue Mountains Eye study.[83] Assessed by macular photography,

ARMD was defined as early or late. The amounts and types of dietary intake were measured via a semi-quantitative questionnaire.

Analyzing data collected in the Third National Health and Nutrition Examination Survey (NHANES III) (n=7,883), Heuberger et al. investigated the relationship between the dietary intake of fat and ARMD in a (single population) cross-sectional study.[84] Non-mydriatic single eye fundus photography was used to assess ARMD status. ARMD was divided into early and late lesions in a way that was similar to the methodology employed by Smith et al.[83] A food frequency questionnaire and a 24-hour recall method permitted the collection of data concerning total fat intake as well as specific dietary sources of fat. Patterns of fish consumption were estimated based on responses to a single item in the food frequency questionnaire.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Two (single population) cross-sectional studies,[83,84], two case control studies,[81,82] one retrospective population-based cohort study[80] and one single prospective cohort study[79] were deemed relevant (Summary Tables 1 through 3; Evidence Table 3: Appendix E[*]).

Cho et al.'s single prospective cohort study was sponsored by the National Eye Institute (US), and the investigators clearly defined their US source population and final sample.[79] Inclusion and exclusion criteria were also well described by Cho et al.[79] Smith and colleagues' (single population) cross-sectional study's source population (Australia), final sample, inclusion and exclusion criteria were not explicitly defined, although reference was made to a previous base study.[83] The sponsoring agencies were the Australian Department of Health and Family Services as well as the Save Sight Institute of The University of Sydney. Seddon et al.'s case control study was sponsored by the National Eye Institute (US).[82] The source population and final sample were explicitly defined, and the inclusion and exclusion criteria were clearly described.

The source population and final sample investigated in Mares-Perlman et al.'s retrospective population-based cohort study were clearly defined.[80] This work was funded by the National Institutes of Health (US). Ouchi et al. performed a very small case-control study (n=21) in Japan, and whose funding source was not provided.[81] Neither their source population nor their inclusion and exclusion criteria were adequately described. The US study by Heuberger et al. employed a single population cross-sectional design.[84] While its source population and final sample were highlighted to some extent, more detail is contained in another research report. The inclusion criteria were broad and they were described in moderate detail. This study was supported by the National Institutes of Health as well as Research to Prevent Blindness.

Population characteristics. Cho et al.'s single prospective cohort study included as its source population the study sample of the Nurses' Health Study, which enrolled 121,700 females aged 30 to 55 years in 1976, and the study sample of the Health Professionals Follow Up Study, which included 51,529 health professionals aged 40 to 75 years in 1986.[79] Because ARMD is rare in young individuals, the baseline population was restricted to women 50 years or age or older (age assessed as of 1984; n=55,865) and men ages 50 years of age or older as of

[*] Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

1986 (n=33,357). Also excluded were those patients who did not complete a baseline food frequency questionnaire or who completed it inadequately, those with implausible energy intakes, those who reported ARMD or non-melanoma/non-skin cancer, and those not responding to ARMD status questions at followup.

At baseline, Cho et al.'s total sample population included 42,743 women and 29,746 men.[79] Additional patients were added every 2 years, increasing the total sample, by 1994, to 71,486 women and 41,474 men. The average baseline age of their full sample was 56 years. Their racial and other demographic characteristics were not provided in the report. A total of 567 cases of ARMD were documented: 351 in women (over 635,873 person-years of followup in the 12-year cohort) and 216 in men (over 300,242 person-years of followup in the 10-year cohort). Confirmation of the diagnosis was attempted in all cases via medical record review or by contacting the patient's ophthalmologist. A subset of patients had retinal photographs taken to further document the diagnosis.

Smith et al.'s Blue Mountains Eye Study investigated vision and common eye diseases in an Australian urban population of 3,654 people who were 49 years of age or older.[83] The 145-item food frequency questionnaire was returned by 3,267 participants, with 2,900 useable questionnaires. A total of 312 cases of ARMD were identified, 228 of who had adequately filled out the food frequency questionnaire. Other baseline demographic information for this study was not provided (i.e., age, gender, race, geographic details).

Seddon et al.'s Eye Disease Case Control Study was designed to identify potential risk factors for a number of retinal disorders, including advanced ARMD.[82] Cases and controls were selected between May 1986 and December 1990 from five large urban US ophthalmic centers. Eligible cases needed to be between 55 and 80 years of age, and with exudative ARMD identified within 1 year of enrollment. There were 426 eligible cases, of which 349 agreed to participate in the study. Their average age was 71 years, and 58% were female. Controls were identified from the same study base as the cases. Of the 646 controls who were eligible for inclusion, 504 agreed to participate. Their average age was 68 years, and 58% were female. The distribution of reasons for non-participation was similar across cases and controls, and cases and controls were frequency matched for age, sex and source clinic. The sample included only six non-white subjects with advanced ARMD, and so the study was essentially restricted to a white population.

Mares-Perlman and colleagues' Beaver Dam Eye Study population was located in south central Wisconsin.[80] A 50% sample of the non-institutionalized Beaver Dam Eye Study participants were used for the nutritional aspect of the study (n=2,429). Some had moved or died (n=24), some could not be located (n=6) and some could not respond to verbal interviews (n=23). Of the remaining potential subjects, 90% agreed to participate (n=2,152). All participants provided data concerning dietary intake in the past year, and a total of 93% (n=2,003) were able to supply dietary information from 10 years preceding the interview. Of these 2,003 patients, 1,968 had gradable fundus photographs. The mean age of the sample was 61 years, and the vast majority were white participants.

The Ouchi paper provided few details regarding the source or sampled population.[81] The paper only revealed that there were eight male and three female ARMD patients (average age 65.8 years), in addition to eight male and two female controls (average age: 64.4 years). No other data regarding the source or study population were described.

The NHANES III Survey was conducted from January 1988 through December 1994.[84] It included a nationally representative sample of the non-institutionalized civilian US population. There was purposeful over-sampling of black subjects, Mexican-Americans and adults over 60 years of age. The sample was restricted to those between the ages of 40 and 79 years. A total of 7,405 patients between 40 and 79 years of age were included in the analysis for early ARMD, of whom 644 had the disease. Only patients 60 years of age or older were included in the analysis for late ARMD (n=4294), of whom 53 had the disease. The percentages of patients who did not meet eligibility criteria, who refused to participate or who did not adequately respond to the questionnaire, were not provided. Baseline demographic characteristics were not reported but the analysis was presented as having controlled for them.

Intervention/exposure characteristics. The definition of the exposure varied across studies. Some reported specific omega-3 fatty acid intake, others provided total omega-3 fatty acid intake data, while a third approach measured overall or specific fish consumption as a proxy for omega-3 fatty acid intake.

Cho et al. used a 130-item food frequency questionnaire to assess dietary intake in the previous year.[79] Estimates of participants'omega-3 fatty acid intake (e.g., EPA, DHA) over the followup period were divided into quintiles according to the energy-adjusted cumulative average omega-3 fatty acid intake. Total fish intake and the type of fish intake were also observed. Smith et al.'s sparse details included reference to a base study, which had used a 145-item food frequency questionnaire previously validated and modified to assess the Australian diet.[88] Estimates of specific omega-3 fatty acid intake were not provided, with the exposure being the number of servings of fish per unit time. Seddon et al.[82] employed a food frequency questionnaire to calculate energy-adjusted consumption scores as quintiles of intake in a manner similar to what Cho et al. did.[79] The exposure was defined in two ways: as total omega-3 fatty acid consumption and as number of fish servings per week.

The dietary food questionnaire used by Mares-Perlman et al. in the Beaver Dam Study was described in some detail.[80] Total intake of fish and shellfish served as proxies for omega-3 fatty acid intake. Ouchi et al. defined their exposure as fish intake frequency per week, and data were obtained via a questionnaire.[81] Additional details were neither provided nor referenced. It was impossible to ascertain whether the intake being referred to was "current" or "typical/in the past." Heuberger et al. implemented a 24-hour recall method, while also dividing intake into quintiles based on total energy. A 66-item food frequency questionnaire permitted the estimation of the monthly consumption of fish.

Outcome characteristics. Across included studies, ARMD outcomes were invariably measured dichotomously, that is, as the presence or absence of the disease. What differed somewhat between studies was the exact definition of ARMD and how it was actually measured.

Cho et al. defined the primary outcome as any ARMD decreasing vision to 20/30 or worse.[79] It was a self-reported assessment, although reviews of medical records or ophthalmologic consultations were relied upon to verify the diagnosis. Although their precise definition of ARMD subtypes was not provided, in their analysis ARMD was divided into: early and dry, wet and advanced, and wet and advanced with geographic atrophy. Of note, none of the "ARMD-negative" self-reports were subjected to any confirmatory tracking or followup.

Smith et al.[83] and Heuberger et al.[84] followed the Wisconsin age-related maculopathy grading system, which divides ARMD into early, late atrophic and late neovascular stages. Stereoscopic macular photography was used to determine ARMD category. Seddon et al. explicitly defined ARMD as exudative and advanced, which they defined as visual acuity being worse than 20/20 or drusen in either eye plus evidence of choroidal neovascularization.[82] ARMD was determined by screening photography lists and reviewing medical records.

Mares-Perlman et al. defined early ARMD as soft or involving reticular drusen or any drusen in the presence of retinal pigment epithelial changes.[80] Advanced ARMD required the identification of geographic atrophy or choroidal neovascularization. Outcomes were established using photography. Ouchi et al. identified ARMD as exudative, in the presence of choroidal neovascularization, via fundoscopic examination along with both fluorescein angiography and indocyanine green angiography.[81] Diagnoses were confirmed, over 6 months, on the basis of disease progression.

Study quality and applicability. Of the six included studies, only the case-control study by Seddon et al. achieved the highest possible total quality grade of A (Summary Matrix 1).[82] Four studies, including Cho et al.'s single prospective cohort study,[79] Mares-Perlman et al.'s retrospective population-based cohort study,[80] and the single population cross-sectional studies by Smith et al.[83] and Heuberger et al.,[84] attained a total quality grade of B. Ouchi et al.'s case-control study failed to achieve even one study quality point, which yielded a total quality grade of C. The studies by Cho et al.,[79] Mares-Perlman et al.,[80] and Heuberger et al.[84] each attained an applicability rating of I, which indicates the highest generalizability to the North American population. By virtue of their inclusion of an almost exclusively white population, the Seddon et al. study's applicability rating was II.[82] Both Smith et al.[83] and Ouchi et al.'s[81] studies received the lowest applicability rating of III. All three studies receiving an applicability rating of I also attained a total quality grade of B.[79,80,84] It should be noted that the latter three studies employed different research designs.

Summary Matrix 1: Study quality and applicability of evidence regarding the association of omega-3 fatty acid intake and onset of age-related macular degeneration (all designs)

		Study Quality								
		A			B			C		
Applicability	I	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
					Cho	2001	>111k			
					Mares-Perlman	1995	1968			
					Heuberger	2001	7883			
	II	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
		Seddon	2001	853						
	III	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
					Smith	2000	2900	Ouchi	2002	21

n = number of allocated/selected participants; RCT = [A]Adequate vs [U]Unclear allocation concealment; k = 1000's

Qualitative Synthesis of Individual Study Results

To prepare their multivariate analysis, Cho et al. divided fat intake into quintiles.[79] Confounders (see below) were explicitly described and entered into the analysis. While intake of LA, AA, EPA, DHA, white-meat fish or dark-meat fish (e.g., mackerel, salmon, sardines, bluefish, swordfish) intake were not significantly associated with ARMD based on multivariate analysis, consumption of canned tuna fish (RR: 0.61; 95%CI: 0.45, 0.83) and of all fish (RR: 0.65; 95%CI: 0.46, 0.91) each showed a statistically significant inverse relationship with ARMD. Individuals who ate any type of fish more than four times per week had a lower risk of ARMD than those who ate it fewer than or equal to three times per month (RR: 0.65, 95%CI: 0.46-0.91). Subgroup analyses of data following the classification of ARMD cases (early vs dry vs wet ARMD), and for advanced ARMD (i.e., wet ARMD, and early and dry ARMD with geographic atrophy) revealed results similar to the situation where ARMD cases were combined (data not reported).

Fat intake was divided into quintiles, and confounders (see below) were included in Smith et al.'s multivariate analysis.[83] They found that only for low fish intake (i.e., 1-3 times/month vs < 1/month; OR: 0.23 95%CI [0.08-0.63]) did the exposure appear to act in protective fashion with respect to late ARMD. This pattern contradicts results from unadjusted analyses concerning fish intake and late ARMD. The latter revealed a significant protective effect across all intensities of the exposure, albeit without suggesting a dose-dependent relationship. Results of multivariate and univariate analysis basically agreed that no significant inverse association existed between fish intake and early ARMD.

An appropriate multivariate analysis, with confounders explicitly described (see below), was conducted by Seddon et al.[82] They found that combined EPA and DHA intake was not protective against advanced ARMD. Then, when the data were stratified for LA consumption, only the test for trend ($p<0.05$) suggested that combined EPA and DHA intake might protect against advanced ARMD for those exclusively consuming lesser amounts of LA (i.e., $\leq$5.5 g/day vs $\geq$5.6 g/day). Multivariate analyses, on the other hand, did not indicate that any intensity of fish intake, for those consuming greater or lesser amounts of LA, protected against advanced ARMD. The exact same pattern regarding a significant test for trend ($p<0.05$) associated exclusively with a lesser consumption of LA, compared with no significant multivariate analytic associations for either greater or lesser amounts of LA consumption, was observed for fish intake ($\geq$2 servings/week vs <1 serving/week) and advanced ARMD.

In the Beaver Dam Eye Study, Mares-Perlman et al. collected data on several covariates (see below), which were then entered into multivariate analysis.[80] The investigators found that, while the direction of the results suggested a possible protective role for seafood consumption in both early and late forms of ARMD, neither of these associations was statistically significant. Tests for trend likewise failed to support a protective role of seafood consumption in both forms of ARMD.

Ouchi et al. only conducted univariate analyses.[81] They observed that fish intake frequency (per week) did not differ between patients with advanced ARMD and controls. This was the only study of the six included ones which analyzed biomarkers data. Statistically significant between-group differences in plasma fatty acid fractions were not found. Using RBC

composition data, DHA (p=0.006) and AA levels (p=0.001) were significantly higher in advanced ARMD patients compared with controls. The meaning of these results is unclear.

Heuberger et al. divided the exposure data into quintiles, and conducted an appropriate multivariate analysis, including explicitly described confounders (see below).[84] They found that fish intake frequency was not associated with early or late ARMD.

Impact of Covariates and Confounders

Except for the Ouchi study,[81] which did not purport to study the influence of any covariates, an extensive assessment of covariates was performed in these six included studies. In the Cho et al. investigation, covariates included age, race, smoking, body mass index, energy, lutein and zeaxanthin intake, alcohol intake, physical activity, postmenopausal hormone use and occupation.[79] A direct calculation of sun exposure was not included, however. Smith et al. adjusted for age, sex, current smoking and family history of late ARMD.[83] Seddon et al. assessed the impact of age, sex, clinical center, education, caretenoid intake, measured systolic blood pressure, self-reported physical activity level, alcohol intake, body mass index, smoking status, and total caloric intake.[82] Mares-Perlman et al.[80] evaluated gender, smoking history, alcohol intake, time spent outdoors, dietary caretenoid intake, history of diabetes, cardiovascular disease and hypertension.

Covariates studied by Heuberger et al. were extensive.[84] They included age, sex, smoking status, hypertension, HDL and cholesterol levels, physical activity, eye color and estrogen use. They also examined serum levels of C-reactive protein, fibrinogen, triglycerides, LDL cholesterol, caretenoids, and vitamins E, C, and A. The analysis was then conducted, taking into account comorbid conditions (cardiovascular disease, diabetes, and hypertension) in an attempt to reduce any biases from recent dietary modifications related to their presence.

The statistical analyses in the five studies where covariates were entered into multivariate analysis did not necessarily control for all of the same factors, measure them in the exact same way (e.g., smoking status) or enter them into their analysis in the same or similar stepwise fashion. Moreover, the studies did not measure omega-3 fatty acid intake in the same way. That said, the studies did not observe the same patterns of result concerning the protective role of omega-3 fatty acid intake and ARMD. Thus, it was not possible to establish which covariables had the most consistently strong influences on study outcomes.

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Slowing the Progression of Age-related Macular Degeneration?

As observed in Summary Table 4 (below), derived from Evidence Table 1 (Appendix E*), a single RCT published in 2002 met eligibility criteria in investigating the question of omega-3 fatty acids' possible value in slowing the progression of ARMD.[76]

Overview of Relevant Study's Characteristics and Results

The only study addressing this question was a small, poorly designed RCT (n=35; 21 males; average age: 72 years) conducted by Scorolli et al. at a single university center in Bologna, Italy.[76] Patients with bilateral exudative ARMD, yet who were not myopic, were randomized to receive either: 1) photodynamic therapy (PDT) as well as 48 hours before the laser application, and for the 3 months following this therapy, an oral "cocktail" of 200 mg/day of antioxidant vitamin E in addition to 1000 mg/day PUFA from 600 mg/day LA, 200 mg/day ALA and 200 mg/day DHA (n=20); or 2) PDT alone (n=15). Neither the delivery of vitamin E and PUFAs, nor the energy/calories from these sources, was controlled for using some form of placebo, for example. This failure to control for the supplementation in a research design, that also failed to permit the effects of vitamin E, the omega-6 fatty acid (i.e., LA) and omega-3 fatty acids (i.e., ALA, DHA) from being teased apart, made it impossible to ascribe any possible clinical benefits to either or both of the omega-3 fatty acid components. How the exposure was delivered (e.g., capsules) was also not described. The two main outcomes were visual acuity and retinal metabolic function. Visual acuity was measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart in logMAR (i.e., minimum angle of resolution) units. Retinal metabolic function was assessed as recovery time after the Magder flicker test. The latter measures retinal metabolic function after a bright macular light stimulus. Both outcomes were measured 20, 40 and 60 days after the PDT. Only univariate analyses were conducted.

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Summary Table 4: Omega-3 fatty acid intake to slow the progression of age-related macular degeneration (RCT)

Author, Year, Location: Length & Design	Study groups[1]		Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)		
Scorolli, 2002, Italy: 3 mo parallel RCT[76]	PDT + 200 mg/d vitamin E + 600 mg/d LA + 200 mg/d ALA + 200 mg/d DHA (n=20)	PDT alone (n=15)	Jadad total: 2 [Grade: C]; Schulz: Unclear	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; LA = linoleic acid; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; d = day(s); wk = week(s); mo = month; wt = weight; Δ = change; PDT = photodynamic therapy; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear)

The RCT report did not describe many trial elements. It did not define a source population or identify the number of screened patients, those who were excluded, or those who withdrew. It did, however, delineate the inclusion and exclusion criteria. Inclusion criteria included the presence of a neovascular membrane under the fovea in one eye which had a logMAR visual acuity between 0.7 and 0.3. Exclusion criteria included age under 55 years, prior ocular surgery, and a history of (other) retinal disease. No details concerning allowable, restricted or taken cointerventions were provided. There was no mention of compliance. No key covariates were measured. There were no descriptions of an *a priori* sample size estimation, power given the present sample, or a plan for interim analysis. Neither the identity of the manufacturers nor the purity of the exposure materials were identified

This trial received a Jadad total quality score of 2, indicating low quality, and an allocation concealment rating of Unclear. The lowest ranking was assigned with respect to applicability (i.e., III). Given the existence of only one relevant study, a summary matrix was considered unnecessary.

The recovery time after macular flash was significantly shorter in the PDT plus antioxidant/PUFA group compared with the PDT alone group at 20 days only ($p<0.001$). There was a trend to improvement at 40 days for the treated group but it was not significant. This trend was even smaller at 60 days. There was no difference in visual acuity between the two groups at any time point.

What is the Evidence that Omega-3 Fatty Acids Decrease the Rate of Progression *to* Advanced Forms of Age-related Macular Degeneration?

As observed in Summary Table 5 (below), derived from Evidence Table 3 (Appendix E*), one single prospective cohort study published in 2003 met eligibility criteria in investigating the question of omega-3 fatty acids' possible value in decreasing the rate of progression *to* advanced forms of ARMD.[60]

Overview of Relevant Study's Characteristics and Results

As part of the Progression of ARMD Study, Seddon et al. analyzed data from a single prospective cohort involving 261 patients drawn from a Boston hospital-based retina practice specializing in ARMD.[60] Of the 397 patients eligible for the study between May 1988 and July 1989, 92% were enrolled. Of the 366 enrollees, 36 did not complete the study and their data were not analyzed. Subjects were 60 years of age or older (mean: 72.8 years) and were primarily white (99.9%). The patients had non-exudative ARMD at entry into the cohort, and had to have at least one eye with best corrected vision of 20/200 or better. Any patient with cancer other than non-melanoma skin cancer was excluded for fear that this diagnosis would alter the recent diet. The average followup time was 4.6 years (from less than 1 year to more than 7 years). Nineteen people were censored because of loss to followup and eight patients' data were not used because of inadequate or missing answers. All 27 patients did not differ significantly from the others with regards to age or education, although more women than men were lost to followup.

Summary Table 5: Association between omega-3 fatty acid intake and decreasing the rate of progression to advanced forms of age-related macular degeneration (observational study)

Author, Year, Location: Length & Design	Study groups[1]		Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)		
Seddon, 2003, US: 4.6 y (mean) single prospective cohort study[60]	n=261 ARMD pts, 101 of whom progressed to advanced ARMD		Total quality: 8 [Grade: A]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; d = day(s); wk = week(s); mo = month; wt = weight; Δ = change; ARMD = age-related macular degeneration

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Exposure status was assessed via a validated food frequency questionnaire. Fish intake was used as a proxy for omega-3 fatty acid intake. The questionnaire was mailed to patients before their first study visit and they were asked about their average consumption in the previous year. Review, coding and entry of data were masked.

The outcome was defined as progression to either geographic atrophy or neovascular disease. It was assessed by stereo fundus photographs and graded using a 5-point system. The system was modified from the one used during the Age Related Eye Disease Study (AREDS). Inter-grader reliability was assessed and was deemed to be good to very good (weighted kappa of 0.84). Any progression to grade 4 (extensive geographic atrophy) or grade 5 (an exudative choroidal neovascular membrane), or from grade 4 to grade 5 at any followup visit was considered a positive outcome. Each patient could only progress once in the followup period, counting only the first eye that progressed. Regression was not considered to be an option.

The Seddon et al. study received a total quality grade of A and an applicability rating of II, with the latter due to its almost exclusively white population.

From a final sample of 261 patients with ARMD, 101 progressed to advanced ARMD. A Cox proportional hazards analysis was performed, controlling for many covariates. Adjustments were made for age, gender, total energy intake and protein intake, number of years of education, smoking status, body mass index (BMI), systolic blood pressure, cardiovascular disease, self-reported alcohol intake and physical activity. Individual nutrients reported in the AREDS were also controlled for, including zinc, and vitamins C and E. The analysis also stratified for LA intake falling above or below the median.

The results indicated that fish intake did not affect the progression of ARMD to an advanced form overall, or in the high LA consumption group, but did protect against its advancement in the low (below median consumption) LA consumption group (RR: 0.36; 95%CI 0.14, 0.95).

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Slowing the Progression of Retinitis Pigmentosa?

As observed in Summary Tables 6 and 7 (below), derived from Evidence Tables 1 and 2 (Appendix E*), four studies, including one RCT,[73] one comparative before-after study,[77] and two noncomparative before-after studies,[72] met eligibility criteria in investigating the question of omega-3 fatty acids' possible value in slowing the progression of retinitis pigmentosa. The two noncomparative before-after studies were described in a single report.[72] These quasi-experimental studies were published between 1995 and 2004.

Overview of Relevant Studies

Hoffman et al. conducted a 4-year RCT comparing 400 mg/day DHA (n=23) and an identical looking and tasting gelatin placebo capsule (n=21), containing 400 mg/day corn/soy oil triglyceride, among male patients (mean age: 16 years; range 4-38 years) with X-linked retinitis

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

pigmentosa (XLRP).[73] Arguing that low levels of DHA in XLRP might influence retinal function, they aimed to elevate DHA RBC concentrations and to determine the effects of supplementation on the progression of XLRP. Patients were primarily recruited from an RP registry in the southwestern part of the US. The primary outcome was cone electroretinography (ERG) response to a 31 Hertz (Hz) flicker. Secondary ocular outcomes included rod ERG response, Humphrey visual field, fundus photography, visual acuity, dark adaptation, responses to a visual activity questionnaire and a patient opinion survey. Covariates assessed were age, race, body weight, and gene mutation. Safety outcomes (i.e., adverse events) were complemented by data from analyses of serum samples for: fatty acid content, antioxidants, total antioxidant capacity, platelet aggregation, alanine aminotransferase activity, and lipoprotein lipid profiles. Outcomes were assessed every 6 months. Descriptions in the report did not reveal inappropriate methods of handling or analyzing lipid samples.

Summary Table 6: Omega-3 fatty acids to slow the progression of retinitis pigmentosa (RCT)

Author, Year, Location: Length & Design	Study groups[1]		Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)		
Hoffman, 2004, US: 4 y parallel RCT[73]	400 mg/d DHA (n=23)	400 mg/d corn/soy oil triglyceride placebo (n=21)	Jadad total: 4 [Grade: A]; Schulz: Adequate	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear)

Dagnelie et al. performed a comparative before-after study over 6 months involving 20 volunteers, recruited over the internet from an RP list, who were then divided into two groups.[77] One group (n=10) received lutein alone (40 mg/day for 9 weeks, 20 mg/day thereafter), while the second group (n=10) received lutein (40 mg/day for 9 weeks, 20 mg/day thereafter) plus 500 mg/day DHA, vitamin B complex (dose not reported) and 600 mg/day digestive enzymes. The study aimed to study the impact of lutein supplementation. Ten patients were not discouraged from on-study consumption of additional, prestudy supplements (e.g., vitamin A palmitate and/or beta carotene), thereby further compounding the failure to give a placebo to the "lutein alone" group to control for the supplementation received by the other group. Only 13 of the 16 patients were specifically identified with RP, with the remaining three patients (n=2 in lutein alone group) exhibiting other retinal degenerations outside the focus of the present review. The primary outcomes were self-tested visual acuity and central visual acuity evaluated weekly for 14 weeks and bi-weekly thereafter. Age, gender eye color and RP disease type were also recorded.

Summary Table 7: Omega-3 fatty acids to slow the progression of retinitis pigmentosa (quasi-experimental studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Internal validity	Applicability
Dagnelie, 2000, US, Canada & 7 other countries: 6 mo comparative before-after study[77]	Lutein (40 mg/d for 9 wk, 20 mg/d thereafter) + 500 mg/d DHA + vitamin B complex (dose not reported) + 600 mg/d digestive enzymes (n=10)	lutein alone (40 mg/d for 9 wk, 20 mg/d thereafter) (n=10)	Total quality: 2 [Grade: C]	III
Hoffman, 1995, US: 6 wk noncomparative before-after study (Study 1)[70]	3 g/day purified fish oil (0.7 g/day DHA, 1.3 g/day EPA) (n=3)		Total quality: 4 [Grade: C]	X
Hoffman, 1995, US: 3 wk noncomparative before-after study (Study 2)[70]	EPA ethyl ester (dose not reported) (n=3)		Total quality: 3 [Grade: C]	X

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change

Hoffman et al. performed two small studies of omega-3 fatty acid supplementation, where visual function was a secondary outcome.[72] Although controls were included in each trial, they received the same supplementation as did the two studies' respective autosomal dominant RP (Study 2: attributable to rhodopsin mutations) patient groups. Controls' results were also never provided. For the purposes of the present review, it was thus decided to examine only the data from the RP patients, effectively making each of these designs a noncomparative before-after study. Several ocular parameters were measured in each study, including ERG, visual acuity and visual fields. But, only ERG results were reported. Covariates were not assessed in either study.

In both studies, the diet of participants was modified first, so as to reduce possible variability in on-study background omega-3 fatty acid intake.[72] Then, in Study 1, three autosomal dominant RP patients were given a 3 g/day oral dose of a purified fish oil (0.7 g/day DHA, 1.3 g/day EPA) concentrate for 6 weeks. In Study 2, three autosomal dominant RP patients were given a purified preparation of EPA (i.e., EPA ethyl ester; 99.4% purity; dose not reported) for 3 weeks. In each study, 0.2 mg/g tert-butyl-hydroquinone and 2 mg/g tocopherols were added, as antioxidants, to maintain the exposure's freshness. Whether or not capsules were used to deliver the exposures is unclear. A key focus of each study was the impact of supplementation on RBC fatty acid contents.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. The inclusion/exclusion criteria in Hoffman et al.'s RCT were well documented, and randomization was discussed in detail.[73] Masking was implied but not

explicitly detailed. Compliance was measured as RBC DHA content. A sample size calculation and descriptions of losses to followup were provided. An intention-to-treat analysis was undertaken. No details regarding interim analysis were provided. Numerous funding sources were identified (see Evidence Table 1: Appendix E*).

Dagnelie et al.'s eligibility criteria were poorly detailed.[77] Their funding source was not provided.[77] These investigators provided few details regarding the selection criteria. Selection criteria for Hoffman et al.'s two small studies were sparse.[72] Their research was supported by the National Retinitis Pigmentosa Foundation Inc (US) and by the National Eye Institute.[72]

Population characteristics. Male patients with XLRP in Hoffman et al.'s RCT were recruited from the Southwest Eye Registry of the Retina Foundation and from clinical centers supported by the Foundation for Fighting Blindness.[73] Eligibility criteria included a retina specialist's diagnosis of RP, a family history consistent with X-linked inheritance, a large amplitude cone response, and a baseline diet that did not purposefully include large amounts of omega-3 fatty acids. Fifty-two individuals were assessed for eligibility and 44 were randomized.

The source population in the Dagnelie et al. study[77] study was not clearly documented.[77] The sample came from an internet RP list, yet further details regarding recruitment were not provided. Of the 30 listed patients who initially showed interest, 20 decided to enroll in the study. Of these 20, four did not provide sufficient data and hence the final analyzed sample included 16 participants. The patients came from nine different countries, with 60% from the US (n=7) and Canada (n=5). Age and gender were noted in the study. The genetics of RP inheritance was varied.

In Hoffman et al.'s two noncomparative before-after studies, the source populations were not described at all.[72] In the fish oil study (Study 1), the mean age was 31.7 years (n=2/3 male). In the EPA study (Study 2), the mean age was 29.3 years (n=2/3 female). For Study 2, the rhodopsin gene mutations were documented.

Intervention/exposure characteristics. Hoffman et al.'s RCT report clearly defined the intervention received by both study groups and its method of delivery via capsules.[73] The daily dose of two 500 mg capsules provided a total fat content of 1000 mg/day for both study groups. Those patients taking the DHA content essentially received about 10 mg of DHA per kilogram of body weight per day. The DHA-enriched oil came from a single-cell algal source and was provided as a highly purified triacylglycerol. The investigators provided descriptions concerning the purity of their omega-3 fatty acid contents, and their source company (Martek Biosciences Corporation, US).

The purity of Hoffman et al.'s noncomparative before-after Study 2 exposure was identified, as was the source of their omega-3 fatty acid contents for both studies (Fish Oils Test Materials Program, US).[72] Dagnelie et al. mentioned the names of manufacturers of their supplements, yet no purity data were supplied.[77] These same investigators did not report compliance data.

In the three studies that evaluated the fatty acid content of biomarkers, no notable inappropriate methods to extract, prepare, store or analyze lipids were described.[72,73] No study report in the whole review included details as to whether, or how, the presence of methylmercury was tested or eliminated from an omega-3 fatty acid exposure.

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Outcome characteristics. Visual outcomes were recorded annually and the total duration of the Hoffman et al. RCT was 4 years.[73] Their primary outcome was cone ERG response amplitudes to a 31 Hz flicker under maximal pupil dilation. Rod response was assessed as a secondary outcome. A Humphrey visual field 30-2 was also performed and the mean defect was the specific outcome used. Fundus photos were taken as per the ETDRS protocol, and grading was completed. The Visual Activities Questionnaire was also given to all patients. A patient survey of the perceived benefit of the intervention was included. Additional outcomes included specific biological safety data: total fatty acid content, and their relative ratios, vitamin A and E levels (in ug/dL), total antioxidant capacity in synthetic vitamin E equivalents, platelet aggregation (impedance units), alanine aminotransferase activity (in U/L) and lipoprotein lipid profiles (mg/dL). Patients were also requested to report all adverse events.

In the Dagnelie study, the investigators created six visual acuity charts in the form of Microsoft Word™ files.[77] Patients were instructed to use the six charts in rotation on their monitor at arm's length and not to change the working distance. Patients entered the number of letters seen in this binocular test on a weekly report form. For central visual field testing, the patients had to create their own field via instructions given to them. The field area seen was recorded by the patient and submitted via the internet. Participants submitted data each week for 26 weeks and included subjective data on glare, dark and light adaptation, night vision, color vision, depth perception, peripheral vision, and adverse event data with respect to allergy or irritation in the eyes. Each subjective answer was binary, but a more detailed questionnaire was filled out at the end of the study (using a non-validated scale).

In the two Hoffman et al. noncomparative before-after studies, best corrected visual acuity was performed using Bailey-Lovie eye charts.[72] The better eye was then used for the rest of the testing. Kinetic visual fields were obtained with Goldman IV4e spot sizes. Full field ERGs were obtained and the protocol followed international standards.

Study quality and applicability. While the Hoffman et al. RCT received a total quality grade of A and an applicability rating of II (i.e., only males were enrolled), the three quasi-experimental studies by Dagnelie et al.[77] and Hoffman et al.[72] each attained a total quality grade of C (Summary Matrix 2). Of the latter three studies, only the one conducted by Dagnelie et al. received an applicability grade (i.e., III).[77] Hoffman et al.'s two studies did not provide sufficient information to permit determinations of applicability.[72] These studies were therefore excluded from the summary matrix.

Summary Matrix 2: Study quality and applicability of evidence regarding the association of omega-3 fatty acid intake and progression of retinitis pigmentosa (all designs)

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
		Hoffman[A]	2004	44						
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author	Year	n	Author	Year	n
								Dagnelie	2000	20

n = number of allocated/selected participants; RCT = [A]Adequate vs [U]Unclear allocation concealment; k = 1000's

Qualitative Synthesis of Individual Study Results

By the fourth year of Hoffman et al.'s RCT, the average loss of cone function in the DHA supplementation group was 25% lower than what was observed in the control group; but, this difference was not statistically significant.[73] Given that five patients were deemed noncompliant based on RBC levels of DHA, secondary analyses were performed to explore the relationship between DHA RBC level and ERG progression. None of the results achieved a level of statistical significance, however. Rod ERG loss was 48% lower in the DHA group compared with the control group, yet this difference was also not statistically significant. The rod and cone loss showed effect modification by age. Specifically, the rod functional loss was significantly reduced in the prepuberty group supplemented with DHA compared with placebo (p=0.04), and the cone functional loss was significantly reduced compared with placebo in the post-puberty group supplemented with DHA (p=0.038).

Visual field, acuity and dark adaptation outcomes did not differ between the groups.[73] Fundus photographs showed significantly less progression in the DHA group when compared with placebo (p=0.04). Visual activity questionnaire results were not different in the two groups, but significantly more patients receiving DHA supplementation felt their treatment had benefited them compared with placebo patients. Stratification for genetic mutation status did not yield between-group differences.[73] There were no between-group differences in the results relating to the biological safety assessment. Self-reported adverse event data for the Hoffman et al. RCT are provided in association with the last question in this Chapter.

In the Dagnelie et al. study, there were statistically significant improvements in visual acuity and kinetic visual fields for the 16 participants (p=0.05).[77] Analysis by supplement type (lutein alone vs lutein plus omega-3 fatty acids plus vitamin B and enzymes) failed to observe a significant difference for either outcome, but there was a trend for improvement in both outcomes for the lutein alone group. Either way, given the study design it was impossible to isolate the specific impact of the omega-3 fatty acids on clinical outcomes. Dagnelie et al.'s study report did not present outcome data organized to allow for a meaningful investigation of only those data from patients with specific types of RP.[77] In Hoffman et al.'s two noncomparative before-after studies, the ERG results showed no statistically significant before-after changes.[72]

Impact of Covariates and Confounders

In Hoffman et al.'s RCT, age, race and body weight were recorded.[73] A gene mutation analysis was also performed, distinguishing between the RPGR mutation and the RP24 mutation. Dagnelie et al. measured age, race, country of origin, baseline supplementation, type of RP and the genetic component of RP.[77] However, there was a paucity of detail concerning the regression models designed to assess the influence of these possible covariates. In Hoffman et al.'s two noncomparative before-after studies' reports, age, gender and rhodopsin gene mutation data were provided.[72] However given the extremely small sample sizes within each study, meaningful effect modification analysis could not be performed.

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Slowing the Progression of Proliferative Retinopathy in Patients with Diabetic Retinopathy?

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Slowing the Progression of Clinically Significant Macular Edema in Patients with Diabetic Retinopathy?

As observed in Summary Table 8 (below), derived from Evidence Table 2 (Appendix E*), a noncomparative before-after study published in 1997 met eligibility criteria in investigating two questions. Given that 12 patients with diabetes were identified with proliferative retinopathy, this study was included in the review. As well, this study constitutes at best an indirect investigation of the question of omega-3 fatty acids' possible value in slowing the progression of clinically significant macular edema in patients with diabetic retinopathy. The impact of the intervention on macular edema was not directly evaluated although conditions associated with macular edema were observed. Given that this study investigates each of the two questions in limited fashion, it is systematically reviewed only once.

Overview of Relevant Study's Characteristics and Results

Sorokin et al. evaluated 48 patients (n=20 males; mean age: 56 years) with diabetic retinopathy (DR), 14 of whom had type I diabetes.[75] There were also 12 non-diabetic controls, whose data were not pertinent to the present review. Although it is likely that the sample was selected from the investigators' institution, this was not explicitly stated. Patients were divided into four groups, based on degree of severity: 1) "Preclinical" (i.e., DR detected only by angiography; n=12); "Manifest DR" (i.e., microaneurysms; n=10); 3) "Exudating DR" (i.e., lipid exudation; n=14); and, 4) "Proliferative DR" (n=12). Few other details were provided. With

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

respect to the diagnostic evaluation of the patients, it should be noted that, of the four stages, only stage 4 meets North American standards. All patients received a standard daily dose of 4 g of Eiconol (DHA+EPA) for 3 months. The method of delivery was not indicated, however. No other details concerning the omega-3 fatty acid intervention (e.g., purity; how freshness was maintained) were described.

Summary Table 8: Omega-3 fatty acids intake to slow the progression of proliferative retinopathy and clinically significant macular edema in patients with diabetic retinopathy (quasi-experimental study)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Internal validity	Applicability
Sorokin, 1997, Russia: 3 mo noncomparative before-after study[75]	4g/d DHA+EPA (n=48)		Total quality: 1 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; d = day(s); wk = week(s); mo = month; wt = weight; Δ = change

Primary and secondary outcomes were not distinguished. Moreover, the serum concentrations of cholesterol and triglyceride, whose data were provided, were not relevant to this review. Another outcome was the microcirculation of the bulbar conjunctiva, which the authors described as a proxy for retinal microcirculation. However, in North America this is not considered standard diagnostic practice, and hence this outcome was not considered relevant for this review. A third outcome entailed the fluorometric assessment of fluorescein leakage (measured as concentration) into the vitreous, a relevant but proxy outcome for diabetic retinopathy in North America. The fourth outcome was evaluated using the photostress test, which measures photoreceptor recovery after light stimulation. This is also a proxy outcome. Finally, there was a before-after clinical comparison of the eye fundus, which is a North American gold standard. However, neither the details of the method of exam (e.g., clinic recording, photographs) nor the quantification of the results were provided in the report. No confounders were investigated.

Results indicated that 36.7+/-2.8% of patients demonstrated a larger number of functioning capillaries within 1 mm of the "field of vision." It is unclear exactly to what the investigators were referring by this term. A decrease of 24.1+/-1.9% in the presumed vitreous permeability of fluorescein dye was found among 72.7+/-1.7% of patients with exudative and proliferative DR. The photostress test showed that the original visual acuity factor reduced by 0.3+/-0.05 among 39.1+/-1.4 % of the treated patients when compared to their baseline level ($p<0.05$). Although details are sparse with respect to these data or the results of tests of significance, these outcomes were described as having been improved in patients who took the supplements, but especially in those patients with the least advanced forms of diabetic retinopathy. There was also a "more intense resolution of diabetic hemorrhages" after the administration of the intervention (data not

reported). This study received a total quality grade of C and an applicability rating of III. The latter was assigned because of the background diet of the study participants.

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Preventing Age-related Cataracts?

As observed in Summary Table 9 (below), derived from Evidence Table 3 (Appendix E*), two single population cross-sectional studies met eligibility criteria in investigating the question of omega-3 fatty acids' possible value in preventing age-related cataracts.[85,86] These studies were published in 2000 and 2002.

Overview of Relevant Studies' Characteristics and Results

As part of the Blue Mountains Eye Study, Cumming et al. conducted a (single) population-based cross-sectional study examining several diet variables and the three main types of cataract in elderly urban dwellers.[86] A door to door census of the region was undertaken. All permanent residents of the area were invited to attend a local clinic for a detailed eye examination if they were born in 1942 or earlier. Of the 4,433 eligible people identified, 3,654 attended the study clinic between January 1992 and January 1994. Of the participating patients, 3,267 completed the questionnaire and 2,900 (median age: 65 years; range: 49-97 years) provided usable data on nutrient intake.

Photographic assessments of dilated pupils were used to establish cataract status. The method employed a Topcon slit lamp camera system and followed an established protocol (i.e., Beaver Dam Study). A 145-item food frequency questionnaire, modified for the Australian diet, was also employed.[86] Cataracts were assessed as nuclear, cortical or posterior subcapsular. Two masked graders assessed the photographs and established an inter-rater agreement between 0.57 and 0.79. The method of adjudication was not discussed.

The only assessment for omega-3 fatty acid intake was by distant proxy, namely, via descriptions of the intake of broccoli and spinach, each of which contains small amounts of omega-3 fatty acids (i.e., ALA). Data relating to PUFA consumption could not be used to indicate omega-3 fatty acid intake, given that omega-3 and omega-6 fatty acid types of PUFA were not distinguished. Several covariates that were established by interview-assisted questionnaire, including risk factors for cataract, were controlled for: smoking history, education, use of oral or inhaled corticosteroids, a history of diabetes or hypertension. Sun related damage was assessed visually by examining subjects' arms, hands and faces and was recorded on an ordinal scale. The study was supported by the Australian Department of Health and Family Services and the Save Sight Institute, University of Sydney.

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Summary Table 9: Association between omega-3 fatty acid intake and onset of age-related cataracts (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Internal validity	Applicability
Cumming, 2000, Australia: single population cross-sectional study[86]	Elderly urban dwellers (median age: 65 y) (n=2,900)		Total quality: 5 [Grade: B]	III
Arnarsson, 2002, Iceland: single population cross-sectional study[85]	Pts ≥50 y of age (n=1,045)		Total quality: 5 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change

As part of the Reykjavik Eye Study (August to October 1996), Arnarsson et al. included 1,045 persons in a single population cross-sectional study examining risk factors for nuclear lens opacities.[85] The source and sample populations were clearly described. A random sample was taken from the population census. It included 1,700 citizens from Reykjavik who were at least 50 years of age. Of the 1,379 individuals who were eligible and could be located, 1,045 of them were interviewed and examined. All were Caucasian. Further demographic details of the overall baseline population were not provided. Patients underwent an eye examination that included slit and retroilluminated images of the lens, using a Nidek camera. Whether or not all patients' pupils were dilated was not stated. Patients also filled in an in-depth questionnaire. Cataract was assessed via anterior segment photographs. The diagnosis and grading of nuclear lens opacities followed the Kanazawa Medical University (KMU) system, which roughly follows the Lens Opacity Classification System II (LOCS II) system. All grades of nuclear lens opacity were combined to afford an analysis evaluating the presence, or absence, of cataract. The method of adjudication, the number of evaluators, and whether they were masked, were not described in this paper.

A 26-item food frequency questionnaire was employed.[85] Several proxies for omega-3 fatty acid intake were studied, including consumption of cod-liver oil, fish, plant oil, herring, sardines, and shrimp. Several covariates were controlled for, including ultraviolet (UV) exposure (typical outdoor exposure over time, and cumulated). The latter was a covariate that was controlled for only by Mares-Perlman et al.[80] in their ARMD study (see above). Other factors assessed in Arnarsson et al.'s study were: age, asthma, diabetes, cardiovascular disease, smoking, alcohol consumption, pseudoexfoliation glaucoma, computer usage, infrared light exposure, iris color, hyperopia, glaucoma, use of antihypertensive medication, and the use of cholesterol lowering drugs, systemic corticosteroids or allopurinol.[85] These covariables were measured via interview, examination and by questionnaire. The study was performed at the Department of Ophthalmology in Reykjavik in cooperation with the Department of Ophthalmology, Kanazawa

Medical University. Although the funding source for this study was not given, it is well known that this study had been funded by the National Medical Research funding agency of Iceland.

Each study received a total quality grade of B and an applicability rating of III, the latter indicating little potential for their results to be meaningfully extrapolated to the North American population (Summary Matrix 3).

Summary Matrix 3: Study quality and applicability of evidence regarding the association of omega-3 fatty acid intake and onset of age-related cataracts (observational studies)

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author	Year	n	Author	Year	n
					Cumming	2000	2900			
					Arnarsson	2002	1045			

n = number of allocated/selected participants; RCT = [A]Adequate vs [U]Unclear allocation concealment; k = 1000's

The Reykjavik Eye Study data presented by Arnarsson et al. revealed no statistically significant associations between nuclear cataract and the consumption of omega-3 fatty acid foods or oils obtained from fish or seafood.[85] The Blue Mountains Eye Study found an inverse association between consumption of all PUFA content and cortical cataract.[86] However, this observation cannot be used to address the research question for the reason described earlier. There was no association between the consumption of broccoli or spinach and nuclear cataract.

What is the Evidence for Efficacy of Omega-3 Fatty Acids in Slowing the Rate of Progression of Age-related Cataracts?

As observed in Summary Table 10 (below), derived from Evidence Table 2 (Appendix E*), one noncomparative before-after study published in 2001 met eligibility criteria in investigating the question of omega-3 fatty acids' possible value in slowing the rate of progression of age-related cataracts.[78]

Overview of Relevant Study's Characteristics and Results

Among the studies included in this review, only one even indirectly addressed the question of the relationship between omega-3 fatty acid consumption and the slowing of the progression of age-related cataracts. It was a noncomparative before-after study conducted by Suzuki et al.[78]

* Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/03eyetp.htm

Fifteen volunteers were given a daily supplement of DHA. Fourteen of these individuals had pre-existing cataract at the time of supplementation. Of these participants, three also had glaucoma. The fifteenth subject exclusively exhibited glaucoma. The source population was not well described, however. Study participants were drawn from 30 volunteers (mean age: 72 years; range: 58-74 years) participating in a dementia study. All lived in a nursing home for the aged. Visual acuity was measured before and after DHA supplementation, although this focus was secondary to the assessment of dementia (i.e., the primary outcome). However, the study did not explicitly measure changes in cataract status; rather, it measured visual acuity in patients with cataract. Covariates were not measured. A funding source was not provided.

Summary Table 10: Omega-3 fatty acids intake to slow the progression of age-related cataracts (quasi-experimental study)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Internal validity	Applicability
Suzuki, 2001, Japan: 3 mo noncomparative before-after study[78]	0.54 g/d DHA (n=14/15 pts with cataract)		Total quality: 2 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; d = day(s); wk = week(s); mo = month; wt = weight; Δ = change

Participants each received six capsules per day containing a total of 0.54 g odorless DHA oil for 3 months. They maintained their normal diet, ingesting approximately 0.73 g/day DHA and 0.53 g/day EPA. While the manufacturer of the exposure was identified (Sugo, Co.), purity data were not described. As well, the method by which the oil was deodorized was not provided. No mention was made of whether anything had been added to the oil to maintain its freshness.

The outcome was visual acuity, measured using Landolt's rings, before and after 3 months of supplementation. No measurements or photographs of cataracts were taken at any time in this study. No covariates were assessed. This study received a total quality grade of C and an applicability rating of III.

Results indicated that vision improved in 10 of 15 patients, while nine of 14 patients with cataracts showed an improvement in vision (no results of tests of significance reported). Given the nature of the outcome, however, it remains unknown whether the cataracts themselves were reduced.

What is the Evidence for the Risk of Short and Longterm Adverse Events Related to the Intake of Omega-3 Fatty Acids?

Adverse events are often underreported in study reports; therefore, failure to report any does not constitute evidence that none occurred. That said, no report of an interventional study in our review explicitly stated that no exposure-related events had been observed. A number of interventional studies, employing various populations, interventions/exposures and followup durations, did not report either having solicited adverse effects data from study participants or having received such reports.[72,75,76,78] Dagnelie et al. asked patients to report adverse effects, yet no data were supplied.[77] The use of interventional "cocktails" containing multiple active ingredients in the Dagnelie et al.[77] and Scorolli et al.[76] studies would have prevented the meaningful attribution of any specific harms to the intake of omega-3 fatty acids, had they been observed and reported. Only Hoffman et al.'s RCT investigation of the impact of DHA supplementation on XLRP both solicited and reported the occurrence of adverse effects.[73]

Ten study participants reported only short-term, minor adverse events over the 4 years of Hoffman et al.'s trial with XLRP patients.[73] No patients were forced to withdraw from the study due to any of these effects. Six placebo group patients (age range: 13-32 years) and four patients receiving 400 mg/day DHA (age range: 9-19 years) noted some adverse effects. Placebo group patients described: bruising (n=2 events), with post-event followup revealing that both instances were related to physical contact sports; a sinusitis (n=1) preceding prolonged epistaxis (n=1); prolonged bleeding (n=1), although a post-event bleeding time test revealed that bleeding time was within normal limits; eructation (i.e., "burp back;" n=1); nausea (n=1); and, flatulence (n=1). The nausea lasted less than a week, and both the eructation and flatulence were related to the consumption of the corn/soy oil contents. One instance each of apnea, fainting and a "weird feeling" were established as unrelated to the study by parents or family physician.

Summary Table 11: Interventional studies reporting adverse events (e.g., side effects) or contraindications

Author, Year, Location: Length & Design	Study groups[1]		Safety data
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	
Hoffman, 2004, US: 4 y RCT[73]	400 mg/d DHA (n=23)	400 mg/d corn/soy oil triglyceride placebo (n=21)	Placebo group (n=6 pts): bruising* (n=2 events); a sinusitis (n=1) preceding prolonged epistaxis (n=1); prolonged bleeding (n=1); eructation (i.e., burp back; n=1); nausea (n=1); & flatulence (n=1); DHA group (n=4 pts): eructation (n=1 event); acne* (n=1); headache* (n=2); ear infection* (n=1); fatigue* (n=1); & weight gain* (n=1).

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; *Established that "not study related;" **No explicit description that adverse events specifically linked to exposure, only that associated with participants in a specific study group; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; grp = group; wk = week(s); mo = month

The DHA group reported a single case of eructation related to capsule consumption.[73] Other adverse events included: acne (n=1 event); headache (n=2); ear infection (n=1); fatigue (n=1); and, weight gain (n=1). The participants' parents or family physician described the latter five effects as normal events of adolescence.

Half of the 10 patients with adverse event reports each experienced more than one adverse event during the course of the 4-year trial.[73] However, only one of these circumstances (i.e., a sinusitis, then prolonged epistaxis in a patient receiving placebo) was identified in the study report. Seven of the youngest patients initially had to take four half-sized capsules to achieve their daily DHA dose because they had difficulty swallowing the regular capsules. Over time, however, these patients were able to swallow their daily dose via two full-sized capsules like the other study participants.

Given this safety profile, it appears that DHA intake was associated with few minor, mainly, gastrointestinal effects. The doses of oil and DHA from this intervention would be considered low, when compared to other interventional studies trying to influence respiratory[71] or mental health outcomes with omega-3 fatty acids. Finally, Hoffman et al.'s biological safety assessment (i.e., plasma antioxidant capacity; vitamin A concentration; whole blood platelet aggregation; liver function enzyme activity; plasma lipoprotein lipid profiles) indicated that this low dose DHA was not associated with any identifiable safety risk.[73] However, while significant between-group differences on these safety outcomes were not observed, both study groups exhibited lower platelet aggregation and vitamin E values than the laboratory reference standards.[73] Finally, plasma vitamin E levels exhibited a nonsignificant trend towards lower concentrations in the last 2 years of the study, suggesting that future interventional studies should surveil these on-study values.

Chapter 4. Discussion

Overview

Only 16 studies, described in 16 published journal reports, were deemed relevant for inclusion in this systematic review. These studies addressed nine of the 23 questions that we posed in this evidence synthesis. This includes a focus on the possible adverse effects of the intake of omega-3 fatty acids. A brief overview of the studies is now presented, and it is organized in terms of which eye disease/visual impairments constitute the most important public health concerns, particularly in developed countries.

The eye disease/visual impairment likely constituting the most important public health concern is ARMD, and it was investigated by the largest number of studies. Eight studies examined either its primary[79-84] or secondary prevention.[60,76] The ARMD studies involved various research designs, including one RCT[76] and various observational designs.[60,79-84] Therefore, half of the included studies examined the possible protective influence of the intake of omega-3 fatty acids on ARMD.

The next most important health concern is vascular disease of the retina in patients with diabetes. However, only one (quasi-experimental) study investigated the secondary prevention of events related to diabetic retinopathy.[75] Three studies examined the questions of primary[85,86] or secondary prevention[78] with respect to cataract. These primary and secondary prevention studies employed observational[85,86] and quasi-experimental designs,[78] respectively. The possible impact of the intake of omega-3 fatty acids on RP was examined in four studies,[72,73,77] with a report published by Hoffman et al. describing two of these investigations.[72] Study designs included one RCT[73] and three quasi-experimental designs.[72,77] No study was found which investigated outcomes related to occlusions of the retinal veins or arteries.

For each question, in turn, we now present a synthesis of the key findings. This includes a critical appraisal of the individual studies from which the results were drawn. Attention is paid to the numbers, size, quality and applicability (i.e., to relevant North American populations) of studies in trying to ascertain larger patterns of result. The broader implications of these findings, including potential future research, are highlighted. We begin with the cross-cutting issue of safety.

Evidence Synthesis and Appraisal

Only one interventional study collected adverse event data from study participants. When they carefully observed the possible links between the characteristics of their intervention (i.e., source of exposure, amount of omega-3 fatty acid content, numbers of capsule, etc.), Hoffman et al. reported only minor, invariably transient, effects primarily of a gastrointestinal variety.[73] None produced a discontinuation. This benign safety profile is consistent with the profiles

observed both in our review of the impact of omega-3 fatty acids on asthma[71] and our recently completed synthesis examining the impact of omega-3 fatty acids on mental health. Yet, the very low doses of both the omega-3 fatty acids (400 mg/day DHA) and the oil in which it was contained could account for Hoffman et al.'s results.[73] Moreover, when the adverse event data in Hoffman et al.'s placebo group are juxtaposed with those safety data obtained from participants receiving the omega-3 fatty acids, one possible interpretation is that the minor adverse effects were more closely linked to the daily consumption of oil than to the omega-3 fatty acid contents in the oil.[73] The placebo exposure contained some omega-6 fatty acid content. The ability of purified forms of omega-3 fatty acid exposures (e.g., ethyl esterifications) to contribute to maintaining blinding in experimental studies, due in large part to the minimization of the exposure's taste and odor, could not be evaluated because there were virtually no studies with which to assess this possibility.

There are sufficient between and within study conflicts (e.g., results of univariate vs multivariate analyses) in the results to preclude drawing any inference that is conclusive with respect to the value of the intake of omega-3 fatty acids to prevent ARMD (i.e., primary prevention). If it can be assumed that the study designs likely best suited to address this question should be both controlled and prospective, none of the included studies would qualify.

The only prospective study, which was conducted by Cho et al., included a large sample and appropriately conducted multivariate analysis, and controlled for key confounders.[79] These investigators observed that the consumption of canned tuna fish or more than four fish servings per week each played a protective role against ARMD.[79] Subgroup analyses purportedly revealed similar results (no data reported) when ARMD cases were classified by subtype (i.e., wet ARMD, and early and dry ARMD with geographic atrophy), and for advanced ARMD. However, Cho et al.'s results also indicated that several types of oily fish well known to have high concentrations of DHA and EPA (i.e., sardines, mackerel) failed to show a similar, protective effect. These discordant observations will require an explanation before anything conclusive can be asserted based on this study alone.

Moreover, Cho et al.'s study design did not a priori employ a separate, unexposed cohort as a control to establish a comparison with individuals consuming omega-3 fatty acids. Finally, while their dietary intake assessment was quite comprehensive, an assessment of the possible misclassification of non cases (i.e., no ARMD) was not performed. This is likely a result of the exposure-outcome question failing to be the primary focus of this study. That said, this observational study's sample exhibited strong applicability to the North American population.

The remaining relevant studies cannot resolve the divergent primary prevention results described by Cho et al., however. The two controlled studies employed a case-control design, and focused on whether the intake of omega-3 fatty acids exclusively protected against advanced forms of ARMD.[81,82] Seddon et al.'s study conducted appropriate multivariate analyses, which controlled for key confounders. Then, either with or without stratification for LA intake, Seddon et al. failed to find statistically significant associations between advanced ARMD and any intensity of fish intake, or combined EPA and DHA intake.[82] At best, tests for trend suggested a possible protective value of fish consumption for advanced ARMD in this sample population primarily consisting of white Americans. When LA intake was then controlled for in Seddon et al.'s study, the results of a test for trend suggested effective protection against advanced ARMD only when LA consumption was low.[82] The possible meaning of this finding is discussed below. Results of Ouchi et al.'s very small case-control study (n=21) were produced by univariate

analysis, involved a population whose results offer little potential for generalizability to the North American population, and revealed no association between fish intake and advanced ARMD.[81]

Heuberger et al.'s single population cross-sectional study, with multiple covariates entered appropriately into multivariate analysis, revealed that fish intake frequency was not associated with early or late ARMD.[84] Smith et al.'s multivariate analysis of data from a single population cross-sectional study also provided no evidence of a significant association between fish intake and either early or late ARMD.[83] However, the type of study design employed by these two studies cannot be considered ideal to address the question of prevention. Causality cannot be inferred without some degree of temporal separation between exposure and outcome. This is why prospective designs are preferred. Mares-Perlman et al.'s retrospective population-based cohort study, while potentially affected by recall bias, likewise showed no protective role of seafood consumption in early or late forms of ARMD.[80]

These six included studies varied in their definitions of the exposure, clinical outcome and/or confounders, which together with their conflicting results, makes it impossible to draw a definitive conclusion regarding the potential of the intake of omega-3 fatty acids to prevent the onset of either early or late ARMD. And, neither study quality nor applicability can serve to clarify the inconclusive picture revealed by these six studies. The meaning of Ouchi et al.'s biomarker results is unclear.

The nature of the RCT design and the "cocktail-like" exposure employed by Scorolli et al. made it impossible to examine the specific impact of omega-3 fatty acids on slowing the progression of ARMD.[76] A small sample size, the uncommonness and dubious clinical relevance of the visual recovery outcome, low study quality, and little or no applicability to the North American population suggest that there are, at present, no data with which to meaningfully address this research question.

Seddon et al.'s single prospective cohort study found that fish intake did not affect the progression to advanced ARMD overall, or in a high LA consumption group, but did protect against the progression to advanced ARMD in the low (below median consumption) LA consumption group.[60] This parallels what was observed exclusively via a significant test for trend in the Seddon et al. study described earlier with reference to its investigation of the influence of the intake of omega-3 fatty acids on preventing the onset of advanced ARMD.[82] The implications of this observation are discussed below. Both Seddon et al. studies exhibited the highest absolute study quality scores observed in the entire systematic review.[60,82] Nevertheless, the results from neither study can be used as yet to provide a conclusive answer to their respective research questions. The results from the Seddon et al. study addressing the progression to advanced ARMD require replication.[60]

The four studies examining whether the intake of omega-3 fatty acids slows the progression of RP do not provide a conclusive answer to this question.[72,73,77] Hoffman et al.'s good quality RCT constituted the most rigorous test and revealed conflicting results.[73] That said, rod and cone functional loss showed effect modification by age, with rod loss significantly reduced in the prepuberty group supplemented with DHA compared with placebo, and cone loss significantly reduced in the post-puberty group supplemented with DHA compared with placebo. The observation that certain analyses failed to reveal statistically significant between-group differences could be explained by this having been an underpowered trial.[73]

By virtue of its research design, which did not permit the isolation of the specific impact of omega-3 fatty acids on slowing the progression of RP, results from Dagnelie et al.'s internet-based comparative before-after study cannot be used to meaningfully address this question.[77] In Hoffman et al.'s two very small noncomparative before-after studies of short duration, ERG results did not reveal statistically significant changes following supplementation.[72] Thus, until Hoffman et al.'s RCT[73] is replicated with a much larger sample size, little that is conclusive can be said about the potential value of the intake of omega-3 fatty acids in slowing the progression of RP.

Sorokin et al.'s noncomparative before-after study received a low study quality score and failed to resolve the questions of whether the intake of omega-3 fatty acids can slow the progression of either proliferative retinopathy or clinically significant macular edema in patients with diabetic retinopathy.[75] This study did not constitute the best test of either of these possibilities, however. The most relevant clinical outcome by North American standards entailed fundus assessments, yet few details were reported. Covariates were not measured, and the univariate analysis of the data was flawed. Thus, the results of this study are inconclusive with respect to these two possible benefits of the intake of omega-3 fatty acids in diabetic retinopathy.

Although both the Arnarsson et al.[85] and Cumming et al.[86] studies are well known population-based risk factor studies, in neither of them was the association between the intake of foods or oils containing omega-3 fatty acids and age-related cataract prevalence the primary question. That said, no statistically significant associations were observed. Cross-sectional designs constitute very limited tests of this question.

Suzuki et al.'s noncomparative before-after study did not assess cataract status as its clinical outcome, preferring instead to examine visual acuity.[78] Thus, with improvements in visual acuity unlikely to have been produced by reduced cataract formation, this study does not directly address the question of whether the intake of omega-3 fatty acids can slow the rate of progression of age-related cataracts. .

Overall, we identified very few relevant studies per research question, which is the first important observation stemming from this review. Second, where multiple studies were found to address a given question, small sample sizes and either specific flaws or notable variability in the research designs, as well as in the definitions of the study populations, exposures/interventions, clinical outcomes, or covariates/confounders employed to investigate it, made it impossible or inappropriate to consider conducting a quantitative synthesis (i.e., meta-analysis) or a systematic appraisal of the role played by key covariates/confounders (e.g., reliable relationships between clinical and biomarker effects in interventional studies). Moreover, if it can be assumed that the best tests of these questions concerning prevention would involve study designs that are both prospective and controlled, while including large samples, other than the two RCTs,[73,76] none of the studies would qualify. Finally, many of the included studies received low total quality scores and exhibited limited or no applicability to the North American population. The implications of these observations are considered next.

Clinical Implications

The intake of omega-3 fatty acids in the present review's collection of interventional studies was not associated with moderate or severe adverse events. Supplementation was well-tolerated, with some mild and transient, mostly gastrointestinal events occurring occasionally. This finding may misrepresent what actually occurred in these studies if safety data were under-reported.

Nothing conclusive can be asserted with respect to the possible eye health benefits accruing to the intake of omega-3 fatty acids. At the same time, nothing at all can be said with respect to the potential eye health-related value of various sources (e.g., marine, plant), types (e.g., DHA, EPA, ALA) or doses/serving sizes of (foods containing) omega-3 fatty acids. Likewise, nothing can be said about for whom (e.g., subpopulations) these exposures/interventions might (not) be beneficial. Much more research is required.

Research Implications and Directions

ARMD is a significant public health problem. Treatment of dry ARMD with antioxidant vitamins provides only a small benefit, while treatment of advanced ARMD with PDT may provide greater statistical, than clinical, evidence of benefit. These observations, seen in light of an ageing North American population, suggest that ARMD may soon become an even greater public health challenge. That said, the question of its progression to advanced forms is likely *the* question in the field of ARMD. The development of early ARMD is of lesser clinical importance and may be an inevitable part of ageing. Advanced forms, on the other hand, cause considerable morbidity. This includes greater loss of vision and a decreased quality of life. Progression to advanced forms can carry a similar burden.

The possible worsening of this public health problem associated with an ageing population likely justifies additional research, and with a special focus on the secondary prevention of advanced forms of ARMD. The ideal study would likely enroll patients at high risk for development of advanced ARMD. Incident cases of advanced forms of ARMD would serve as the primary outcome (e.g., geographic atrophy or choroidal neovascular net formation). An adequately powered RCT could be conducted to test the placebo-controlled efficacy of omega-3 fatty acid supplementation. Indeed, there exists a biologically plausible relationship between omega-3 fatty acid intake and ARMD progression, given there are high levels of omega-3 fatty acids, especially DHA, in the retina.[60]

To exercise control over the type of omega-3 fatty acids and its dosing, and thereby maximize the interpretability of results, specific capsulized doses of purified DHA should likely be employed as the active intervention. Servings of food, or even oils poured from bottles, can lead to situations whereby within- and between-subject variability in daily on-study intake of omega-3 fatty acids can confound study results.[71] Thus, proxies for omega-3 fatty acids (e.g., fish intake) should likely be avoided. Given the relative safety of omega-3 fatty acid supplementation, a high dose exposure might be wise, to avoid a false negative trial result.

The purification of DHA would minimize active contents' odor and taste, which in turn should help maintain experimental blinding. Given that it does not contain PUFA content, liquid paraffin could be used as the placebo content. At this point in time, however, it is unknown which dose(s) might prove efficacious, and so pilot work beforehand in uncontrolled studies is indicated. Moreover, additional preliminary work could recommend that a blend of DHA and EPA be used instead of DHA alone. The final trial design could accommodate multiple levels of dosing or combinations of omega-3 fatty acid type. Also, pilot research could help define the minimum duration of supplementation required to notice a (lack of) benefit. Ideally, it would be helpful if followups lasted on the order of years, given that progression to key milestones (e.g., advanced ARMD) likely does not occur rapidly. Finally, it is possible that endocannabinoids and lipoxins, which have been linked to LC PUFAs, will prove more biologically important than the omega-3 fatty acids themselves. Pilot research is indicated.

The two ARMD studies conducted by Seddon and colleagues have suggested that any trial should likely control, either experimentally or analytically, for the intake of omega-6 fatty acids.[60,82] They noted eye health benefits associated with omega-3 fatty acid intake only in those participants consuming lower levels of LA. This observation provides tentative support for the hypothesis that omega-3 fatty acid supplementation is more likely to have a clinical impact if omega-6 fatty acid intake is minimized. Omega-3 and omega-6 fatty acids stand in competitive relationship for enzymes (e.g., desaturases) and for positioning in cell membranes, and if there is large intake of omega-6 fatty acids, omega-3 supplementation may fail to (enter cell membranes from which to) make a clinical difference.[71] Seddon and colleagues' observations suggest to us that, at minimum, the measurement of LA intake could help identify those individuals and eye diseases/visual impairments for whom omega-3 fatty acid supplementation might prove clinically beneficial.[60,82]

In effect, consideration should be given to accounting for the on-study omega-6/omega-3 fatty acid intake ratio from both supplementation and the background diet in making sense of study outcomes. The intervention could be even more complex: e.g., actively decreasing the intake of omega-6 fatty acids, while omega-3 fatty acid intake is increased. This may be important given that certain investigators have suggested that various types of disease are linked to higher omega-6/omega-3 fatty acid intake ratios;[46-58] and, above a certain value, this intake ratio could preclude consumed omega-3 fatty acids from becoming incorporated within the human biosystem (i.e., cell membranes), and in turn contributing to (ameliorating) eye health. Trial investigators might consider accounting for prestudy/baseline omega-6/omega-3 fatty acid intake levels as well. The reader is reminded that populations in different geographic locations and countries vary in terms of their omega-6/omega-3 fatty acid intake ratio,[46-58] and often in no small part because of their intake of marine sources of omega-3 fatty acids.[71] It is with this understanding that the present review's indices of applicability were defined, with the North American population as the reference point.

Confounders also requiring consideration include, but are not restricted to, exposure to sunlight, smoker status, and alcohol consumption. The latter two variables can influence both health status and essential fatty acid status.[59,60] No evidence reviewed here indicated the presence of reliable empirical relationships between (e.g., blood lipid) biomarker content and ARMD, or any other eye health outcomes.

RP is a relatively rare condition, but its public health importance is notable because it affects young and very young individuals. The impact can be observed as the loss of many potential

years of vision. Another measure of RP's public health significance is the relatively large number of funding organizations and support groups whose central focus is this condition.

However, clinical research with regards to RP is complicated by a few observations. While RP is a rare disorder, its forms are quite heterogeneous. That said, an intervention found to be efficacious for XLRP may produce minimal or no benefit in autosomal dominant RP. Furthermore, even a single genetic classification such as XLRP refers to an heterogeneous set of genetic entities.

It is our view that, at this time, more observational research should be taken to begin to identify the specific links between exposures to omega-3 fatty acids and the onset as well as progression of the different RP subtypes. If prospective cohort studies were undertaken that used dietary intake data obtained from existing RP registries, reasonable, RCT-testable hypotheses could be generated. These prospective studies could also permit the identification of promising exposures and intervention lengths for each of the RP subtypes. It is possible that supplementation would be needed before a critical time period of programmed cell death. The reviewed study of XLRP by Hoffman et al. is a laudable effort, whose replication should include a larger sample size.[73]

As one of the most important morbidities associated with diabetes mellitus, diabetic retinopathy is the most important ophthalmic public health problem among adults of working age. There is face value to expecting that omega-3 fatty acids might be helpful in diabetic retinopathy, given that lipid exudation plays such an important role in background and preproliferative retinopathy. Given the extremely flawed nature of the single study identified by our review, it is our view that research with this focus has essentially not begun.[75] Therefore, prospective observational designs (e.g., cohort study) likely constitute the best option with which to begin studying the value of omega-3 fatty acids in diabetic retinopathy. The key outcome would be clinically significant macular edema, as it has been measured in all previous ETDRS studies. Important covariates to assess include control of diabetes via HgA1c, blood pressure, and smoker status.

Cataracts are the most important cause of blindness worldwide, while also constituting one of the most costly burdens on Western health care systems. Unfortunately, little is understood about its primary prevention. A nutritional contribution to cataract formation is nevertheless conceivable given its higher prevalence in underprivileged populations.

The sparse evidence identified by our review[85,86] suggests that some prospective observational studies be conducted first. The two cross-sectional studies could shed little or no light on possible causal links between exposures and outcomes. A prospective cohort study, which entails clear documentation of the intake of omega-3 fatty acids and regular lens assessments, might be the ideal starting point. Stratification by type of cataract would be essential to account for this source of clinical heterogeneity. Also important would be to control for possible etiologic factors such as smoking, sunlight exposure, and medication use.

As it was observed with respect to ARMD, cataract progression, and not its formation, has the largest public health impact. A mild nuclear sclerotic cataract, which reduces visual acuity by one or two lines, is usually well-tolerated by patients. However, progression to advanced forms of cataract significantly affects one's ability to drive and quality of life. A prospective cohort study, which identifies the impact of the intake of omega-3 fatty acids on the progression of cataracts from mild to severe, would be an ideal study focus.

Given that studies were not found to have examined the relationship between the intake of omega-3 fatty acids and either retinal vein or retinal artery occlusions, preliminary observational work is likely indicated. Finally, since several questions of pertinence to this systematic review could be addressed within a longterm (e.g., 10-year) prospective cohort design, one such study could simultaneously investigate many of the outcomes that our review sought to examine (e.g., cataract, diabetic retinopathy, ARMD, and perhaps even progression of some forms of RP).

If future research is going to produce data that are unequivocally applicable to North Americans, it will likely need to enroll either North American populations or populations exhibiting a high omega-6/omega-3 fatty acid intake ratio similar to what has been observed in the diet of North Americans. It is our view that the dietary omega-6/omega-3 fatty acid intake ratio may eventually be seen to play an important role in the prevention and treatment of various forms of eye disease/visual impairment.

Limitations of the Review

While there are some limitations characterizing the present systematic review, almost none could likely be considered a serious impediment to the interpretation of the evidence we identified and synthesized. Overall, we found too few studies investigating a given question, and employing an appropriate research design of sufficient size and sound methodology, to have these limitations alter the view that, at present, we cannot conclude anything definitive about the eye disease/visual impairment-specific or overarching roles of omega-3 fatty acids in eye health. As well, the possible roles played by likely covariates and confounders could not be evaluated as planned. We were limited in what we could observe because of the paucity of relevant studies per question, and because many studies did not specifically investigate the influence of these variables. Or, if they did, the definition of these factors varied to some extent.

As stated in Chapter 2, in light of the relatively limited details often provided in reports about the ways in which lipid samples were extracted, stored and analyzed, we could only readily identify situations where investigators described inappropriate methods. It is unclear how this state of affairs might have influenced the very few observations we gleaned from the evidence base concerning the role of omega-3 fatty acids in eye health.

Time constraints made it impossible to complete dual-assessor appraisals of the quality (i.e., internal validity) or applicability of studies. One experienced quality assessor conducted these evaluations. At the same time, we conducted these quality assessments using items we either modified from existing instruments, or which we had to develop outright because no similar tools existed (e.g., noncomparative before-after studies). A design-specific, total quality score was then generated for each study, from which a single summary value was derived (i.e., A, B, C). This simplification permitted the entry of these values into summary matrices. However, the design-specific cutpoints used to assign these values were established without any validational basis, and so their value is likely extremely limited. The applicability indices, while continuing the work we did when we systematically reviewed the evidence for the health effects of omega-3 fatty acids on asthma,[71] also did not receive any validational support. Nevertheless, given the limited number of studies addressing a specific question, and using a design whose data could meaningfully elucidate it, it is unlikely that these shortcomings could have had a meaningful

impact on the limited "take home messages" highlighted by our review. Formal statistical assessments of the impacts of study quality or applicability on study outcomes could not be conducted. Finally, with meta-analysis deemed impossible or inappropriate, an examination of the possible presence and impact of publication bias could not be conducted.

Conclusion

Based on the studies identified by this review, it is apparent that clinical research has only scratched the surface with respect to understanding the possible utility of the intake of omega-3 fatty acids as a primary or secondary prevention in eye health. Moreover, seen from the point of view of clinical research's typical, linear arc—which moves from basic science to observational research to RCTs, and culminating in the systematic review/meta-analysis of the observations obtained by these primary studies—there is a paucity of solid observational research with which to construct an experimental framework affording the meaningful conduct of RCTs. For example, there is little understanding of the exact sources, types and doses of omega-3 fatty acids, or even the possible duration of their use, which might usefully serve as definitions of a prevention-centered "intervention" for any of the eye diseases/visual impairments examined in our review. Moreover, a single study reporting adverse event data likely does not permit laying to rest all possible concerns regarding the short- or long-term safety of such an intervention.

It is therefore our view that much more research will need to be conducted before anything conclusive can be asserted with respect to the effects of omega-3 fatty acids on eye health. It is also our understanding that sorting out the possible benefits of the intake of omega-3 fatty acids in eye health might profit from taking into consideration the impact of the concurrent intake of omega-6 fatty acids and, by definition, the omega-6/omega-3 fatty acid intake ratio. Finally, any notable causal or correlational relationships observed between the omega-6/omega-3 fatty acid intake ratio and the development or progression of eye disease/visual impairment may then be "explained" by future studies, which focus on observing patterns of omega-6/omega-3 fatty acid content in peripheral, or even brain, biomarkers.

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Abbreviations

AA (20:4 n-6)	Arachidonic acid
AI	Adequate Intake
ALA (18:3 n-3)	Alpha linolenic acid
cAMP	Cyclic adenosine monophosphate
C5a	Complement fragment 5a
COX	Cyclooxygenase
DHA (22:6 n-3)	Docosahexaenoic acid
DTS	Dense tubular system
EAR	Estimated Average Requirement
EFA	Essential fatty acid
EPA (20:5 n-3)	Eicosapentaenoic acid
GLA (18:3 n-6)	Gamma linolenic acid
HDL	High density lipoprotein
IFN	Interferon
IgE	Immunoglobulin E
IL	Interleukin
LA (18:2 n-6)	Linoleic acid
LC PUFA	Long-chain polyunsaturated fatty acid
LDL	Low density lipoprotein
LT	Leukotriene
PG	Prostaglandin
PPAR	Peroxisome proliferator activated receptor
PUFA	Polyunsaturated fatty acid
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowances
SREBP	Sterol regulatory element binding protein
Tg	Triglycerides
TNF	Tumor necrosis factor
Tx	Thromboxane
VLDL	Very low density lipoprotein

Search Strategy 1

Medline, Pre-medline, Embase, Cochrane Library on Ovid

1. exp Retinal Vessels/
2. Retinal Degeneration/
3. exp Macular Degeneration/
4. Retinal Drusen/
5. exp Neovascularization, Pathologic/
6. exp Diabetic Retinopathy/
7. Retinal Vasculitis/
8. Retinal Vein Occlusion/
9. Retinal Artery Occlusion/
10. exp Retinitis/
11. Fluorescein Angiography/
12. Macular Edema, Cystoid/
13. (retinal adj5 thrombosis).tw.
14. sub?retinal neovascular$.tw.
15. (fluorescence adj5 angiography).tw.
16. (fundus adj5 fluorescence adj photography).tw.
17. ((central or branch) adj5 retinal adj5 occlus$).tw.
18. ((retinal or choroidal) adj5 neovascularization).tw.
19. ((vein or artery) adj5 retinal).tw.
20. ((macul$ or retina$ or choroid$) adj5 (degener$ or neovasc$)).tw.
21. ((wet or dry or nonexudative) adj5 macular adj5 degeneration$).tw.
22. ((age-related or senile) adj5 macular adj5 degeneration$).tw.
23. (ARMD or AMD).tw.
24. (cystoid adj5 macular adj5 edema).tw.
25. (geograph$ adj3 atrophy).tw.
26. (clinically significant adj5 macular adj5 edema).tw.
27. CSME.tw.
28. Cataract/
29. exp Cataract Extraction/
30. lens opacit$.tw.
31. angiogenesis.mp.
32. ((aspiration$ or operation$ or removal or surger$) adj5 cataract).tw.
33. (maculopath$ adj5 age$).tw.
34. exp Retinitis Pigmentosa/
35. (pigment$ adj5 retinopath$).tw.
36. ((rod cone or rod-cone) adj5 dystroph$).tw.
37. (tapetoretina$ adj5 degeneration).tw.
38. (proliferative adj5 retinopathy).tw.
39. ((age related or age-related) adj5 cataract).tw.
40. ((nuclear sclero$ or posterior subcapsular or cortic$) adj5 cataract).tw.
41. or/1-40
42. exp fatty acids, omega-3/
43. fatty acids, essential/
44. Dietary Fats, Unsaturated/
45. linolenic acids/
46. exp fish oils/
47. (n 3 fatty acid$ or omega 3).tw.

48. docosahexa?noic.tw,hw,rw.
49. eicosapenta?noic.tw,hw,rw.
50. alpha linolenic.tw,hw,rw.
51. (linolenate or cervonic or timnodonic).tw,hw,rw.
52. menhaden oil$.tw,hw,rw.
53. (mediterranean adj diet$).tw.
54. ((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$).tw.
55. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
56. (fish adj2 oil$).tw.
57. (cod liver oil$ or marine oil$ or marine fat$).tw.
58. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
59. (fish consumption or fish intake or (fish adj2 diet$)).tw.
60. diet$ fatty acid$.tw.
61. or/42-60
62. dietary fats/
63. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
64. random$.tw.
65. exp clinical trials/ or evaluation studies/
66. follow-up studies/ or prospective studies/
67. or/63-66
68. 62 and 67
69. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
70. (omega 3 or n 3).mp.
71. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
72. 70 and 71
73. 61 or 68 or 69 or 72
74. 41 and 73

Search Strategy 2

CAB Health on Silverplatter

#1 "retina-" in SU(527 records)
#2 explode "eye-diseases" in SU(4645 records)
#3 explode "retinitis-" in SU(515 records)
#4 (macular near degener*) in ti,ab,id(115 records)
#5 age-related-macular-degeneration in ID(15 records)
#6 ((central or branch) near5 retinal near5 occlus*) in ti,ab,id(23 records)
#7 ((vein or artery) near5 retinal) in ti,ab,id(41 records)
#8 ((macul* or retina* or choroid*) near5 (degener* or neovasc*)) in ti,ab,id(225 records)
#9 ((wet or dry or nonexudative) near5 macular) in ti,ab,id(1 records)
#10 ((age-related or senile) near5 macular near5 degeneration*) in ti,ab,id(86 records)
#11 (ARMD or AMD or AMD) in ti,ab,id(185 records)
#12 (cystoid near5 macular near5 edema) in ti,ab,id(3 records)
#13 (geograph* near atrophy) in ti,ab,id(3 records)
#14 (clinically significant near5 macular near5 edema) in ti,ab,id(1 records)
#15 (Diabet* near5 Retinopath*) in ti,ab,id(183 records)
#16 (retina* near5 thrombosis) in ti,ab,id(4 records)
#17 lens opacit* in ti,ab,id(35 records)
#18 ((aspiration* or operation* or removal or surger*) near5 cataract) in ti,ab,id(135 records)
#19 (maculopath* near5 age*) in ti,ab,id(33 records)
#20 (fluoresce* near5 angiography) in ti,ab,id(65 records)

Appendix A. Search Strategies (continued)

#21 angiogen* in ti,ab,id(317 records)
#22 (sub?retinal neovascular*) in ti,ab,id(27 records)
#23 ((sub?retinal neovascular*) in ti,ab,id) or (angiogen* in ti,ab,id) or (((age-related or senile) near5 macular near5 degeneration*) in ti,ab,id) or (((wet or dry or nonexudative) near5 macular) in ti,ab,id) or (((macul* or retina* or choroid*) near5 (degener* or neovasc*)) in ti,ab,id) or (((vein or artery) near5 retinal) in ti,ab,id) or (((central or branch) near5 retinal near5 occlus*) in ti,ab,id) or (age-related-macular-degeneration in ID) or ((macular near degener*) in ti,ab,id) or (explode "retinitis-" in SU) or (explode "eye-diseases" in SU) or ("retina-" in SU) or ((fluoresce* near5 angiography) in ti,ab,id) or ((maculopath* near5 age*) in ti,ab,id) or (((aspiration* or operation* or removal or surger*) near5 cataract) in ti,ab,id) or (lens opacit* in ti,ab,id) or ((retina* near5 thrombosis) in ti,ab,id) or ((Diabet* near5 Retinopath*) in ti,ab,id) or ((clinically significant near5 macular near5 edema) in ti,ab,id) or ((geograph* near atrophy) in ti,ab,id) or ((cystoid near5 macular near5 edema) in ti,ab,id) or ((ARMD or AMD or AMD) in ti,ab,id)(5769 records)
#24 omega 3(1102 records)
#25 ("essential-fatty-acids" in SU) or ("linolenic-acid" in SU)(1944 records)
#26 ("docosahexaenoic-acid" in SU) or ("eicosapentaenoic-acid" in SU)(1541 records)
#27 explode "plant-oils" in SU(5613 records)
#28 explode "fish-oils" in SU(2061 records)
#29 "fish-consumption" in SU(269 records)
#30 "polyenoic-fatty-acids" in SU(4159 records)
#31 "polyunsaturated-fats" in SU(336 records)
#32 "dietary-fat" in SU(1480 records)
#33 (n 3 fatty acid* or omega 3) in ti,ab,id(3126 records)
#34 (docosahexanoic or docosahexaenoic) in ti,ab,id(2049 records)
#35 (eicosapentanoic or eicosapentaenoic) in ti,ab,id(1710 records)
#36 (alpha linolenic)in ti,ab,id(865 records)
#37 (linolenate or cervonic or timnodonic) in ti,ab,id(179 records)
#38 (mediterranean diet) in ti,ab,id(305 records)
#39 ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or menhaden) and oil*) in ti,ab,id(2004 records)
#40 (walnut* or butternut* or soybean* or pumpkin seed*) in ti,ab,id(1922 records)
#41 (fish oil* or cod liver oil* or marine oil* or marine fat*) in ti,ab,id(2766 records)
#42 (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*) in ti,ab,id(2069 records)
#43 (fish consumption or fish intake) in ti,ab,id(478 records)
#44 (diet* fatty acid*) in ti,ab,id(1499 records)
#45 (ropufa or maxepa or omacor or efamed or resq or epagis or almarin or coromega) in ti,ab,id(92 records)
#46 ((omega 3 or n 3) and (polyunsaturated fat* or pufa or dha or epa or long chain or longchain or lc*)) in ti,ab,id(2404 records)
#47 "long-chain-fatty-acids" in SU(588 records)
#48 (fish and diet) in ti,ab,id(3113 records)
#49 (explode "essential-oils" in SU) or (explode "olive-oil" in SU) or (explode "palm-oils" in SU) or (explode "plant-oils" in SU) or (explode "seed-oils" in SU)(7977 records)
#50 explode "fish-liver-oils" in SU(210 records)
#51 ("long-chain-fatty-acids" in SU) or (((omega 3 or n 3) and (polyunsaturated fat* or pufa or dha or epa or long chain or longchain or lc*)) in ti,ab,id) or ((ropufa or maxepa or omacor or efamed or resq or epagis or almarin or coromega) in ti,ab,id) or ((diet* fatty acid*) in ti,ab,id) or ((n 3 fatty acid* or omega 3) in ti,ab,id) or ("dietary-fat" in SU) or ("polyunsaturated-fats" in SU) or ("polyenoic-fatty-acids" in SU) or ("fish-consumption" in SU) or (explode "fish-oils" in SU) or (explode "plant-oils" in SU) or (("docosahexaenoic-acid" in SU) or ("eicosapentaenoic-acid" in SU)) or (("essential-fatty-acids" in SU) or ("linolenic-acid" in SU)) or (omega 3) or ((fish consumption or fish intake) in ti,ab,id) or ((salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*) in ti,ab,id) or ((fish oil* or cod liver oil* or marine oil* or marine fat*) in ti,ab,id) or ((walnut* or butternut* or soybean* or pumpkin seed*) in ti,ab,id) or (((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or menhaden) and oil*) in ti,ab,id)

or ((mediterranean diet) in ti,ab,id) or ((linolenate or cervonic or timnodonic) in ti,ab,id) or ((alpha linolenic)in ti,ab,id) or ((eicosapentanoic or eicosapentaenoic) in ti,ab,id) or ((docosahexanoic or docosahexaenoic) in ti,ab,id) or (explode "fish-liver-oils" in SU) or ((explode "essential-oils" in SU) or (explode "olive-oil" in SU) or (explode "palm-oils" in SU) or (explode "plant-oils" in SU) or (explode "seed-oils" in SU)) or ((fish and diet) in ti,ab,id)(23294 records)

#52 ((explode "almond-oil" in SU) or (explode "castor-oil" in SU) or (explode "coconut-oil" in SU) or (explode "cottonseed-oil" in SU) or (explode "groundnut-oil" in SU) or (explode "jojoba-oil" in SU) or (explode "linseed-oil" in SU) or (explode "maize-oil" in SU) or (explode "melon-seed-oil" in SU) or (explode "mustard-oil" in SU) or (explode "palm-kernel-oil" in SU) or (explode "rapeseed-oil" in SU) or (explode "rice-oil" in SU) or (explode "safflower-oil" in SU) or (explode "sesame-oil" in SU) or (explode "soyabean-oil" in SU) or (explode "sunflower-oil" in SU) or (explode "tung-oil" in SU) or (explode "wheat-germ-oil" in SU)) or (("cod-liver-oil" in SU) or ("menhaden-oil" in SU))(3270 records)

#53 #51 or #52(23294 records)

#54 #23 and #53(147 records)

Letter to Industry Representatives from the Three EPCs Investigating the Health Benefits of Omega-3 Fatty Acids

May 2, 2003

Dear _____,

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. I will be out of town next week and will respond to any questions when I get back. If you have any questions that you would like addressed before I return, please contact Donna Mead at the address above.

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
maclean@rand.org

Relevance Assessment Form

Please respond to the first 6 questions.*Use the comments box to identify duplicate reports, a key review whose references should be checked, anomalies, etc.

a. **Inclusion criteria**:

1. Does this report describe a study involving human participants?
   YES Can't Tell NO

2. Does this study evaluate the role of omega-3 fatty acid intake (diet and/or supplementation) as an intervention/exposure?
   YES Can't Tell NO

3. Is the purpose of the study to investigate the effect (e.g., efficacy) of omega-3 fatty acid intake on: a. (e.g., preventing; slowing the progression of) advanced stage vascular diseases of the retina, or, age-related cataracts; b. slowing the progression of retinitis pigmentosa; c. the rate of cataract surgery in ageing populations; or d. the rate of progression *to*, or *of*, advanced forms of macular degeneration?

b. **Exclusion criterion**:

4. If this is a narrative or systematic review, opinion piece or editorial, letter, guideline or policy paper, etc., does it *exclusively* describe studies already reported elsewhere (i.e., it does not present any empirical evidence published for the first time)?
   YES Can't Tell NO

c. **Context**:

5. The study appears to *also or instead* concern omega-3 fatty acids as an intervention/exposure associated with the following human health/disease domains *(select at least one option; click on all that apply)*:
   __transplantation
   __cancer
   __neurology
   __child/maternal health
   __mental health
   __none of the above

6. Is this report written in English?
   YES NO

7. Comments box

***All questions were used in both screening levels.**

Data Abstraction Form

Instructions: ***Please answer each question.*** Selecting response options means clicking on them. A text box ("BOX") requires that you provide specific data, and allows you to provide clarification, as needed (e.g., when the available data are not straightforward). When data are not reported (= NR), the question does not apply (= N/A), you cannot tell what/where the data are in the report (= CT), the data are not broken down (= NBD) to permit the required abstraction (e.g., by study group), or you have no comment to make (= NC), type the code in the BOX.

'Participants' refers to study participants. 'Group' refers to a study group, arm or cohort or, in a crossover design, a study phase. Often, you will be asked to abstract 'full' sample data as well as by group. If requested group data are not available, abstract full sample data and label it as such.

If more than one report describes this study, draw on each to abstract study data. This means that, for question 2, record all of the relevant report Refid#s, and for question 3, record all of the relevant reports' data. When you are abstracting data from multiple reports for a given study, point out any inconsistencies.

If the research report describes more than one unique study, answer in this eForm all the questions for the *first reported study* while immediately notifying the review manager that another data abstraction form is required.

Initials of reviewer: **BOX**

Reference identification #s (Refid#s) of all report(s) referring to this study, including duplicate reports, data-splitting reports, additional follow-ups, re-analyses, etc.: **BOX**

First author's last name, year of publication, country(s) in which study conducted (*from each relevant report*), [# study sites] (e.g., Smith, 1988, Canada [1 site]): **BOX**

Number of unique, review-relevant studies that this report describes (*if more than one, notify review manager*): **BOX**

Publication status, per report/Refid# referring to this study (e.g., Refid 3000=journal publication, Refid 6=conference abstract):

Peer-reviewed journal publication
Journal publication
Conference abstract/poster
Book
Book chapter
HTA/technical report
Thesis
Unpublished document
Study sponsor's internal report
Internet document/material
Other
BOX

Identity of funding source(s), including category per source (e.g., government, industry, private/non-industry, hospital), and what each provided: **BOX**

Please select all of the questions this study addresses:
Degenerative Diseases of the Retina: Macular Degeneration

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related macular degeneration?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of age-related macular degeneration?
- What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration in diabetics?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *to* advanced forms of macular degeneration in patients with cataracts?
- What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration in diabetics?
    - What is the evidence that omega-3 fatty acids decrease the rate of progression *of* advanced forms of macular degeneration in patients with cataracts?

Degenerative Diseases of the Retina: Retinitis Pigmentosa

- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinitis pigmentosa (i.e., an inherited retinal dystrophy)?

Vascular Diseases of the Retina: Retinal Vein or Retinal Artery occlusions

- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal vein occlusion?
- What is the evidence for efficacy of omega-3 fatty acids in preventing retinal artery occlusion?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal vein occlusion?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of retinal artery occlusion?

Vascular Diseases of the Retina in Diabetics:

- What is the evidence for efficacy of omega-3 fatty acids in preventing proliferative retinopathy in diabetics?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of proliferative retinopathy in diabetics?

- What is the evidence for efficacy of omega-3 fatty acids in preventing clinically significant macular edema in patients with diabetic retinopathy?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the progression of clinically significant macular edema in patients with diabetic retinopathy?

Cataracts:

- What is the evidence for efficacy of omega-3 fatty acids in preventing age-related cataracts?
- What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts?
    - What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in diabetics?
    - What is the evidence for efficacy of omega-3 fatty acids in slowing the rate of progression of age-related cataracts in patients with age-related macular degeneration?
- What is the evidence that omega-3 fatty acids decrease the rate of cataract surgery in ageing populations?

Adverse Events:

- What is the evidence for the risk of short and long-term adverse events related to the intake of omega-3 fatty acids?

Study design (*select one*):

a. RCT parallel design
b. RCT crossover design
c. RCT factorial design
d. Controlled clinical trial (non-RCT)
e. Multiple prospective cohorts
f. At least one prospective cohort and one retrospective cohort
g. Case-control
h. Cross-sectional
i. Before-after (pre-post)
j. Single prospective cohort
k. Single retrospective cohort
l. Case series (noncomparative)
m. Case study
n. Cross-national ecological analysis
o. Other: **BOX**

Any notable details (e.g., restricted randomization; blocking size) or problems (i.e., no or inappropriate run-in or washout procedures or durations; study stopped prematurely): **BOX**

Full sample eligibility criteria (e.g., population [e.g., pediatric vs adult, required diagnosis, permitted or mandatory comorbid conditions], intervention(s)/medication(s) [mandated vs permitted], cointervention(s) [mandated vs permitted]) (*complete both*):

Inclusion criteria: **BOX**
Exclusion criteria: **BOX**

Were the same eligibility criteria employed with reference to each study group? (*select one*)

a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable (e.g., a single group study)

Adequacy of reporting of eligibility criteria (*select one*):

a. Likely adequate (= not inadequate)
b. Likely inadequate (= missing, incomplete or conflicting data)

Adequacy of eligibility criteria:

a. Likely adequate (= not inadequate)
b. Likely inadequate (e.g., the inclusion criteria will not lead to the study of the target population the investigators intend to study; populations with diagnoses/conditions outside the investigators' intended scope, yet who show the same symptoms/signs as the target population, have not been identified as requiring exclusion)

Sample sizes (by population, if appropriate) (*complete all*):

Total # individuals screened: **BOX**
selected/allocated participants (full [e.g., n=12]; by group [e.g., group 1 n=5; group 2 n=7]): **BOX**
completers (= final followup)/total (full; per group) (e.g., group 1: n=4/5; group 2: n=6/7): **BOX**

Settings (*complete both*):

Type(s) of setting (e.g., tertiary care hospital vs. community facility) (full; by group): **BOX**
Proportion of participants in relatively controlled (e.g., inpatients) settings during study (full; by group): **BOX**

Study period (*complete all*):

Intervention length (d, wk, mo, y) (*by group only if it varies*): **BOX**
Study duration, including units (h, d, wk, mo) (includes intervention length + run-in period duration, washout duration[s], etc.): **BOX**
Run-in duration/protocol: **BOX**
Washout duration/protocol: **BOX**

Did participants in each study group receive the intervention/exposure for the same length of time? (*select one*)

a. Yes
b. No
c. Unclear

d. Not reported
e. Not applicable (e.g., a cross-sectional survey)

Was the same study procedure employed with reference to each study group? (*select one*)
a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable

Were participants in each study group assessed at the same number of followups, and with the same timing, during the study (*select one*)?
a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable (e.g., a cross-sectional survey)

Number and timing of followups (e.g., at 6 y of age), and any definition of the 'length of followup required to observe an/no impact of the exposure/intervention:' **BOX**

Adverse events, and losses to followup (*complete both*):
withdrawals vs. # dropouts, with reasons (full; by group): **BOX**
Adverse events/side effects and contraindications (full; by group): **BOX**

Basic population characteristics (*complete all*):
Mean age (mean (range) y) of all relevant participants at study onset (full; by group, by population): **BOX**
Percentage of males (full; by group): **BOX**
Racial composition (proportions: full; by group) (e.g., Caucasian 50%, Asian 50% per group) **BOX**
Level of education (full; by group): **BOX**

Pre-study/baseline eye, and general, health history (*complete all*):
At/by baseline, primary eye-related diagnosis (e.g., wet vs dry ARMD; nuclear sclerosis vs posterior subcapsular vs cortical vs mixed cataracts; autosomal dominant vs autosomal recessive vs X-linked vs other RP) (full; by group): **BOX**
Severity (full; by group): **BOX**
Prognosis (full; by group): **BOX**
Age at onset, age at diagnosis, and duration (i.e., time since diagnosis) (full; by group): **BOX**
Diagnostic method and tests (full; by group): **BOX**
Surgeries/therapies/medications (number; types, doses: e.g., photodynamic therapy; laser photocoagulation; visudyne; ASA; other antiplatelets; drops; vitrectomy), and responses thereto (full; by group): **BOX**

Lutein, beta carotene, anti-oxidant and other supplement (e.g., vitamins, minerals) intake, or CAM therapies, with (daily, weekly or monthly) source and dose/servings (full; by group): **BOX**

Concurrent conditions, or general health status (e.g., myopia; hyperopia; uveitis; choroideremia; ocular albinism, cone-rod dystrophy; high blood pressure; diabetes mellitus; cardiac disease; blood dyscrasias; lymphoma; leukemia; hypercoagulation state; clotting disorders; vasculitis; giant cell arteritis; dyslipidemia; renal disease; significant lipid profile), with severity, time since diagnosis, and duration (i.e., time since diagnosis) (full; by group): **BOX**

Medication/treatments per concurrent condition (e.g., insulin; oral hypoglycemics; estrogen use), with doses/frequency (full; by group): **BOX**

Exposure to sunlight (full; by group): **BOX**

Smoking, alcohol (ab)use, and illicit drug use history/status (full; by group): **BOX**

Other notable characteristics/conditions (e.g., pregnant; blue eyes; oral contraceptive use; steroid use) (full; by group): **BOX**

Pre-study/baseline n-3 intake (*complete all*):

Pre-study/baseline total (daily, weekly or monthly) n-3 intake *via diet and/or supplementation*, with amount per n-3 type (EPA, DHA, ALA), and source (e.g., fish servings; walnuts; flaxseed oil) (*by group*) (e.g., group 1: 1.8g/d EPA, 1.2g/d DHA, from 3 fish oil capsules/d; and, NR [likely EPA &/or DHA], from 1-2 fish servings/wk; group 2: 0g/d EPA, 0g/d DHA, water placebo; and, NR, 0 fish servings/wk): **BOX**

Pre-study/baseline total (daily, weekly or monthly) dietary n-6/n-3 intake (*by group*) (e.g., group 1: 15/1; group 2: 10/1): **BOX**

Pre-study/baseline % (daily, weekly or monthly) caloric/energy intake from fat (*by group*): **BOX**

Absolute and *relative* n-3 fatty acid content of the pre-study/baseline diet (full; by group): **BOX**

Types of pre-study/baseline diet (*proportion of participants on each diet: in full; by group*):

High fish diet
Fish-vegetarian diet
Low fish diet
Low fat diet
High fat diet
Mediterranean diet
Other
Unclear
Not reported
BOX

How was the pre-study dietary intake of n-3, n-6 and n-6/n-3 evaluated/estimated (*select all that apply*)?

Nutritionist-administered quantitative food-frequency survey(s)
Nutritionist-administered semi-quantitative food-frequency survey(s)
Self-administered quantitative food-frequency survey(s)
Self-administered semi-quantitative food-frequency survey(s)
Parent-administered quantitative food-frequency survey(s)
Parent-administered semi-quantitative food-frequency survey(s)
Direct measurement(s) of food intake
Survey(s) (e.g., 24-hour recall): **BOX**
Survey(s), yet no details provided
Other: **BOX**
Unclear
Not reported
Not applicable

Total amount of dietary n-3 intake (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Total amount of n-3 intake from supplementation (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Total amount of n-3 intake from diet and supplementation (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Dietary n-6/n-3 intake (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

% caloric/energy intake from fat (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Pre-study/baseline biomarkers data (by biomarker: e.g., RBCs; for DHA, EPA, AA, AA/EPA, AA/DHA, AA/EPA+DHA levels, with units (e.g., % total fatty acids; absolute amount) (full; by group): **BOX**

DHA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

EPA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

EPA+DHA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

AA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

AA/DHA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

AA/EPA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

AA/EPA+DHA status (per biomarker) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

ON-STUDY

How was on-study dietary intake of n-3 or n-6/n-3 evaluated/estimated (*select all that apply*)?

Nutritionist-administered quantitative food-frequency survey(s)
Nutritionist-administered semi-quantitative food-frequency survey(s)
Self-administered quantitative food-frequency survey(s)
Self-administered semi-quantitative food-frequency survey(s)
Parent-administered quantitative food-frequency survey(s)
Parent-administered semi-quantitative food-frequency survey(s)
Direct measurement(s) of food intake
Survey(s) (e.g., 24-hour recall): **BOX**
Survey(s), yet no details provided
Other: **BOX**
Unclear
Not reported
Not applicable

On-study GROUP 1 (highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

On-study GROUP 2 (next highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all; click* here *if there are no more study groups*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

On-study GROUP 3 (next highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all; click* here *if there are no more study groups*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

On-study GROUP 4 (next highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all; click* here *if there are no more study groups*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

On-study GROUP 5 (next highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all; click* here *if there are no more study groups*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

On-study GROUP 6 (next highest dose n-3 [or lowest n-6/n-3 ratio if both n-3 and n-6 are modified] study first, active comparator next (e.g., n-6), placebo control last) (*complete all; click* here *if there are no more study groups*):

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via all sources* (diet+supplementation), per n-3 type (e.g., NR, at least 3g/d EPA+DHA): **BOX**

total (daily, weekly or monthly) n-6 and/or n-6/n-3 intake from diet+supplementation: **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures (e.g., drops; lutein, beta carotene, anti-oxidants; vitamins, minerals), with dose/serving/frequency: **BOX**

n allocated-selected/ n completed (e.g., n=24/21): **BOX**

protocol (e.g., what is mandated vs. permitted), with method and target values, to modify daily, weekly or monthly n-6 or n-6/n-3 intake (e.g., increase daily n-3 intake to Y% of total daily fat intake, decrease daily n-6 intake to X% of total daily fat intake; e.g., none, participants told to maintain background diet) (by group): **BOX**

Briefly describe whether there was a clearly planned and instituted difference, between study groups, in their (daily, weekly or monthly) total-gram n-3 and/or n-6/n-3 intake: **BOX**

Briefly describe whether there was a clearly planned and instituted equivalence, across study groups, of (daily, weekly or monthly) caloric/energy intake from study-relevant exposures/interventions: **BOX**

Briefly describe any problems with compliance whereby notable deviations (e.g., decreases) from the planned amounts of intake (e.g., supplementation; servings) in one or more of the study groups violated the difference(s) established *a priori* between study groups for n-3 and/or n-6/n-3 intake or the equivalence established *a priori* across study groups for caloric/energy intake (full; by group): **BOX**

Briefly describe whether, and which, study groups/participants were asked to maintain their (pre-study/baseline) background diet while on-study (full; by group): **BOX**

Briefly describe whether, and how, without specific instruction to do so, or with specific instruction *not* to do so, participants' (pre-study/baseline) background diet was altered while on-study (full; by group): **BOX**

Briefly describe whether, and which, study groups/participants were asked to maintain their (pre-study/baseline) therapies/medications (e.g., drops) while on-study (full; by group): **BOX**

Briefly describe whether, and how, without specific instruction to do so, or with specific instruction *not* to do so, participants' (pre-study/baseline) therapies/medication (e.g., drops) were altered while on-study (full; by group): **BOX**

Briefly describe any evidence of selection bias: **BOX**

Primary eye-related diagnosis (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Severity and prognosis of eye-related condition(s) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Age at onset, age at diagnosis, and duration (i.e., time since diagnosis) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline were taken into consideration in the study analysis: **BOX**

Surgeries/therapies (number; types) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Medications, with types/doses (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Lutein, beta carotene, anti-oxidant and other supplement (vitamins, minerals) or CAM use, with types/doses **(*complete all*):**

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Concurrent conditions (e.g., diabetes), including severity, age at onset, time since diagnosis, and duration (i.e., time since diagnosis) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Medication/treatments (e.g., estrogen use) per concurrent condition (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Exposure to sunlight (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Smoking, alcohol (ab)use and illicit drug use (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Other characteristics/health status (e.g., blue eyes; oral contraceptives; steroid use) (*complete all*):

Significant (e.g., p-value; stated result of statistical test) pre-study/baseline between-group difference(s) (specify direction of difference(s): e.g., n-3 > pb): **BOX**

Significant (e.g., p-value; stated result of statistical test) between-group difference(s) in within-group changes from baseline, to each followup (specify nature of change(s), by followup: e.g., final followup = n-3 > pb): **BOX**

Specify whether any significant between-group differences at pre-study/baseline or regarding within-group changes from baseline, to each followup, were taken into consideration in the study analysis: **BOX**

Complete All

Name of n-3 product (e.g., Almarin, Coromega, Eiconol; Efamed, Epagis, MaxEPA, Menhaden oil, ResQ, Omacor, Ropufa, etc.): **BOX**
Manufacturer (*per product*): **BOX**
Purity data (*per product*): **BOX**
Presence of other, potentially active agents in n-3 product (*per product*): **BOX**
n-3 composition (%) of the exposure (e.g., 18% EPA, 12% DHA in each fish oil capsule) (*per product*): **BOX**

Reported method(s) to maintain the freshness (i.e., preclude rancidity) of n-3 exposures/interventions (e.g., added anti-oxidants to capsules, with fish oil exposure, to minimize oxidation): **BOX**

Reported method(s) to eliminate methylmercury from fish or its products/derivatives: **BOX**

Note any descriptions of inappropriate methods of lipid extraction/preparation (e.g., failure to extract blood after a [overnight] fasting period; failure to collect blood in EDTA- or EGTA-containing vials): **BOX**

Note any descriptions of inappropriate methods of lipid storage (e.g., failure to store samples at –70 to –80 degrees C if not analyzed immediately): **BOX**

Note any descriptions of inappropriate methods of lipid analysis (e.g., failure to conduct lab measurements on coded samples by technicians blinded to participants' identity and allocation; failure to use a standard protocol [e.g., Bligh & Dyer] requiring, for example, purging samples with nitrogen, or using thin-layer chromatography or gas liquid chromatography): BOX

Adequacy of method to deodorize smell of especially fish oil exposure (*select one*):

Adequate = reported that study participants could not reliably guess which exposure they received
Inadequate = reported that participants could reliably guess which exposure they received
Unclear = incomplete or conflicting data reported
Not reported = no method reported, or method reported but no data reported
Not applicable = did not use an exposure requiring or permitting such a method (e.g., flaxseed; full fish servings)

If this is a controlled study, briefly describe whether clinical outcome data from all study groups (e.g., active vs placebo) were simultaneously entered into data analysis: **BOX**

If this is a controlled study, briefly describe whether biomarker data from all study groups (e.g., active vs placebo) were simultaneously entered into data analysis: **BOX**

Data were analyzed according to which criterion (*select one*)?

Intention-to-treat (all randomized/enrolled)
Those receiving at least one dose/serving
Those completing the study (i.e., with final follow-up data)
Unclear
Other: **BOX**

Was the study adequately powered to detect a difference? **BOX**

Any further comments about the study: **BOX**

THE END

Quality Assessment Form—Randomized Controlled Trials

1. Randomization: Was the study described as randomized (i.e. including words such as randomly, random, randomization)? **Yes = 1** **No = 0** **=___**

A trial reporting that it is 'randomized' is to *receive one point.* Trials describing an appropriate method of randomization (table of random numbers, computer generated*) receive an additional point*. **Appropriate = 1** **Not appropriate = 0** **= ___**

However, if the report describes the trial as randomized and uses an inappropriate method of randomization (e.g. date of birth, hospital numbers), *a point is deducted*.

TOTAL POINTS: **0** **1** **2** **SCORE = ___**

2. Double-blinding: Was the study described as double-blind? **Yes = 1** **No = 0 =___**

A trial reporting that it is 'double-blind' is to *receive one point.* Trials that describe an appropriate method of double-blinding (identical placebo: color, shape, taste) are to *receive an additional point*. **Yes = 1** **No = 0** **=___**

However, if the report describes the trial as double-blind and uses an inappropriate method (e.g. comparison of tablets vs. injection with no dummy), *a point is deducted*.

TOTAL POINTS: **0** **1** **2** **SCORE = ___**

3. Withdrawals and dropouts: Was there a description of withdrawals and dropouts?
Yes = 1 **No = 0** **SCORE = ___**

A trial reporting the number of and reasons for withdrawals or dropouts is to *receive one point.* If there is no description, *no point is given*.

JADAD TOTAL SCORE = ___

4. Adequacy of Allocation Concealment: (*circle one*):

-Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes,
etc……. **ADEQUATE**

-Alternation; reference to case record # or date of birth,
etc……. **INADEQUATE**

-Allocation concealment is not reported, or, fits neither
category…….. ……... **UNCLEAR**

Quality Assessment Form—All Other Study Designs

CONTROLLED STUDY DESIGNS

DESIGN: (QUASI-EXPERIMENTAL) COMPARATIVE BEFORE-AFTER STUDY

1. Description of validated method(s) to identify the target population
a. Yes = 1
b. No = 0
c. Unable to determine = 0

2. Control for selection bias
a. Yes = 1
b. No = 0
c. Unable to determine = 0

3. Description of withdrawals/dropouts
a. Yes = 1
b. No = 0
c. Unable to determine = 0

4. Comparability of study groups on the basis of the design or analysis: exposure to sunlight
a. Study controls for exposure to sunlight at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

5. Comparability of study groups on the basis of the design or analysis: background diet
a. Study controls for background diet (omega-6/omega-3 fatty acid intake) at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

6. Comparability of study groups on the basis of the design or analysis: caloric/energy intake
a. Study controls for caloric/energy intake at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

7. Comparability of study groups on the basis of the design or analysis: smoking history
a. Study controls for smoking history at baseline and in light of possible changes during intervention period = 1

b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

8. Comparability of study groups on the basis of the design or analysis: comorbid conditions (e.g., diabetes; cardiovascular disease)
a. Study controls for comorbid conditions at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

9. Description of a validated primary clinical outcome measure(s)
a. Yes = 1
b. No = 0
c. Unable to determine = 0

10. Blind assessments of outcome
a. Yes = 1
b. No = 0
c. Unable to determine = 0

11. Description of type and amount of omega-3 fatty acid content in the intervention/exposure
a. Yes = 1
b. No = 0
c. Unable to determine = 0

DESIGN: CASE-CONTROL STUDY (Newcastle-Ottawa, with assessment of an additional confounder)

1. Is the case definition adequate?
a. yes, with independent validation (e.g., clinical/research diagnostic criteria) (1 point)
b. yes: e.g., record linkage or based on reports
c. no description

2. Representativeness of the cases
a. consecutive or obviously representative series of cases (1 point)
b. potential for selection biases, or not stated

3. Selection of controls
a. community controls (1 point)
b. hospital controls
c. no description

4. Definition of controls
a. no history of disease (requires clinical diagnostic criteria to determine this) (1 point)

b. no description of source

5. Comparability of cases and controls on the basis of the design or analysis: exposure to sunlight
a. study controls for exposure to sunlight at baseline and in possible changes during "intervening period" (1 point)
b. study fails to control for this confounding influence

6. Comparability of cases and controls on the basis of the design or analysis: smoking history
a. study controls for smoking history at baseline and in possible changes during "intervening period" (1 point)
b. study fails to control for this confounding influence

7. Comparability of cases and controls on the basis of the design or analysis: omega-6 fatty acid intake
a. study controls for omega-6 fatty acid intake at baseline and in possible changes during "intervening period" (1 point)
b. study fails to control for this confounding influence

8. Ascertainment of exposure
a. validated dietary assessment questionnaire or structured interview where blind to case/control status (1 point)
b. interview not blinded to case/control status
c. written self-report or medical record only
d. no description

9. Same method of ascertainment for cases and controls
a. yes (1 point)
b. no

10. Non-response rate
a. same rate for both groups (1 point)
b. non respondents described
c. rate different and no designation

UNCONTROLLED STUDY DESIGNS

DESIGN: (QUASI-EXPERIMENTAL) NONCOMPARATIVE BEFORE-AFTER STUDY

1. Description of validated method(s) to identify the target population
a. Yes = 1
b. No = 0
c. Unable to determine = 0

2. Control for selection bias
a. Yes = 1
b. No = 0
c. Unable to determine = 0

3. Description of withdrawals/dropouts
a. Yes = 1
b. No = 0
c. Unable to determine = 0

4. Controlled for in the analysis: exposure to sunlight
a. Study controls for exposure to sunlight at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

5. Controlled for in the analysis: background diet (omega-6/omega-3 fatty acid intake)
a. Study controls for background diet (omega-6/omega-3 fatty acid intake) at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

6. Controlled for in the analysis: caloric/energy intake
a. Study controls for caloric/energy intake at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

7. Controlled for in the analysis: smoking history
a. Study controls for smoking history at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

8. Controlled for in the analysis: comorbid conditions (e.g., diabetes; cardiovascular disease)
a. Study controls for comorbid conditions at baseline and in light of possible changes during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

9. Description of a validated primary clinical outcome measure(s)
a. Yes = 1
b. No = 0

c. Unable to determine = 0

10. Blind assessments of outcome
a. Yes = 1
b. No = 0
c. Unable to determine = 0

11. Description of type and amount of omega-3 fatty acid content in the intervention/exposure
a. Yes = 1
b. No = 0
c. Unable to determine = 0

DESIGN: SINGLE PROSPECTIVE COHORT STUDY (Modified Newcastle-Ottawa)

1. Representativeness of the exposed cohort
a. Truly or somewhat representative of the average individual at no (or elevated) risk for eye disease/visual impairment in the community = 1
b. Selected group of users e.g., nurses, volunteers = 0
c. No description of the derivation of the cohort = 0

2. Ascertainment of exposure
a. Validated dietary assessment questionnaire or structured interview = 1
b. Written self-report = 0
c. No description = 0

3. Demonstration that outcome of interest was not present at start of study
a. Yes = 1
b. No = 0
c. Unable to determine = 0

4. Description of a validated method to quantify the amount, per type, of omega-3 fatty acids
a. Yes = 1
b. No = 0
c. Unable to determine = 0

5. Assessment of outcome
a. Independent blind assessment = 1
b. Record linkage = 1
c. Self-report = 0
d. No description = 0

6. Was followup long enough for outcomes to occur?

a. Yes (5 years) = 1
b. No = 0
c. Unable to determine = 0

7. Adequacy of followup of cohort
a. Complete followup, all subjects accounted for = 1
b. Subjects lost to followup unlikely to introduce bias, small number lost, at least 90% followup, or description provided of those lost = 1
c. Followup rate of less than 90% and no description of those lost = 0

8. Analytic control for confounding: exposure to sunlight
a. Yes = 1
b. No = 0
c. Unable to determine = 0

9. Analytic control for confounding: omega-6 fatty acid intake or omega-6/omega-3 fatty acid intake ratio
a. Yes = 1
b. No = 0
c. Unable to determine = 0

10. Analytic control for confounding: smoking history
a. Yes = 1
b. No = 0
c. Unable to determine = 0

DESIGN: SINGLE POPULATION CROSS-SECTIONAL STUDY

1. Description of appropriate sampling technique(s) to identify the sample population
a. Yes = 1
b. No = 0
c. Unable to determine = 0

2. Description of a validated method to identify/diagnose the target eye disease/visual impairment
a. Yes = 1
b. No = 0
c. Unable to determine = 0

3. Description of a validated method to identify the current intake of (foods or supplements containing) omega-3 fatty acids
a. Yes = 1
b. No = 0
c. Unable to determine = 0

4. Description of a validated method to quantify the amount, per type, of omega-3 fatty acids
a. Yes = 1
b. No = 0
c. Unable to determine = 0

5. Analytic control for confounding: exposure to sunlight
a. Yes = 1
b. No = 0
c. Unable to determine = 0

6. Analytic control for confounding: smoking history
a. Yes = 1
b. No = 0
c. Unable to determine = 0

7. Analytic control for confounding: severity of eye disease/visual impairment
a. Yes = 1
b. No = 0
c. Unable to determine = 0

8. Analytic control for confounding: intake of (foods or supplements containing) omega-6 fatty acids, or the omega-6/omega-3 fatty acid intake ratio
a. Yes = 1
b. No = 0
c. Unable to determine = 0

9. Response rate (at least 75%):
a. Yes = 1
b. No = 0
c. Unable to determine = 0

DESIGN: RETROSPECTIVE SINGLE POPULATION COHORT STUDY

1. Description of appropriate sampling technique(s) to identify the sample population
a. Yes = 1
b. No = 0
c. Unable to determine = 0

2. Description of a validated method to identify/diagnose the target eye disease/visual impairment

a. Yes = 1
b. No = 0
c. Unable to determine = 0

3. Description of a validated method to identify the past/typical intake of (foods or supplements containing) omega-3 fatty acids
a. Yes = 1
b. No = 0
c. Unable to determine = 0

4. Description of a validated method to quantify the amount, per type, of omega-3 fatty acids
a. Yes = 1
b. No = 0
c. Unable to determine = 0

5. Analytic control for confounding: exposure to sunlight
a. Yes = 1
b. No = 0
c. Unable to determine = 0

6. Analytic control for confounding: smoking history
a. Yes = 1
b. No = 0
c. Unable to determine = 0

7. Analytic control for confounding: severity of eye disease/visual impairment
a. Yes = 1
b. No = 0
c. Unable to determine = 0

8. Analytic control for confounding: intake of (foods or supplements containing) omega-6 fatty acids, or the omega-6/omega-3 fatty acid intake ratio
a. Yes = 1
b. No = 0
c. Unable to determine = 0

9. Response rate (at least 75%):
a. Yes = 1
b. No = 0
c. Unable to determine = 0

Applicability Indices

For studies involving at least one target population identified with an eye disease/visual impairment:[1]

Assign 'I' to a target study population of otherwise "healthy" North American (or similar) individuals identified with an eye disease/visual impairment diagnosed using a "typical" North American methodology/nomenclature, with or without comorbid conditions, potentially receiving "typical" North American types of treatment (e.g., medication types and doses) for the primary diagnosis, representing a somewhat broad socio-demographic spectrum (i.e., gender, race), and eating a diet "typical" of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio of at least 15).

Assign 'II' to a target study population of otherwise 'healthy' North American (or similar) individuals identified with an eye disease/visual impairment, *likely* diagnosed using a 'typical' North American methodology/nomenclature, with or without comorbid conditions, *likely* receiving 'typical' North American types of treatment (e.g., medication types and doses) for the primary diagnosis, *yet* representing a more circumscribed socio-demographic picture (e.g., Asian-American/Canadian), and likely eating a diet "somewhat different" from that of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio notably less than 15, yet likely not reaching a value of 4, such as observed in Japan).

Assign 'III' to a target study population identified with an eye disease/visual impairment, with or without comorbid conditions, potentially diagnosed using a methodology/nomenclature other than a "typical" North American one, receiving treatment (e.g., medication types and doses) for the primary diagnosis that is potentially "atypical" of North America, representing a population whose socio-demographic characteristics are notably "atypical" of a broad spectrum North American population, and eating a diet that is "notably different" from that of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio perhaps reaching a value of 4, such as observed in Japan, or 38-50, as observed in urban India).

Assign 'X' when applicability cannot be ascertained due to incomplete or conflicting reporting of the details concerning the target study population, particularly relating to the primary diagnosis/condition and/or the background diet.

[1]Note that a control group (e.g., within a case control design) might have been composed of individuals without an identified psychiatric diagnosis or condition.

For studies involving a target population with or without a known elevated risk for an eye disease/visual impairment:

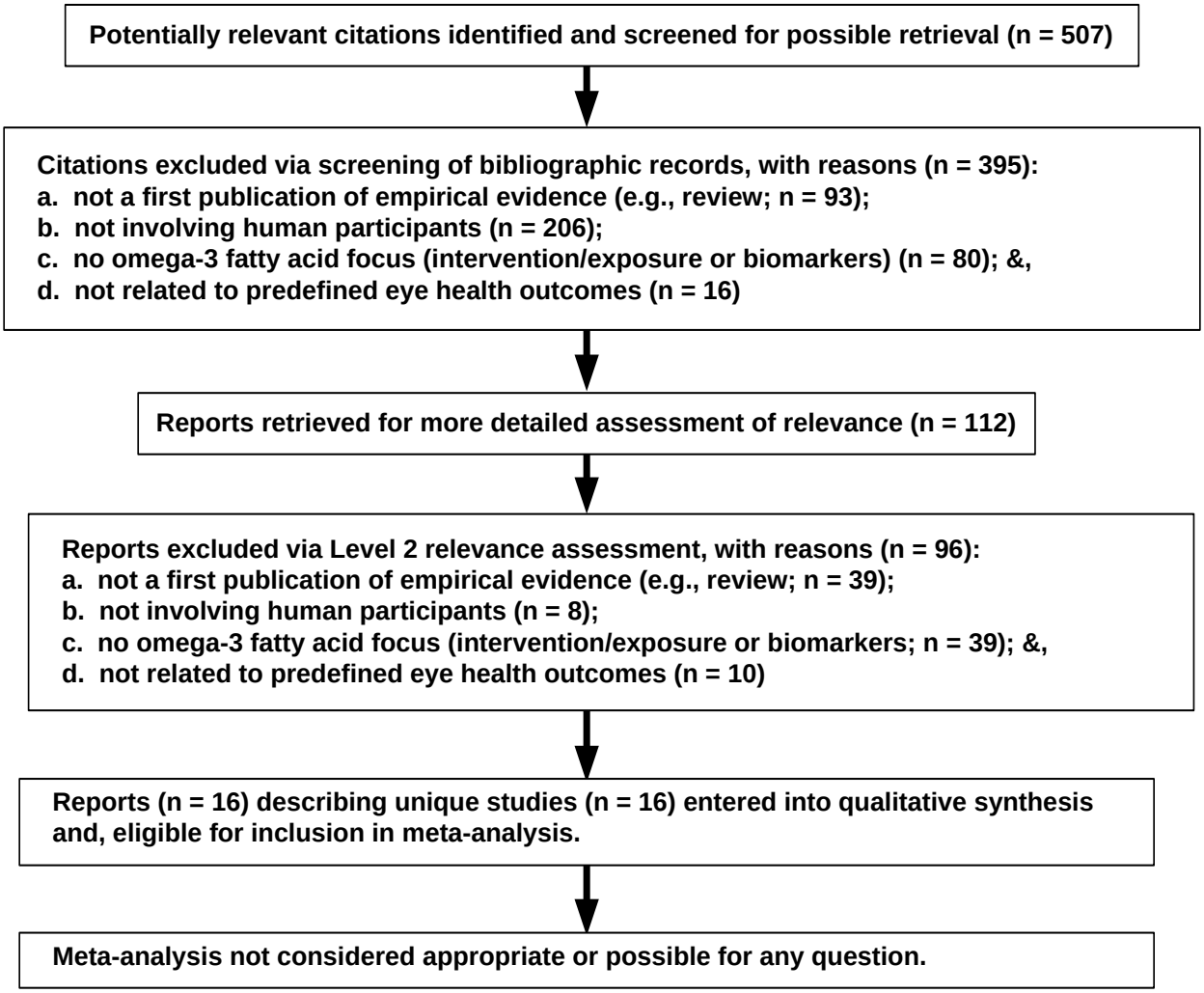
Assign 'I' to a target study population of otherwise "healthy" North American (or similar) individuals, with or without a known elevated risk for onset of an eye disease/visual impairment, representing a somewhat broad socio-demographic spectrum (i.e., gender, race), and eating a diet "typical" of a broad spectrum North American population (e.g., with an omega-6/omega-3 intake ratio of at least 15).

Assign 'II' to a target study population of otherwise "healthy" North American (or similar) individuals, with or without a known elevated risk for onset of an eye disease/visual impairment, *yet* representing a more circumscribed socio-demographic picture (e.g., Asian-American/Canadian), and likely eating a diet "somewhat different" from that of a broad spectrum North American population (e.g., with an omega-6/omega-3 intake ratio notably less than 15, yet likely not reaching a value of 4, as observed in Japan).

Assign 'III' to a target study population of otherwise "healthy" individuals, with or without a known elevated risk for onset of an eye disease/visual impairment, *yet* representing a very circumscribed population whose socio-demographic characteristics are "notably atypical" of a broad spectrum North American population, and eating a diet that is "notably different" from that of a broad spectrum North American population (e.g., with an omega-6/omega-3 intake ratio perhaps reaching a value of 4, such as observed in Japan, or 38-50, as observed in urban India).

Assign 'X' when applicability cannot be ascertained due to incomplete or conflicting reporting of the details concerning the target study population, particularly relating to the background diet.

Modified QUOROM Flow Chart



Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 1: Randomized controlled trial evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hoffman, 2004, US [1]: 4 y parallel RCT {1021}	• Inclusion: diagnosed RP, family history consistent with XLRP (ruling out dominant/ recessive RP) • Exclusion: Excessive fish intake/fish oil supplementation	• Enrolled/completed: n=44/41 • Age (M & range): 16 (4-38) y • % Male: 100 • Race: White (87%), Black (2%), Hispanic (11%) • Disease: XLRP • Duration: NR • Interventions: NR • Concurrent: NR • Biomarkers (S between-grp differences): NR	• 400 mg/d DHA • Via 2 500 mg DHASCO oil capsules/d (Martek Biosciences Corporation) • DHASCO oil contains mainly triacylglycerol, with 40% of its total fatty acids being DHA • Diet: NR • Cointerventions: NR • n=23/22	• Identical pb capsules, free of n-3, containing corn/soy oil and triglycerides (Martek Biosciences Corporation) • Capsules/d: NR, though likely matched • Diet: N/R • n=21/19	• Jadad total quality score: 4 [Grade: A] • Allocation concealment: Adequate • Applicability: II • Funding: Foundation Fighting Blindness

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; y = year; mg = milligram; d = day; grp = group; pb = placebo; S = significant; RP = retinitis pigmentosa; XLRP = X-linked retinitis pigmentosa

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 1: Randomized controlled trial evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Scorolli, 2002, Italy [1]: 3 mo parallel RCT {33}	• Inclusion: Neovascular membrane between 0.3-0.5 mm, VA corrected in logMAR between 0.7-0.3 • Exclusion: Age < 55 y, prior surgical intervention, history of retinal disease	• Enrolled/completed: n=35/35 • Age (M & range): 72 (55-86) y • % Male: 60 • Race: NR • Disease: ARMD • Duration: NR • Interventions: NR • Concurrent: NR	• 200 mg/d DHA, 200 mg/d linolenic acid • Cointervention: photodynamic therapy, 600 mg/d linoleic acid, 200 mg/d vitamin E • n=20/20	• Photodynamic therapy • n=15/15	• Jadad total quality score: 2 [Grade: C] • Allocation concealment: Unclear • Applicability: III • Funding: NR

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; y = year; mo = month; mg = milligram; d = day; grp = group; S = significant; VA = visual acuity; ARMD = age-related macular degeneration

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 2: Quasi-experimental study evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Dagnelie, 2000, US, Canada & 7 other countries [1]: 6 mo comparative before-after study {71}	• Inclusion: Belonging to RP mailing list • Exclusion: NR	• Enrolled/completed: n=20/16 • Age (M & range): NR • % Male: NR • Race: NR • Disease: RP • Duration: NR • Interventions: supplements n=14 • Concurrent: NR	• 500 mg/d DHA from 1 capsule at dinner • Carlson Labs "Super DHA 500 mg" • Diet: NR • Cointerventions: lutein: mo 1,2 40 mg/d, mo 3-6 20 mg/d; vitamin B: 1 multi-capsule/d; digestive enzymes: 600mg/d • n=10/9	• lutein: mo 1,2 40 mg/d, mo 3-6 20 mg/d • Diet: NR • n=10/7	• Total study quality: 2 [Grade: C] • Applicability: III • Funding: FOCUS Foundation

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; RCT = randomized controlled trial; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; mo = month; mg = milligram; d = day; grp = group; S = significant; RP = retinitis pigmentosa

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 2: Quasi-experimental study evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hoffman, 1995, Study 1, US [1]: 6 wk non-comparative before-after study {920}	• Inclusion: Good general health, willingness to participate • Exclusion: History of clinically significant bleeding, anti-coagulant therapy, unusual diet	• Enrolled/completed: n=3/3 • Age (M & range): NR • % Male: NR • Race: NR • Disease: adRP • Duration: NR • Interventions: NR • Concurrent: NR • Biomarkers (S between-grp differences): NS	• 3.0 g/d purified fish-oil concentrate (0.7 g/d DHA + 1.3 g/d EPA) • The fish oil contained 24% DHA, 44% EPA, and 0.2 mg/d tertbutylhydroquinone and 2 mg/d tocopherols as antioxidants • Diet: Limited intake of n-3 LCPs and α-linolenic acid • Cointerventions: NR • n=3/3	• N/A	• Total study quality: 4 [Grade: C] • Applicability: X • Funding: National Retinitis Pigmentosa Foundation; National Eye Institute (government); Fish Oil Test Materials Program (Department of Commerce)

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; g = gram; mg = milligram; d = day; grp = group; S = significant; NS = nonsignificant; adRP = autosomal dominant retinitis pigmentosa; LCP = long-chain polyunsaturated fatty acid

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 2: Quasi-experimental study evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hoffman, 1995, Study 2, US [1]: 3 wk non-comparative before-after study {920}	• Inclusion: Good general health, willingness • Exclusion: History of clinically significant bleeding, anti-coagulant therapy, unusual diet	• Enrolled/completed: n=3/3 • Age (M & range): NR • % Male: NR • Race: NR • Disease: adRP • Duration: NR • Interventions: NR • Concurrent: NR • Biomarkers (S between-grp differences): NR	• Highly purified EPA ethyl ester (99.4%) • Dose & delivery: NR • Diet: Limited intake of n-3 LCPs & α-linolenic acid • Cointerventions: NR • n=3/3	• N/A	• Total study quality: 3 [Grade: C] • Applicability: X • Funding: National Retinitis Pigmentosa Foundation; National Eye Institute (government); Fish Oil Test Materials Program (Department of Commerce)

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; grp = group; S = significant; adRP = autosomal dominant retinitis pigmentosa; LCP = long-chain polyunsaturated fatty acid

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 2: Quasi-experimental study evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Sorokin, 1997, Russia [1]: 3 mo non-comparative before-after study {107}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=62/62 • Age (M & SD): DR 56 (2) y; Control 57.3 (2) y • % Male: DR 41.7; Control NR • Race: NR • Disease: DR in 4 grades; preclinical, manifest, exudating, proliferative • Duration: NR • Interventions: NR • Concurrent: DR: Type 1 Diabetes n=14, Type 2 Diabetes n=34; Control NR • Biomarkers (S between-grp differences): NR	• 4 g/d eiconol (cod-liver oil concentrate, a nutrient additive) • via 4 eiconol capsules/d • Eiconol capsules are gelatin capsules containing EPA & DHA (exact composition NR) • Diet: NR • Cointerventions: Hypoglycemic drug • n=48/48	• N/A	• Total study quality: 1 [Grade: C] • Applicability: III • Funding: NR

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; mo = month; g = gram; d = day; grp = group; pb = placebo; S = significant; DR = diabetic retinopathy; SD = standard deviation

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 2: Quasi-experimental study evidence of effects of omega-3 fatty acids on eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Suzuki, 2001, Japan [1]: 3 mo non-comparative before-after study {49}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=15/15 • Age (M & range): 72 (58-84) y • % Male: NR • Race: NR • Disease: Cataract • Duration: NR • Interventions: NR • Concurrent: Glaucoma (n=4)	• 0.54 g/d DHA • via 6 DHA capsules/d, supplier and composition of capsule NR • Diet: approximately 0.73 g/d DHA & 0.53 g/d EPA from normal diet • Cointerventions: NR • n=15/15 (14 pts with cataracts; 1 pt only with glaucoma)	• N/A	• Total study quality: 2 [Grade: C] • Applicability: III • Funding: Bell Rich Co., Ltd.

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; diet = background diet, including omega-3 or omega-6/omega-3 content; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; mo = month; y = year; g = gram; d = day; grp = group; S = significant

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Arnarsson, 2002, Iceland [1]: N/A, single population cross-sectional study {37}	• Inclusion: ≥ 50 y age, citizen of Reykjavik • Exclusion: NR	• Enrolled/completed: n=1,045/993 • Age (M & range): NR • % Male: 44.2 • Race: White (100%) • Disease: cataract • Duration: N/A • Interventions: NR • Concurrent: NR	• n=1,045/993	• N/A	• Total study quality: 5 [Grade: B] • Applicability: III • Funding: NR

[^] Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A= not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Cho, 2000, US [1]: 10-12 y single prospective cohort study {65}	• Inclusion: ≥50 y, (drawn from Nurses' Health Study & Health Professionals F/U study) • Exclusion: Prior diagnosis of AMD or cancer (except non-melanoma skin cancer)	• Enrolled/completed: n=112,960/NR • Age (M & SD): Females: 56 (4) y; Males: 60 (7) y • % Male: 41 • Race: NR • Disease: ARMD • Duration: NR • Interventions: NR • Concurrent: NR	• n=71,486/NR (females) • n=41,474/NR (males)	• N/A	• Total study quality: 5 [Grade: B] • Applicability: I • Funding: National Institutes of Health (government)

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; SD = standard deviation; F/U = followup; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant; ARMD = age-related macular degeneration

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Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Cumming, 2000, Australia [1]: N/A, single population cross-sectional study {497}	• Inclusion: Birth date prior to January 1, 1943 • Exclusion: NR	• Enrolled/completed: 4,433/2,900 • Age (median & range): 65 (49-97) y • % Male: NR • Race: NR • Disease: Cataract • Duration: N/A • Interventions: N/A • Concurrent: NR	• n=2,900	• N/A	• Total study quality: 5 [Grade: B] • Applicability: III • Funding: Australian Department of Health & Family Services (government); Save Sight Institute, University of Sydney

[*] Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; CT = cannot tell; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant

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Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Heuberger, 2001, US [1]: N/A, single population cross-sectional study {471}	• Inclusion: 40-79 y, participated in national health and nutrition examination survey (NHANES III) • Exclusion: NR	• Enrolled/completed: 11,448/7,883 • Age (M & range): NR • % Male: NR • Race: NR • Disease: ARMD • Duration: NR • Interventions: NR • Concurrent: N/A	• n=7,883 pts with exposure & clinical outcome data	• N/A	• Total study quality: 5 [Grade: B] • Applicability: I • Funding: National Institutes of Health (government); Research to Prevent Blindness

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; CT = cannot tell; enrolled = n qualified; completed = n completing the study; y = year; S = significant; ARMD = age-related macular degeneration

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Mares-Perlman, 1995, US [1]: N/A, retrospective population-based cohort study {1040}	• Inclusion: residents of Beaver Dam Wisconsin (US), between ages 45-84 y, participating in Beaver Dam Eye Study & Nutritional Factors in Eye Disease Study • Exclusion: NR	• Enrolled/completed: n=2,152/1,968 • Age (M & SD): 61 (10) y • % Male: NR • Race: NR • Disease: ARMD • Duration: NR • Interventions: NR • Concurrent: NR	• n=1,968 pts with exposure & clinical outcome data	• N/A	• Total study quality: 6 [Grade: B] • Applicability: I • Funding: National Institutes of Health (government)

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); SD = standard deviation; NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant; ARMD = age-related macular degeneration

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Ouchi, 2002, Japan [1] : N/A, case-control study {34}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=21/21 • Age (M & range): AMD 65.8 (55-72) y; control 64.4 (56-71) y • % Male: 76.2 • Race: likely Asian • Disease: ARMD • Duration: NR • Concurrent: NR • Biomarkers (S between-grp differences): RBC-AA ARMD > control; RBC-DHA ARMD > control	• n=11Advanced ARMD cases	• n=10/10 healthy controls	• Total study quality: 0 [Grade: C] • Applicability: III • Funding: NR

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant; RBC = red blood cell; ARMD = age-related macular degeneration

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Seddon, 2001, US [5]: N/A, case-control study {58}	• Inclusion: cases: 55-80 y, live near clinic, diagnosed ocular disease within 1 y of enrolment, ARMD. Controls: outpts without ARMD from same population • Exclusion: NR	• Enrolled/completed: n=1,036/853 • Age (M & range): cases: 71(55-81) y; controls: 68 (55-80) y • % Male: 42 • Race: White (100%) • Disease: ARMD • Duration: NR • Interventions: NR • Concurrent: NR	• n=349 Advanced ARMD cases	• n=504 controls	• Total study quality: 8 [Grade: A] • Applicability: II • Funding: NIH (government); Lions Eye Research Fund Inc; Research to Prevent Blindness Inc

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant; ARMD = age-related macular degeneration

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Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Seddon, 2003, US [1]: 4.6 y (mean) single prospective cohort study {1007}	• Inclusion: Dry ARMD & VA 20/200 or better in ≥ 1 eye, ≥60 y • Exclusion: no English, decreased hearing/ cognitive function	• Enrolled/completed: n=366/261 • Age (M & range): 72.8 (NR) y • % Male: NR • Race: White (99.9%) • Disease: Dry ARMD • Duration: NR • Concurrent: NR	• n=261 ARMD pts	• N/A	• Total study quality: 8 [Grade: A] • Applicability: II • Funding: Foundation Fighting Blindness Inc, Massachusetts Lions Eye Research Fund Inc; Research to Prevent Blindness Inc; the Epidemiology Unit Research Fund, Massachusetts Eye & Ear Infirmary (hospital)

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; grp = group; S = significant; ARMD = Age-related macular degeneration; VA = visual acuity

Appendix E. Evidence Tables and Listing of Included Studies

Evidence Table 3: Observational study evidence for the association between omega-3 fatty acids and eye health

Author, Year, Location [n sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Smith, 2000, Australia [1]: N/A, single population cross-sectional study {78}	• Inclusion: ≥ 49 y of age • Exclusion: NR	• Enrolled/completed: n=3,654/2,900 • Age (M & range): NR • % Male: NR • Race: NR • Disease: ARMD; early n=240, late n=72, diagnosed using Wisconsin Age-related Maculopathy Grading System • Duration: NR • Concurrent: NR	• n=2,900 pts with exposure & clinical outcome data	• N/A	• Total study quality: 5 [Grade: B] • Applicability: III • Funding: Australian Department of Health & Family Services (government); Save Sight Institute, University of Sydney

*Proceeding from the highest n-3, of lowest n-6/n-3, content of intervention/exposure; n-3 = omega-3 fatty acid(s); n-6 = omega-6 fatty acid(s); length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; dose = daily dose or serving size; biomarkers = fatty acid content of blood lipid biomarkers (i.e., EPA, DHA, AA, EPA/EPA, AA/DHA, AA/EPA+DHA); NR = not reported; N/A = not applicable; n = number of participants; enrolled = n qualified; completed = n completing the study; y = year; S = significant; grp = group; ARMD = age-related macular degeneration

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Appendix F. Additional Acknowledgements

The UO-EPC gratefully acknowledges the following individuals who served on our Technical Expert Panel (TEP). Acknowledgement does not reflect endorsement of this report.

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Appendix F. Additional Acknowledgements (continued)

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