Evidence Report/Technology Assessment
Number 114

Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases

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Prepared by:
Southern California/RAND Evidence-based Practice Center, Los Angeles, CA

Catherine H. MacLean, MD, PhD
Task Order Director

Amalia M. Issa, MPH, PhD
Walter A. Mojica, MD, MPH
Scientific Reviewers

Sydne J. Newberry, PhD
Editor

Sally C. Morton, PhD
Paul G. Shekelle, MD, PhD
Program Directors

Lara G. Hilton, BA
Programmer/Analyst

Rena Hasenfeld Garland, BA
Project Manager

Jessie McGowan, MLIS
Nancy Santesso, RD, MLIS
Librarians

Shannon Rhodes, MFA
Cony Rolon, BA
Shana Traina, MA
Staff Assistants

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases was requested and funded by AHRQ. 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.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Paul M. Coates, Ph.D.
Director, Office of Dietary Supplements
National Institutes of Health

Kenneth S. Fink, M.D., M.G.A., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

Beth A. Collins-Sharp, R.N., Ph.D.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

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Chapter 1 was written in collaboration with the New England Medical Center Evidence-based Practice Center.

Structured Abstract

Context: It has been suggested that omega 3-fatty acids have beneficial effects in several conditions and disorders affecting the central nervous system, including providing a protective effect on cognitive function with aging; dementia, particularly senile dementia of the Alzheimer's type; multiple sclerosis and some of the peroxisomal biogenesis disorders.

Objectives: To assess the effect of omega-3 fatty acids on 1) cognitive function in normal aging 2) the incidence of dementia, 3) treatment of dementia, 4) the incidence of several neurological diseases, and 5) clinical outcomes related to the progression of multiple sclerosis.

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

Study Selection: We screened 5,865 titles, reviewed 497 studies - of which 62 underwent a detailed review, and found 12 studies that pertained to our objectives. We included controlled clinical trials and observational studies, including prospective cohort, case-control, and case series designs; we excluded case reports. We had no language restrictions.

Data Extraction: We abstracted data on the effects of omega-3 fatty acids and on study design; relevant outcomes; study population; source, type, amount, and duration of omega-3 fatty acid consumption; and parameters of methodologic quality.

Data Synthesis: 1) A single cohort study has assessed the effects of omega-3 fatty acids on cognitive function with normal aging and found no association for fish or total omega-3 consumption. 2 and 3) In four studies (3 prospective cohort studies and one RCT) that assessed the effects of omega-3 fatty acids on incidence and treatment of dementia, a trend in favor of omega-3 fatty acids (fish and total omega-3 consumption) toward reducing risk of dementia and improving cognitive function was reported. 4) Two studies, one cohort and one case-control, that assessed the effects of omega-3 fatty acids on incidence of MS were inconclusive. A single cohort study evaluating the effects of omega-3 fatty acids on incidence of Parkinson's disease found no significant association between dietary intake of omega 3 fatty acids (fish, ALA, EPA, or DHA) and Parkinson's. Another single case-control study found a significant association between maternal fish consumption at least once a week throughout pregnancy and a lower risk of cerebral palsy in offspring. 5) In one RCT, omega-3 fatty acids (fish, ALA, EPA, DHA) had no effect on the progression of multiple sclerosis; two single-arm open-label trials showed improvement in disability with omega-3 supplementation.

Conclusions: The quantity and strength of evidence for effects of omega-3 fatty acids on the neurological conditions assessed vary greatly. Due to the small number of studies that met our inclusion criteria, further research is necessary before substantive conclusions can be drawn. The paucity of evidence in this area suggests that a great deal of epidemiological and clinical research remains to be done before any conclusions can be drawn or policy recommendations can be made regarding the health effects of omega-3 fatty acids on normal cognitive function with aging, dementia, and neurological diseases.

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Number 114

Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases

Summary

Authors: MacLean CH, Issa AM, Newberry SJ, Mojica WA, Morton SC, Garland RH, Hilton LG, Traina SB, Shekelle PG

Introduction

This report was requested by the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH) Office of Dietary Supplements, and several NIH Institutes. It is one of several reports focusing on the role of omega-3 fatty acids (FA) in the prevention or treatment of various diseases. Three Evidence-based Practice Centers (EPCs) produced this series of reports: the Southern California EPC ([SCEPC], based at RAND), the Tufts-New England Medical Center EPC, and the University of Ottawa EPC. This particular report focuses on the effects of omega-3 FA on cognitive function with aging, dementia, and neurological diseases.

Over the past 40 years, an increasing number of physiological functions have been attributed to omega-3 FA, including movement of calcium and other substances into and out of cells; relaxation and contraction of muscles; regulation of clotting and of secretion of substances that include digestive enzymes and hormones; and control of fertility, cell division, and growth. In addition, omega-3 FA may play an important role in brain development and function.[1] Docosahexaneoic acid (DHA; 22:6n-3) is the precursor to a newly-described metabolite called 10,17S-docosatriene, which is part of a family of compounds called resolvins.[2,3] They are released in the brain in response to an ischemic insult and counteract the pro-inflammatory actions of infiltrating leukocytes by blocking interleukin 1-beta-induced NF-kappaB activation and cyclooxygenase-2 expression. DHA also plays a role in retinal rod outer segments by influencing membrane fluidity so as to optimize G protein coupled signaling.[4,5]

The major dietary sources of omega-3 FA in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements.

Methods

Study Questions

We convened a technical expert panel (TEP) composed of distinguished basic scientists and clinicians with established expertise in omega-3 FA, human nutrition, dietary assessment methods, and neurology. The TEP advised us on refining the preliminary questions posed to us by AHRQ, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

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

1. What is the evidence that omega-3 FA play a role in maintaining cognitive function in normal aging?
2. What is the evidence that omega-3 FA affect the incidence of dementia including Alzheimer's disease?
3. What is the evidence that omega-3 FA are effective in the treatment of dementia including Alzheimer's disease?

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4. What is the evidence that omega-3 FA affect the incidence of neurological diseases?
5. What is the evidence that omega-3 FA prevent the progression of multiple sclerosis?

Search Strategy

The following databases were searched: MEDLINE® (1966-2003), PreMEDLINE® (December, 2003), EMBASE (1980-2003), Cochrane Central Register of Controlled Trials (4th Quarter, 2003), CAB HEALTH® (1973-2003), Dissertation Abstracts (1861-2003). All of these databases were searched using the OVID interface, except CAB HEALTH, which was searched through SilverPlatter. Any duplicate records were identified and removed within each search question using Reference Manager® software. The citations obtained from these literature searches were sent to the SCEPC via e-mail. We also reviewed the reference lists of all applicable articles and contacted our technical expert panel as well as industry experts recommended by the Office of Dietary Supplements to identify and obtain unpublished data.

Selection Criteria

Two reviewers independently reviewed each article considered for inclusion in the study. Human controlled clinical trials (randomized and non-randomized), prospective cohort studies, case-control studies, and case series were included; case reports were excluded. For inclusion, studies also had to describe a difference between omega-3 FA content in study arms for all study designs except case series and describe the effect of omega-3 FA on any of the following outcomes: cognitive function with normal aging, incidence of dementia, treatment of dementia, incidence of neurological disease, or progression of multiple sclerosis. The reviewers resolved any disagreements by consensus. Language was not a barrier to inclusion.

Data Extraction and Analysis

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

Results

We screened 5,865 article titles. From these article titles, we chose to review 502 full-text articles, of which 497 were retrievable. Of these full-text articles, 62 met our selection criteria and were chosen for data extraction. After data extraction, 12 articles met our inclusion criteria for our study questions.

Evidence that omega-3 FA play a role in maintaining cognitive function in normal aging. Only one study that met inclusion criteria assessed the role of omega-3 FA in maintaining cognitive function. Fish consumption was only weakly associated with a reduced risk of cognitive impairment and had no association with cognitive decline; omega-3 FA consumption was not associated with either outcome.

Evidence that omega-3 FA affect the incidence of dementia including Alzheimer's disease. Three studies evaluated the effect of omega-3 FA on the incidence of dementia. All three of the studies assessed the incidence of dementia relative to fish consumption; one also assessed risk relative to total omega-3 fatty consumption, and relative to each alpha-linolenic acid (ALA; 18:3n-3); eicosapentaenoic acid (EPA; 20:5n-3), and DHA consumption. Fish was associated with a significant reduction in the incidence of non-Alzheimer's dementia in only one of the studies. Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies but this association was significant in only one study. Total omega-3 FA consumption and consumption of DHA (but not ALA or EPA) were associated with a significant reduction in the incidence of Alzheimer's.

Evidence that omega-3 FA are effective in the treatment of dementia including Alzheimer's disease. Only one study assessed the effects of omega-3 FA for the treatment of dementia. DHA resulted in a small improvement in scores on a dementia rating scale.

Evidence that omega-3 FA affect the incidence of neurological diseases. Four studies addressed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia. Two studies that assessed the association between omega-3 FA intake and the incidence of multiple sclerosis found no significant effects, although one study found a reduced risk with fish consumption among women. The one study that assessed the association between omega-3 FA consumption and the risk for

Parkinson's disease found no significant association for fish, ALA, EPA, or DHA. The one study that assessed the association between maternal omega-3 FA consumption and the risk of giving birth to a child with cerebral palsy found that consumption of fish once a week throughout pregnancy was associated with a lower risk.

Evidence that omega-3 FA prevent the progression of multiple sclerosis. Three studies reported on the effects of omega-3 FA intake on the progression of multiple sclerosis. In one study, treatment with an omega-3 FA supplement, MaxEPA, had no effect on disability or relapse rates. However, two other studies reported a significant reduction in disability and one reported improvement on an index of disease progression.

Thus, the quantity and strength of evidence for effects of omega-3 FA on outcomes in the conditions assessed varied greatly.

Discussion

We offer the following observations and recommendations regarding future research on the effects of omega-3 FA on the neurological conditions reviewed:

- Additional research on the effects of omega-3 FA needs to be performed on all of the conditions reviewed in this report before recommendations regarding the use of omega-3 FA can be made for these conditions.
- Of particular importance, properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g., 3 to 5 years of followup) need to be conducted for dementia, especially Alzheimer's disease, and for multiple sclerosis.
- Studies that assess the effects of omega-3 FA should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 FA consumption.
- Trials of omega-3 FA should include a baseline assessment of dietary omega-3 and omega-6 FA intake.
- In controlled trials that assess the effects of omega-3 FA, analysis should include and report explicit testing of the effects of the omega-3 FA relative to the control substance.
- All studies that assess the effects of omega-3 FA should use standard validated instruments to assess clinical outcomes.
- Observational studies should report data about type of fish consumed and method of preparation.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California Evidence-based Practice Center under Contract No. 290-02-0003. It is expected to be available in February 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. 114, *Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases*. 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 report is one of a group of evidence reports prepared by three Agency for Healthcare Research and Quality (AHRQ)-funded Evidence-Based Practice Centers (EPCs) on the role of omega-3 fatty acids (both from food sources and from dietary supplements) in the prevention or treatment of a variety of diseases. These reports were requested by the National Institutes of Health Office of Dietary Supplements and several institutes at the National Institutes of Health (NIH). The three EPCs – the Southern California EPC (SCEPC, based at RAND), the Tufts-New England Medical Center (NEMC) EPC, and the University of Ottawa EPC – have each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

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

This report focuses on the effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Other reports from the SCEPC focus on cancer and immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases.

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

The Recognition of Essential Fatty Acids

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

Fatty Acid Nomenclature

The fat found in foods consists largely of a heterogeneous mixture of triacylglycerols (triglycerides)--glycerol molecules that are each combined with three fatty acids. The fatty acids can be divided into two categories, based on chemical properties: saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. The term "saturation" refers to a chemical structure in which each carbon atom in the fatty acyl chain is bound to (saturated with) four other atoms, these carbons are linked by single bonds, and no other atoms or molecules can attach; unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond, which allows the attachment of additional atoms to those carbons (resulting in saturation). Despite their differences in structure, all fats contain approximately the same amount of energy (37 kilojoules/gram, or 9 kilocalories/gram).

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

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

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

Table 1.1. Nomenclature of omega-3 fatty acids.

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

*IUPAC=International Union of Pure and Applied Chemistry

Fatty Acid Metabolism

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

Following ingestion, ALA and LA can be converted in the liver to the long chain, more-unsaturated n-3 and n-6 VLCPUFAs by a complex set of synthetic pathways that share several enzymes (Figure 1.1). VLC PUFAs retain the original sites of desaturation (including n-3 or n-6).

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

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

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

Physiological Functions of EPA and AA

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

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

The eicosanoid family includes subgroups of substances known as prostaglandins, leukotrienes, and thromboxanes, among others. As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA (20:4n-6), is the precursor of a group of eicosanoids that include series-2

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

EPA (0522:6 n-3) also affects lipoprotein metabolism and decreases the production of substances – including cytokines, interleukin 1β (IL-1β), and tumor necrosis factor α (TNF-α) – that have pro-inflammatory effects (such as stimulation of collagenase synthesis and the expression of adhesion molecules necessary for leukocyte extravasation [movement from the circulatory system into tissues]).[2] DPA (22:5n-3), the elongation product of EPA, is metabolized to DHA (22:6n-3). DHA (22:6n-3) is the precursor to a newly-described metabolite called 10,17S-docosatriene,[4] which is part of a family of compounds called 'resolvins.'[5] They are in the brain in response to an ischemic insult and counteract the pro-inflammatory actions of infiltrating leukocytes by blocking interleukin 1-beta-induced NF-kappaB activation and cyclooxygenase-2 expression.[6] DHA also plays a role in retinal rod outer segments by influencing membrane fluidity so as to optimize G protein coupled signaling.[7] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs and VLCPUFAs remains unknown, although suppression of omega-6-derived eicosanoid production by omega-3 fatty acids may be involved, because the omega-3 and omega-6 fatty acids compete for common enzymes in the fatty acid metabolic pathway, including delta-6 desaturase, as well as the rate-limiting enzymes in the eicosanoid pathway – phospholipases A2, cyclooxygenase, and lipoxygenase.

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

Dietary Sources and Requirements

Both ALA and LA are present in a variety of foods. LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA is present in some commonly used oils, including canola and soybean oil, and in some leafy green vegetables. Thus, the major dietary sources of ALA and LA are PUFA-rich vegetable oils. The proportion of LA to ALA as well as the proportion of those PUFAs to others varies considerably by the type of oil. With the exception of flaxseed, canola, and soybean oil, the ratio of LA to ALA in vegetable oils is at least 10 to 1. The ratios of LA to ALA for flaxseed, canola, and soy are approximately 1: 3.5, 2:1, and 8:1, respectively; however, flaxseed oil is not typically consumed in the North American diet. It is estimated that on average in the U.S., LA accounts for 89 percent of the total PUFAs consumed, and ALA accounts for 9 percent. Another estimate suggests that Americans

consume 10 times more omega-6 than omega-3 fatty acids.[8] Table 1.2 shows the proportion of omega-3 fatty acids for a number of foods.

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

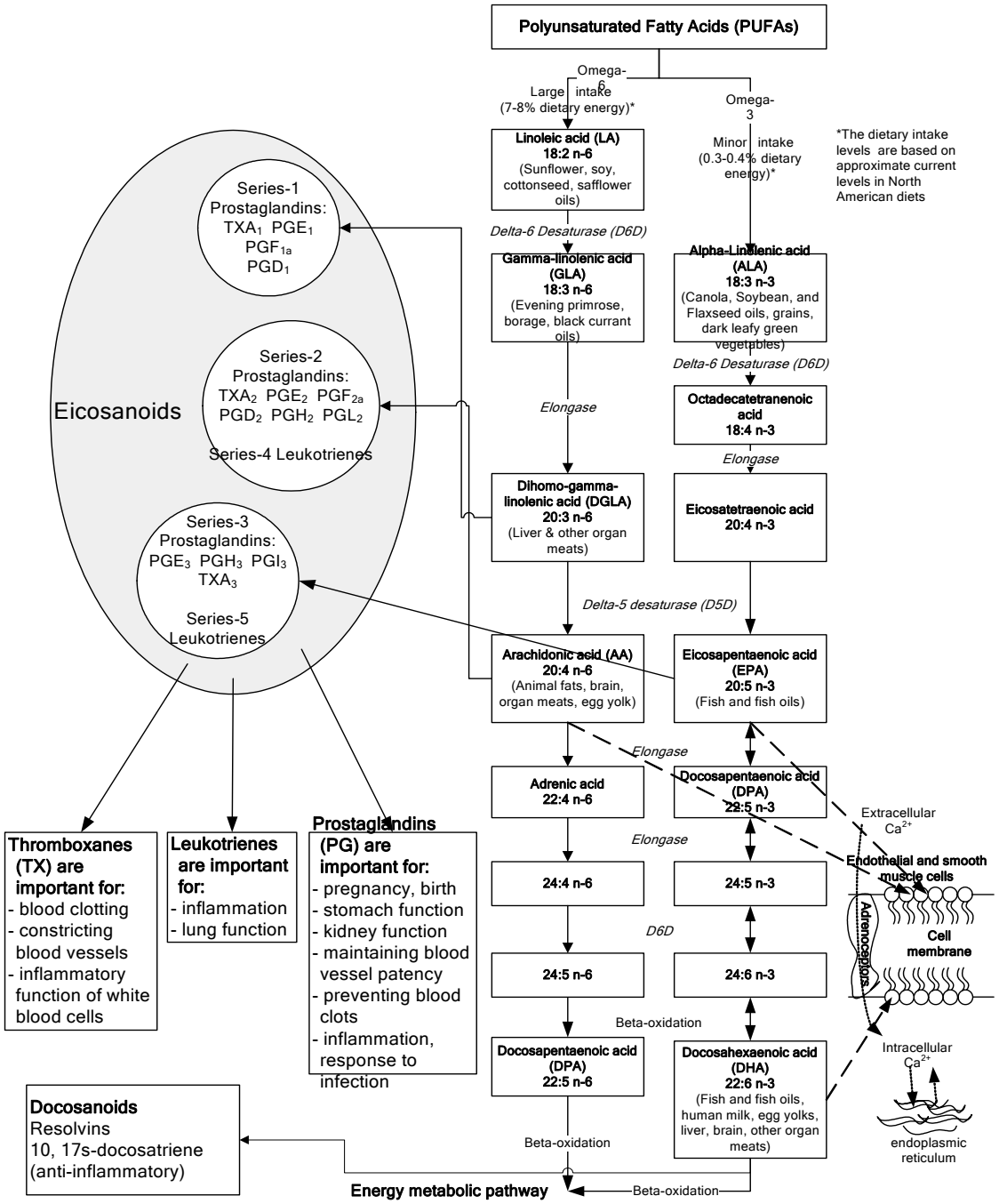


Figure 1.2. Schematic diagram illustrating the role of the metabolism of the essential fatty acids in neuronal signal transduction.

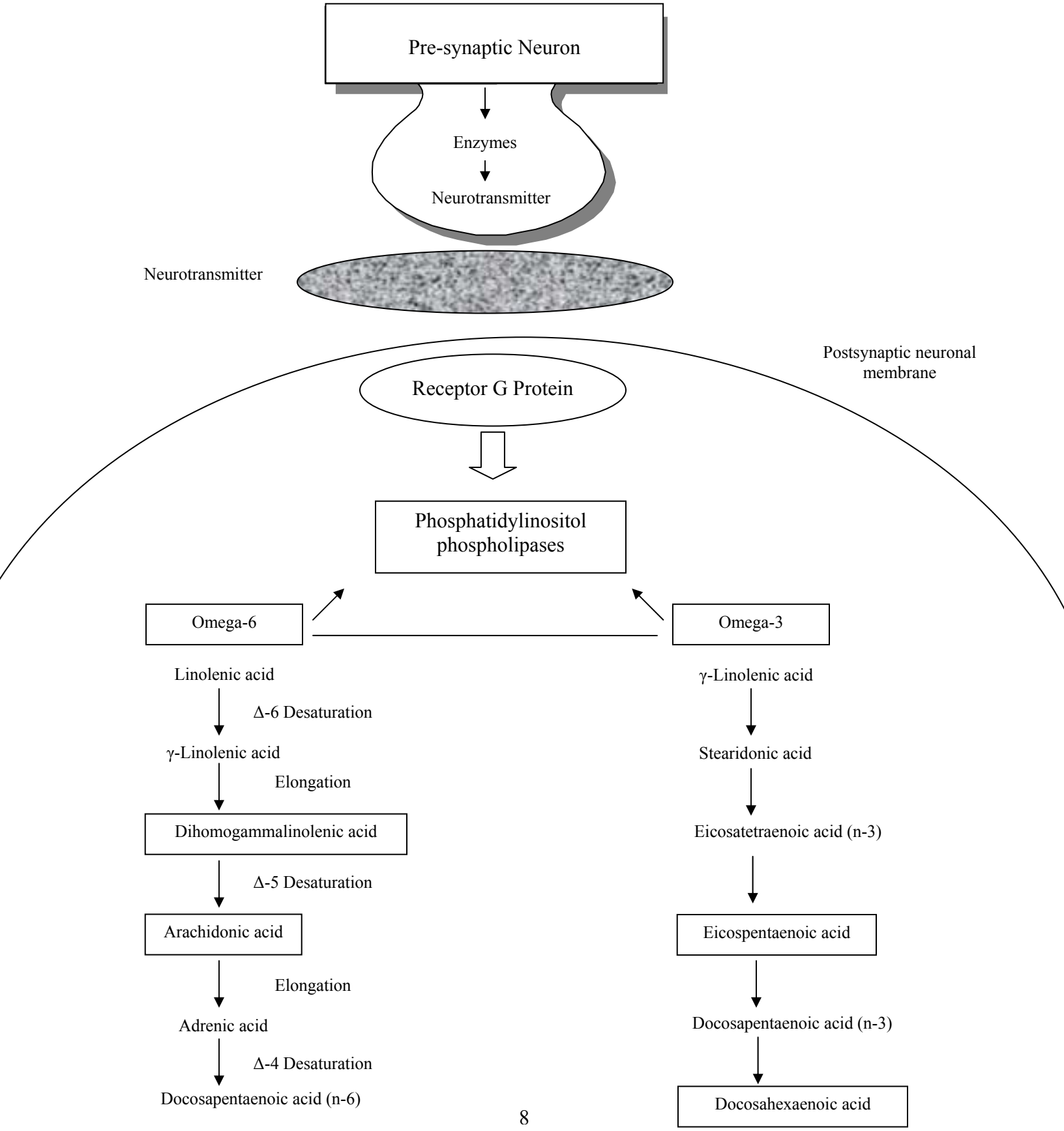


Table 1.2. Sources and proportions of omega-3 fatty acids in common foods and supplements.

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

* Dietary Supplement; † Also called rapeseed oil; ‡ The amounts of ALA, EPA, and DHA in human milk vary greatly as a function of maternal diet; the amount of DHA rarely seems to exceed 25 percent of the total n-3 PUFA content (ALA is present in the greatest amount), but that content as well as the proportion of DHA is assumed to meet the requirements of the infant.

Several lines of research have suggested that the high ratio of omega 6s to low levels of omega-3 fatty acids currently consumed in the U.S. promotes a number of chronic diseases. Whether or not the relatively high intake of omega-6 fatty acids independently contributes to this problem[8] is currently uncertain. Because of the slow rate of elongation and further desaturation of the essential FA, the importance of VLC PUFAs to many physiological processes, and the overwhelming ratio of LA (omega 6s) to ALA (omega 3s) in the average U.S. diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of omega- 3 VLC PUFAs by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of LC omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements, and the primary dietary sources of omega-6 VLC PUFAs are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main sources of dietary intake data for the U.S. population. The CSFII has the advantage of collecting dietary recall data over a period of several days, which may permit estimates of omega-3 intake that more accurately reflect individual intakes than do those of NHANES, which represent 24-hour dietary recalls. However, NHANES intake data have the advantage of being able to be linked to health outcomes. Table 1.3 provides a list of food sources of omega-3 fatty acids.

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

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

Source: Figures adapted from USDA, 2003; * Foods that provide (per serving) 10 percent or more of the Adequate Intake (AI) for ALA or the Acceptable Macronutrient Distribution Range (AMDR) for EPA and DHA (10 percent of the AMDR for ALA); an AI is a recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people (thus, assumed to be adequate) when an RDA cannot be determined; an AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[9]; † Farm-raised Atlantic salmon have nearly identical omega-3 fatty acid levels to wild Atlantic salmon and significantly more omega-3 fatty acids than wild Pacific salmon; ‡ Standard serving size not established; § See table note for Table 1.2.

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

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

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

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

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

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

Source: Adapted from Dietary Reference Intakes Report;[9] * Estimates are based on respondents' intakes on the first day of survey and were adjusted using the Iowa State University method; † For all individuals.

Lacking sufficient evidence from research on the effects or correction of dietary deficiencies to establish Recommended Dietary Allowances (RDAs) for the essential fatty acids, the Food and Nutrition Board (FNB) of the Institute of Medicine[9] has set adequate intakes[ii] (AI) for the essential fatty acids, based on the average intakes of healthy CSFII participants. The AIs for the essential fatty acids vary by age group and sex, as well as for particular conditions such as pregnancy and breastfeeding. For ALA, the AI for men 19 and older, is 1.6 grams/day and the AI for (non-pregnant, non-breastfeeding) women is 1.1 grams/day. The AI for LA is 17 grams/day for men and 11 grams/day for women.

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

[i] The population represented by NHANES III includes individuals ages 2 months and older. Mexican Americans and non-Hispanic African-Americans, children 5 years old and younger, and adults 60 years of age and over were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall data. The NHANES III also included a physical examination and health survey of each participant.

[ii] An Adequate Intake (AI) is defined as "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people, that are assumed to be adequate – used when a recommended dietary allowance cannot be determined."[9] An AI is set when data are insufficient or inadequate to establish an Estimated Average Requirement, on which the RDA is based, and indicate the need for more and better research. The EAR is "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group," based on a specific indicator or criterion of adequacy.

essential nutrients."[9] The AMDR is expressed as a percentage of total energy intake: The AMDR for LA is set at five to 10 percent of usual energy intake, and the AMDR for ALA is 0.6 to 1.2 percent of energy intake. Of this amount, up to 10 percent can be consumed as EPA and/or DHA, the omega-3 VLC PUFAs. For a person who consumes 2000 kcal/day, ALA intake should range from 1.3 to 2.6 grams/day, and EPA/DHA intake can substitute for 0.13 to 0.26 of that quantity. Table 1.3 lists foods that provide 10 percent or more of these recommended intakes per serving, which may be referred to as "good sources." [iii] Table 1.6 provides the actual omega-3 content per 100 gm for a variety of foods.

Physiological Role of Omega-3 Fatty Acids in the Brain

About 50 to 60 percent of the dry weight portion of the human brain consists of lipids. PUFAs constitute approximately 35 percent of that lipid content.[10] Omega -3 fatty acids, particularly EPA and DHA, play important roles in the development and maintenance of normal central nervous system (CNS) structure and function. Along with the omega-6 fatty acid, AA, DHA is a major constituent of neuronal membranes, making up about 20 percent of the brain's dry weight.[11] Synapses contain a high concentration of DHA, which appears to play a role in synaptic signal transduction.[12] The metabolic pathways of the essential fatty acids that play an important role in neuronal signal transduction are schematically illustrated in Figure 1.2. Release of these fatty acids is involved in the phospholipase A_2 cycle following activation of various neurotransmitter receptors. DHA is also important for normal cognitive development.[13] In addition, the anti-inflammatory compounds for which DHA is a precursor may function in the brain to protect against ischemic damage. PUFAs in general play important roles in structural and functional maintenance of neuronal membranes, neurotransmission, and eicosanoid biosynthesis,[10, 14] as well as in the maintenance of membrane fluidity and flexibility and in the modulation of ion channels, receptors, and ATPases. The importance of PUFAs in maintenance of adequate membrane rigidity is evidenced by the loss of fluidity that follows decreased in PUFAs,[15, 16] leading to changes in the orientation and function of receptors and ion channels, such as calcium and sodium channels.[16]

Work in animal models has reported superior learning and memory in animals fed omega-3 fatty acids compared with control animals.[17, 18] In transgenic mouse models, dietary DHA improved memory, increased synapse density and decreased amyloid beta toxicity, thus providing evidence of protection against AD and cognitive decline.[19, 20]

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

Omega-3 Fatty Acids in Neurologic Disorders

Deficiencies in omega-3 FA and/or an imbalance in the ratio of omega-6 FA to omega-3 FA have been implicated in a variety of disorders affecting the CNS, including Alzheimer's disease (AD),[21-26] the peroxisomal biogenesis disorders (a collection of relatively rare neurological conditions, of which Zellweger's syndrome is one of the most common),[27-32] several psychiatric disorders,[9, 11, 13, 33] Parkinson's disease,[34, 35] amyotrophic lateral sclerosis (ALS),[36] Huntington's disease,[37-39] ischemic brain injury,[36] and multiple sclerosis (MS).[40-49] Indeed, dietary intake of omega-3 FA has been associated with a reduced incidence of MS since the early studies of Swank in the 1950s.[50]

Various animal and human studies have suggested several possible biological mechanisms for the role of FA in disease processes. Evidence for a positive association between intake of omega-3 FA and reduction of cardiovascular risk and adverse outcomes,[51] along with the finding that certain forms of dementia have been related to cardiovascular risk factors, suggest that one mechanism linking FA and cognitive function or dementia may be atherosclerosis and thrombotic events.[52] Inflammation is another mechanism that may explain the role that omega-3 fatty acids play in dementia.[53]

Several intervention trials in human infants have investigated the effects of omega-3 FA on cognitive development.[50, 54] Research has also shown these FA to be important in human infant visual development. A meta-analysis of several intervention trials showed that healthy pre-term infants who were administered DHA-supplemented formula had significantly higher visual resolution acuity at two and four months of age compared with infants fed DHA-free formula.[55]

However, few clinical intervention trials have examined the role of omega-3 FA in changes in cognitive function with aging and adult neurological conditions. The studies that have investigated the relationship between omega-3 FA intake and cognitive function, dementia, or other neurological diseases are mainly observational.

Rationale for and Organization of this Report

Epidemiological studies have suggested that groups of people who consume diets high in omega-3 FAs may experience a lower prevalence of certain neurological conditions, particularly cognitive impairment and dementia disorders. In addition, several studies have attempted to assess the effects of adding omega-3 FA to the diet, either as omega-3 FA-rich foods or as dietary supplements (primarily fish oils) in the treatment of certain neurological diseases, notably MS.

In response to this evidence, a number of omega-3 FA-containing dietary supplements that claim to protect against a variety of conditions have appeared on the market. Thus, AHRQ and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) have requested a synthesis of the research to date on the health effects of diets rich in omega-3 FA.

The remainder of this report is organized into four chapters. Chapter Two describes the methods we used to identify and review studies related to the role of omega-3 FA in cognitive function with aging, dementia, and other neurological diseases/conditions. We did not analyze any studies on the role of omega-3 fatty acids in stroke because this topic has been addressed by

the New England EPC in their report on *Effects of Omega-3 Fatty Acids on Cardiovascular Disease.* Chapter Three presents our findings related to the effects of omega-3 FA on those diseases/conditions. Chapter Four presents our conclusions and recommendations for future research in this area.

Table 1.6 The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils.*

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Cooked in dry heat unless otherwise specified)				**Fish, continued**			
Anchovy, European	0.8	1.3	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.3	0.5	0.1	Tuna, Light, Canned in Oil	trace	0.1	trace
Bass, Striped	0.2	0.8	trace	Tuna, Light, Canned in Water	trace	0.2	trace
Bluefish	0.3	0.7	-	Tuna, White, Canned in Oil	trace	0.2	0.2
Carp	0.3	0.3	0.3	Tuna, White, Canned in Water	0.2	0.6	trace
Catfish, Channel, farmed	trace	0.1	0.1	Whitefish, Mixed Sp.	0.4	1.2	0.2
Cod, Atlantic	trace	0.2	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	0.1	0.2	trace	Wolf fish, Atlantic	0.4	0.4	trace
Eel, Mixed Sp.	0.1	0.1	0.6				
Flounder & Sole Sp.	0.2	0.3	trace				
Grouper, Mixed Sp.	trace	0.2	-	**Shellfish (Raw)**			
Haddock	0.1	0.2	trace	Abalone, Mixed Sp., fried	0.1	0.1	0.1
Halibut, Atlantic and Pacific	0.1	0.4	0.1	Clam, Mixed Sp., moist heat	0.1	0.1	trace
Halibut, Greenland	0.7	0.5	0.1	Crab, Alaska King, moist heat	0.3	0.1	-
Herring, Atlantic	0.9	1.1	0.1	Crab, Blue, moist heat	0.2	0.2	-
Herring, Pacific	1.2	0.9	0.1	Crayfish, Mixed Sp., Farmed	0.1	trace	trace
Mackerel, Atlantic	0.5	0.7	0.1	Lobster, Northern, moist heat	0.1	trace	trace
Mackerel, Pacific and Jack	0.7	1.2	0.1	Mussel, Blue	0.3	0.5	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Farmed	0.2	0.2	0.1
Ocean Perch, Atlantic	0.1	0.3	0.1	Oyster, Eastern, Wild	0.3	0.3	0.1
Pike, Northern	trace	0.1	trace	Oyster, Pacific	0.9	0.5	0.1
Pike, Walleye	0.1	0.3	trace	Scallop, Mixed Sp.	0.2	0.2	-
Pollock, Atlantic	0.1	0.5	-	Shrimp, Mixed Sp.	0.2	0.1	trace
Pompano, Florida	0.2	0.5	-	Squid, Mixed Sp., fried	0.2	0.4	0.1
Roughy, Orange	trace	-	trace				
Salmon, Atlantic, Farmed	0.7	1.5	0.1				
Salmon, Atlantic, Wild	0.4	1.4	0.4	**Fish Oils**			
Salmon, Chinook	1.0	0.7	0.1	Cod Liver Oil	6.9	11.0	0.9
Salmon, Chinook, Smoked (lox)	0.2	0.3	-	Herring Oil	6.3	4.2	0.8
Salmon, Chum	0.3	0.5	trace	Menhaden Oil	13.2	8.6	1.5
Salmon, Coho, Farmed	0.4	0.9	0.1	Salmon Oil	13.0	18.2	1.1
Salmon, Coho, Wild	0.4	0.7	0.1	Sardine Oil	10.1	10.7	1.3
Salmon, Pink	0.4	0.6	trace				
Salmon, Pink, Canned	0.8	0.8	0.1				
Salmon, Sockeye	0.5	0.7	0.1	**Nuts and Seeds**			
Sardine, Atlantic, Canned in Oil	0.5	0.5	0.5	Butternuts, Dried	-	-	8.7
Sea bass, Mixed Sp.	0.2	0.6	-	Flaxseed			18.1
Seatrout, Mixed Sp.	0.2	0.3	trace	Walnuts, English	-	-	9.1
Shark, Mixed Sp., battered and fried	0.3	0.4	0.2				
Snapper, Mixed Sp.	0.1	0.3	0.1	**Plant Oils**			
Swordfish	0.1	0.7	0.2	Canola (Rapeseed)	-	-	9.3
Trout, Mixed Sp.	0.3	0.7	0.2	Flaxseed Oil	-	-	53.3
Trout, Rainbow, Farmed	0.3	0.8	0.1	Soybean Lecithin Oil	-	-	5.1
Trout, Rainbow, Wild	0.5	0.5	0.2	Soybean Oil	-	-	6.8
Tuna, Fresh, Bluefin	0.4	1.1	-	Walnut Oil	-	-	10.4
Tuna, Fresh, Skipjack	trace	0.2	-	Wheatgerm Oil	-	-	6.9

Source: Figures adapted from USDA, 2003; * Sp = species.

Chapter 2. Methodology

Objectives

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

Scope of Work

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

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

Original Proposed Key Questions

Preliminary questions for the project were developed by ODS in collaboration with the following NIH Institutes: (a) National Cancer Institute (NCI); (b) National Eye Institute (NEI); (c) National Heart, Lung, and Blood Institute (NHLBI); (d) National Institute of Alcohol Abuse and Alcoholism (NIAAA); (e) National Institute of Allergy and Infectious Diseases (NIAID); (f) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); (g) National Institute of Child Health and Human Development (NICHD); (h) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); (i) National Institute of Mental Health; and (j) National Institute of Neurological Disorders and Stroke (NINDS). The general and disease-specific questions that were originally proposed are detailed in Appendix A.1.

Technical Expert Panel

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

We convened a TEP that focused on neurological diseases and conditions. The TEP was composed of distinguished basic scientists and clinicians, with established expertise in omega-3 FA, human nutrition, dietary assessment methods, and neurology. In addition to the experts that we identified, AHRQ and the NIH Institute of Neurological Disorders and Stroke (NINDS) and Institute on Aging (NIA) recommended a number of industry experts. The members of our technical expert panel are listed by name along with a summary of their key comments and recommendations in Appendix A.2.

Key Questions Addressed in this Report

Based on input from our TEP, the preliminary disease-specific questions were revised. The questions that are addressed in this report are as follows:

- What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function in normal aging?
- What is the evidence that omega-3 fatty acids affect the incidence of dementia including Alzheimer’s disease?
- What is the evidence that omega-3 fatty acids are effective in the treatment of dementia including Alzheimer’s disease?

- What is the evidence that omega-3 fatty acids affect the incidence of neurological diseases?

- What is the evidence that omega-3 fatty acids prevent the progression of multiple sclerosis?

Identification of Literature Sources

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

Jessie McGowan, Senior Information Scientist, and Nancy Santesso, Knowledge Translation Specialist, at the University of Ottawa were responsible for developing a common search strategy for omega-3 FA for the 3 participating EPCs. Nancy Santesso developed a core omega-3 search strategy in collaboration with project librarians, biochemists, nutritionists, and clinicians, who also provided biochemical names, abbreviations, food sources, and commercial product names for omega-3 FA. The literature search was not restricted by language of publication or by study design, in order to increase sensitivity. When possible, the searches were limited to studies involving human subjects. The core search strategy is detailed in Appendix A.4.

For the SCEPC, this core search strategy was incorporated into a search for cognitive function with aging, Alzheimer's disease, and other neurological diseases/conditions. The strategy for this search is detailed in Appendix A.4.

The following databases were searched: Medline (1966-2003), Premedline (December, 2003), Embase (1980- 2003), Cochrane Central Register of Controlled Trials (4th Quarter, 2003), CAB Health (1973-2003), Dissertation Abstracts (1861-2003). All of these databases were searched using the Ovid interface, except CAB Health, which was searched through SilverPlatter. Any duplicate records were identified and removed within each search question using Reference Manager software. The citations obtained from these literature searches were sent to the SCEPC via e-mail.

Two experienced reviewers, Walter Mojica and Amalia Issa, who were blinded to study authors and sources independently evaluated the citations and corresponding abstracts, if available. The reviewers selected article titles that focused on omega-3 FA and normal cognitive function with aging, dementia, and other neurologic diseases/conditions. In addition, they selected article titles that pertained to the disease conditions of the other participating EPCs. Language was not a barrier to inclusion. Articles that either reviewer selected were ordered, as well as those articles whose relevance could not be determined from the title or abstract. The articles were ordered from the UCLA library, or Infotrieve, a Los Angeles-based literature retrieval firm with contacts around the world. The literature was tracked using ProCite and Access software.

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

Evaluation of Evidence

Two experienced reviewers, Walter Mojica and Amalia Issa, independently reviewed each article that was ordered, to determine whether it should be accepted for further study, using a structured screening form (shown in Figure B.1, Appendix B) that included a defined set of inclusive/exclusive criteria (Table A.5.1, Appendix A.5). Walter Mojica is a physician with extensive experience in the science of systematic reviews and evidence-based medicine. Amalia Issa is a clinical neuroscientist with a background in AD research. Briefly, human controlled clinical trials (randomized and non-randomized), prospective cohort studies, case-control studies and case series were included; case reports were excluded. For inclusion, studies also had to describe assessing a difference between omega-3 fatty acids content in study arms for all study designs except case series, and describe the effect of omega-3 fatty acids on any of the following outcomes: cognitive decline with normal aging, incidence of dementia, progression of dementia, incidence of neurological disease, progression of MS. The reviewers resolved any disagreements by consensus. Reviewers were blinded to author and journal when reviewing titles and abstracts, but not when reviewing articles.

Extraction of Data

For the studies that passed our screening criteria, two reviewers independently abstracted detailed data onto a specialized quality review form (QRF) (Figure B.2, Appendix B).

Walter Mojica and Amalia Issa independently reviewed all of the studies. The reviewers resolved differences through consensus, and a senior physician researcher, Catherine MacLean, resolved any disagreements that could not be resolved through this method.

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

We consulted with several outside scientists to complete QRFs for foreign-language articles. Foreign language articles were reviewed as follows. Spanish-language articles were reviewed by Walter Mojica, French-language articles by Amalia Issa who are fluent in these languages. For other foreign-language articles, a single reviewer who is fluent in the language worked with Catherine MacLean to complete the standard abstraction form.

Grading Evidence

Methodologic Quality of Randomized Controlled Trials

To evaluate the quality of the design and execution of trials, we also collected information about the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts, and concealment of allocation. A score for quality was calculated for each trial using a system developed by Jadad (Appendix A.6, Figure A.6.1). The Jadad score rates studies on a scale of 0 to 5. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.[56] Thus, studies with a Jadad score of 3 or more are referred to as "high quality," and studies scoring 2 or less are referred to as "poor quality." For our purposes, if a trial was associated with more than one study, its quality score was equal to the maximum score calculated across its associated studies. Additionally, a generic summary quality score (A, B, C) was assigned to each study based on the combination of its Jadad score and reporting of concealment of allocation (Appendix A.6, Table A.6.1).

Methodologic Quality of Observational Studies

To evaluate the quality of the design and execution of observational studies, we collected information about the validity of ascertainment of cases and exposure, description of withdrawals and dropouts, and adjustment for confounders and blinded assessment of exposure and case status when ascertaining case and exposure status, respectively.[57, 58] We also described whether exposure occurred prior to the outcome, whether study groups were comparable, and whether there appeared to be selection bias. A score for quality was not calculated for observational studies, as there is no validated method to do so.

Applicability

This report focuses on the U.S. population as a whole. To capture the potential applicability of studies to the different populations of interest as defined in the scope of work (namely aging Americans or Americans with dementia or other neurological diseases/conditions), we categorized the populations in the studies we reviewed in terms of 1) applicability to the U.S. population and 2) health state (Appendix A.6, Table A.6.2). In the summary tables, each study receives a combined applicability grade based on the applicability and health state.

Data Synthesis

Because too few studies were identified to perform pooled analyses (meta-analysis), we performed a qualitative synthesis of the evidence.

This report is organized by five different study questions. For each study question we describe the number and design of studies identified that pertained to the question and describe the overall effect of omega-3 fatty acids across the studies. We describe the unit of analysis for

omega-3 consumption, i.e. fish, total omega-3, DHA, EPA or ALA. We summarized the point estimates and statistical testing that were described in the original studies and state when these parameters were not reported. We specifically comment on whether the studies assessed the effects of omega-3 fatty acids on sub-populations, the effects of covariates on outcomes, the effects of omega-3 fatty acid source, dose and exposure duration and sustainment of effect after treatment with omega-3 fatty acids. When these parameters were assessed they were described. We also describe the quality and applicability of the studies for each topic. Of note, we describe whether information on covariates was reported in two ways and for two reasons. First, we report whether covariates had a specific effect on the outcome of interest and the magnitude of the effect if it was significant. Second, we report whether there was adjustment for covariates as a measure of methodologic quality.

Peer Review

This draft report was sent for review to a select group of experts in omega-3 fatty acids, epidemiology, nutrition, and cancer. The names, expertise, and affiliations of the peer reviewers are listed in Table A.7.1, Appendix A. Additionally, this draft report was sent to the members of the TEP for review. Service as a peer reviewer or as a technical expert panelist does not imply agreement or endorsement of the findings of this report.

Chapter 3. Results

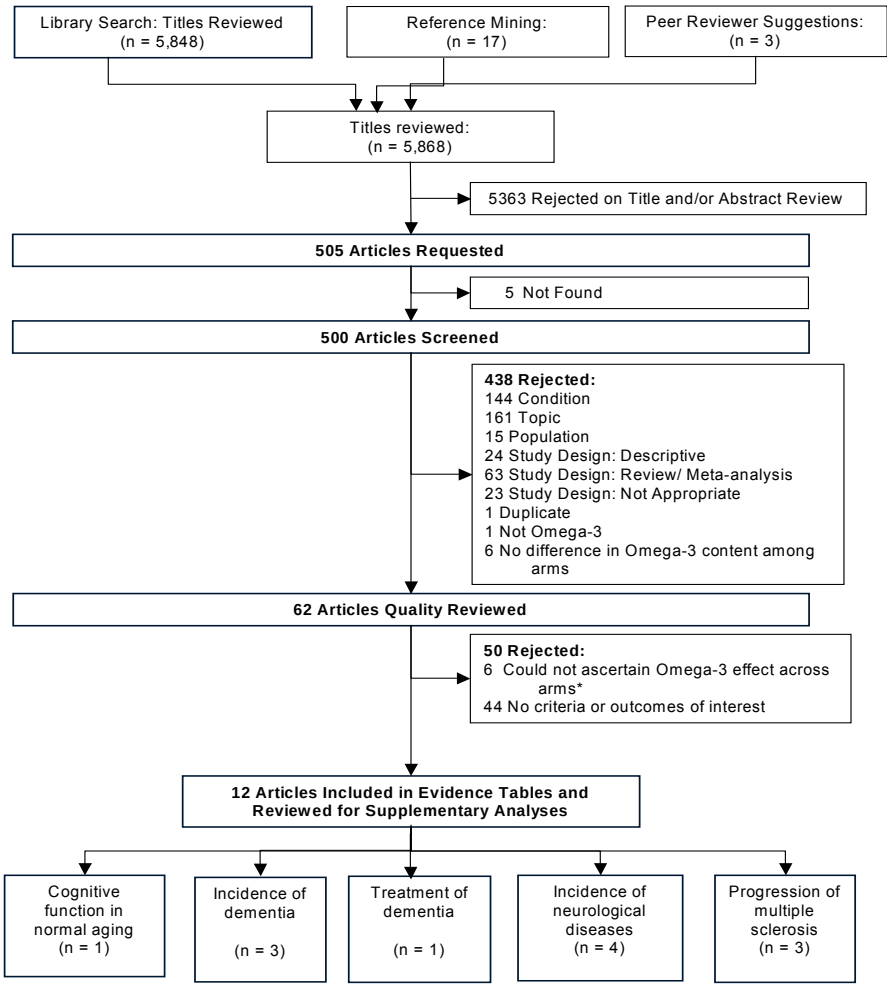
Results of Literature Search

Figure 3.1 displays the flow of the literature review. The University of Ottawa EPC e-mailed us 5,848 citations as a result of their computerized library searches, our reviewers found 17 additional citations as a result of reference mining, and peer reviewers suggested three citations not identified by these sources for a total of 5,868 citations. Our two reviewers considered 505 of these article titles to be relevant to our research topics. We were able to retrieve 500 (99%) of these articles.

Of the 500 articles retrieved, 438 were rejected (Figure 3.1). We identified 62 studies that passed the preliminary screening criteria and went on to the QRF stage. At this stage of review, we further excluded studies from our final analysis set based on study design and whether the study assessed effects of omega-3 fatty acids on topics relevant to this report, i.e. the incidence and treatment of dementia, cognitive decline with normal aging, the incidence of other neurological diseases, and the progression of MS. Among the 62 studies reviewed with a QRF, 50 were rejected. Among the rejected studies, six had no difference in omega-3 fatty acid content among study arms. The other 44 articles that were rejected did not describe a condition, population, or outcome that was relevant to this report. The remaining 12 articles met our inclusion criteria and are described in detail in this report.

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

Figure 3.1. Literature flow.



* Omega-3 effects might not be ascertainable for a variety of reasons, including Omega-3 given in conjunction with another supplement and the effect of Omega-3 not quantified.

Effects of Omega-3 Fatty Acids

Summaries of all evaluated neurological studies can be found in Appendix C (Tables C.1 through C.4).

Cognitive Function in Normal Aging

Overall effect. We identified one study that evaluated the effect of omega-3 FA on cognitive function in community-dwelling elderly persons. This study[59] investigated the association between omega-3 FA and cognitive function in a cohort of 818 community-dwelling men (ranging in age from 64 to 84 years old) living in the Dutch town of Zutphen, who were participants in the Zutphen Elderly Study, a longitudinal study on risk factors for various chronic diseases. Data about dietary intake were collected by trained interviewers in 1985, 1990, and 1993, and data about cognitive function were collected in 1990 and 1993. Complete dietary information was collected on 476 men, and complete information regarding cognitive function was collected on 342 men. The relationship between both fish consumption and total omega-3 fatty acid consumption and both cognitive impairment and cognitive decline were assessed. Cognitive impairment was defined as a MMSE score $\leq$ 25; cognitive decline was defined as a drop of more than two points in the MMSE over a 3-year period, which corresponds to the 15th percentile of change. Compared with no fish consumption, fish consumption was inversely associated with cognitive impairment in crude analyses, but not after adjustment for multiple variables (Table 3.1). Fish consumption was also inversely associated with development of cognitive decline, though not significantly so (Table 3.1). Total omega-3 fatty acid consumption was not related to cognitive impairment or cognitive decline (Table 3.1).

Sub-populations. This study did not evaluate the differential effects of omega-3 FA on distinct subpopulations.

Covariates. Although analyses adjusted for a number of different covariates in a multivariable regression model (Table 3.1), the effects of specific covariates on the association between omega-3 fatty acid consumption and cognitive function were not described.

Effects of source, dose, and exposure duration.

Source: This study assessed omega-3 fatty acid effects in terms of fish consumption and total omega-3 fatty acid consumption. Fish consumption was associated with a reduced risk of cognitive impairment but had no association with cognitive decline; omega-3 fatty acid consumption was not associated with either outcome.

Dose: Dose effect was not assessed for fish. A dose effect was observed for omega-3 fatty acid consumption and cognitive impairment on unadjusted analyses (p for trend = 0.9), but not on adjusted analyses. No dose effect was found with omega-3 fatty acid consumption and cognitive decline.

Exposure Duration: Effects of exposure duration were not assessed.

Sustainment of Effect. Sustainment of effect was not reported.

Quality and Applicability. Parameters of methodologic quality are as follows:

This study adjusted for confounders, had valid ascertainment of exposures and outcomes, ascertained that exposure occurred before outcome measurement, and described withdrawals and drop outs. It did not blind to exposure/outcome and did not describe selection bias.

This study had an applicability rating of II because the population sampled included only males. Thus, although this study represented a relevant sub-group of the target population, it was not representative of the entire target population because of its exclusive sampling of one gender.

Table 3.1. Risk of cognitive impairment or decline in normal aging reported in a cohort study with consumption of omega-3 fatty acids, by categorization of omega-3 fatty acid intake.*

Author, Year Cohort	Outcome	Study arm (quartile, quintile or dose group)	n	Amount	Estimates of effect		
					Age-adjusted OR (95% CI)	Multivariable RR (95% CI)	Multivariable Adjustors
Fish							
Kalmijn, 1997[59] Zutphen Elderly Study	Cognitive impairment	None	NR	none	1.0	1.0	Age, education, cigarette smoking, alcohol consumption, energy intake, baseline MMSE score.
		High	NR	> 0-20 g/day	0.43 (0.23-0.78)	0.63 (0.33-1.21)	
		Total 476			p = 0.004‡	p = 0.13‡	
	Cognitive decline	None	NR	none	NR	1.0	
		High	NR	> 0-20 g/day	NR	0.45 (0.17-1.16)	
		Total 342				p = 0.09‡	
Omega-3 fatty acids†							
Kalmijn, 1997[59] Zutphen Elderly Study	Cognitive impairment	Low	NR	0-37.5 mg/day	1.00	NR	Age, education, cigarette smoking, alcohol consumption, energy intake, baseline MMSE score.
		Medium	NR	37.5-155.5 mg/day	1.09 (0.65-1.80)	NR	
		High	NR	155.5-2,110.5 mg/d	0.96 (0.57-1.62)	NR	
		Total 476			p = 0.9‡		
	Cognitive decline	Low	NR	0-37.5 mg/day	1.00 NR	NR	
		Medium	NR	37.5-155.5 mg/day	0.85 (0.40-1.82)	NR	
		High	NR	155.5-2,110.5 mg/d	0.78 (0.35-1.73)	NR	
		Total 342			p=0.5		

*NR= not reported; † EPA and DHA; ‡ test for trend.

Incidence of Dementia

Overall effect. We identified three prospective cohort studies[21, 23, 67] that evaluated the effect of omega-3 FA on the incidence of dementia (Table 3.2). All three of the studies assessed the incidence of dementia relative to fish consumption; one also assessed risk relative to total omega-3 fatty consumption and relative to consumption of ALA, EPA, and DHA, individually.[23] Fish intake was associated with a significant reduction in the incidence of non-Alzheimer's dementia in all three studies,[21, 67] although in one,[21] statistical significance was barely lost with multivariable adjustment[21] (Table 3.2). Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies; the association was statistically significant in one[67] and nearly so in the other two[21, 23] (Table 3.2). Total omega-3 fatty acid consumption and consumption of DHA were associated with a significant reduction in the incidence of Alzheimer's disease; consumption of ALA and EPA were not[23] (Table 3.2).

Sub-populations. One study assessed whether gender modified the effect of total omega-3 fatty acid consumption or consumption of fish, ALA, EPA, or DHA.[23] Total intake of omega-3 fatty acids was protective in females only (p for interaction= 0.02); gender did not modify the effect of fish, ALA, EPA, or DHA.

Covariates. Two of the studies[23, 67] assessed the influence of covariates on the effect of omega-3 FA on incidence of dementia.

In one study,[23] the multivariable relative risks for intakes of total omega-3 fatty acids, DHA, and EPA did not change when adjusted for vitamin E intake, other fat intake, and cardiovascular disease. In the same study, multivariable risks for intake of ALA were reported as approximately 1.0 with adjustment for vitamin E but not affected by adjustment for cardiovascular disease; intake of ALA was strongly protective among people with the APO-E-4 genotype (RR = 0.08 per natural log {milligram} increase in ALA, p = 0.02).

In the other study,[67] estimates of relative risk did not change with adjustment for cigarette smoking, alcohol consumption, fiber consumption, antioxidant intake, stroke, myocardial infarction, or serum total and high-density lipoprotein cholesterol.

Effects of source, dose, and exposure duration.

Source: Fish consumption was associated with a significantly reduced risk of dementia in three of the studies.[21] In the one study that assessed the effect of total omega-3 fat consumption, ALA, DHA, and EPA on the incidence of dementia, total omega-3 and DHA were associated with significant reduced risk in multivariable analyses; ALA and EPA were not.

Dose: Dose effects were observed for fish in one study[67] and for total omega-3 consumption and DHA in another[23] (p for trend <0.05 for each) (Table 3.2).

Exposure Duration: None of the studies addressed exposure duration.

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

Quality and applicability. Among these three studies, all adjusted for confounders, reported using valid methods to ascertain outcomes, and confirmed that the exposure occurred prior to the outcome.

One study did not describe a valid method to ascertain dietary intake[21] (method used was not described). One of the studies explicitly described whether the investigators were blinded to information on exposure when obtaining data on outcome or on outcome when obtaining data on exposure.[23, 34, 61]

Of the three studies, two[23, 67] had an applicability rating of I (applicable to the general target population of adults). One study received an applicability rating of II because it was performed in France.[21]

Table 3.2. Risk of dementia reported in prospective cohort studies for different categories of consumption of omega-3 fatty acids, by category of consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect		
						Age adjusted RR (95% CI)	Multivariable adjusted RR (95% CI)	Multivariable Adjustors
FISH								
Barberger-Gateau, 2002[21] PAQUID (Personnes Agées QUID) Study	Dementia	1	NR	NR	NR	1.0	1.0	Age, sex, education
		2	1122	124	At least once a week	0.66† (0.47-0.93)	0.73† (0.52-1.03)	
	Alzheimer's disease	1	NR	NR	NR	1.0	NR	
		2	1122	99	At least once a week	0.69† (0.47-1.01)	NR	
		Total 1122		223				
Kalmijn, 1997[67] Rotterdam Study	Total dementia	1	1807	58	≤ 3 g/day	NR	1.0	Age, sex, education, total energy intake.
		2	1773	58	3.0-18.5 g/day	NR	0.8 (0.4-1.4)	
		3	1806	58	> 18.5 g/day	NR	0.4 (0.2-0.9)	
				58			p = 0.03‡	
	Alzheimer's disease without vascular component	1	1807	37	≤ 3 g/day	NR	1.0	
		2	1773	37	3.0-18.5 g/day	NR	0.9 (0.4-1.8)	
		3	1806	37	> 18.5 g/day	NR	0.3 (0.1-0.9)	
				37			p = 0.005‡	
	Dementia with a vascular component	1	1807	12	≤ 3 g/day	NR	1.0	
		2	1773	12	3.0-18.5 g/day	NR	0.6 (0.2-2.5)	
		3	1806	12	> 18.5 g/day	NR	0.7 (0.2-2.8)	
		Total 5386		12			p = 0.39‡	

* NR = not reported, g = grams; † hazard ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table 3.2 (continued). Risk of dementia reported in prospective cohort studies for different categories of consumption of omega-3 fatty acids, by category of consumption.***

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect		
						Age adjusted RR (95% CI)	Multivariable adjusted RR (95% CI)	Multivariable Adjustors
FISH								
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	121	32	never	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	250	39	1-3 servings/ month	0.7 (0.3 - 1.6)	0.6 (0.3-1.3)	
		3	296	43	1 serving/ week	0.5 (0.2 - 1.0)	0.4 (0.2-0.9)	
		4	148	26	≥ 2 servings/week	0.6 (0.2 - 0.9)	0.4 (0.2-0.9)	
		Total 815		140		p = 0.18 ‡	p = 0.07‡	
Omega-3 fatty acids								
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	32	0.9 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	30	1.13 g/day	1.1 (0.4 - 2.9)	1.2 (0.5-3.0)	
		3	NR	22	1.30 g/day	0.5 (0.2 - 1.4)	0.6 (0.2-1.7)	
		4	NR	24	1.49 g/day	0.6 (0.2 - 1.5)	0.7 (0.3-1.6)	
		5	NR	23	1.75 g/day	0.3 (0.1 - 0.7)	0.4 (0.1-0.9)	
		Total 815		131		p = 0.01‡	p = 0.01‡	

NR = not reported, g = grams; † hazard ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table 3.2 (continued). Risk of dementia reported in prospective cohort studies for different categories of consumption of omega-3 fatty acids, by category of consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect		
						Age-adjusted RR (95% CI)	Multivariable adjusted RR (95% CI)	Multivariable Adjustors
ALA								
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	26	0.72 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	33	0.92g/day	1.7 (0.7-3.8)	1.8 (0.8-3.8)	
		3	NR	24	1.06g/day	0.8 (0.4-1.9)	0.8 (0.4-2.0)	
		4	NR	25	1.23g/day	0.8 (0.4-1.7)	0.9 (0.4-2.0)	
		5	NR	23	1.46g/day	0.5 (0.2-1.1)	0.7 (0.3-1.6)	
		Total 815		131		p = 0.01‡	p = 0.10‡	
DHA								
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	28	0.03 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	45	0.05 g/day	0.8 (0.3-2.1)	0.8 (0.3-2.1)	
		3	NR	14	0.06 g/day	0.4 (0.1-1.1)	0.4 (0.1-1.0)	
		4	NR	19	0.07 g/day	0.3 (0.1-0.9)	0.2 (0.1-0.8)	
		5	NR	25	0.10 g/day	0.4 (0.2-1.1)	0.3 (0.1-0.9)	
		Total 815		131		p = 0.05‡	p = 0.02‡	

* NR = not reported, g = grams; † hazard ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table 3.2 (continued). Risk of dementia reported in prospective cohort studies for different categories of consumption of omega-3 fatty acids, by category of consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
EPA										
Morris, 2003 [23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	55	0.0 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	NR§	0.0 g/day	NR§	NR§	NR§	NR§	
		3	NR	35	0.01 g/day	1.0	(0.4-2.4)	1.1	(0.4-2.8)	
		4	NR	14	0.02 g/day	0.5	(0.2-1.2)	0.5	(0.2-1.2)	
		5	NR	27	0.03 g/day	0.9	(0.4-2.1)	0.9	(0.4-2.3)	
		Total 815		131			p = 0.40‡		p = 0.40‡	

* NR = not reported, g = grams; † hazard ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Treatment of Dementia

Overall effect. We identified one study[24] that assessed the efficacy of omega-3 FA as a treatment for dementia. This RCT assessed the effect of supplementation with DHA on cognitive function among 20 elderly nursing home residents with vascular dementia. Cognitive functioning was evaluated using Hasegawa's Dementia rating scale (HDS-R) and MMSE scores at baseline, and after 3, 6, and 12 months. Baseline Hasegawa's Dementia rating scale and MMSE scores were 15 to 22, consistent with mild to moderate dementia. HDS-R and MMSE scores improved in the DHA-treated group but not among patients who were not treated with DHA (Table 3.3). Comparisons between groups were significant at 3 and 6 months for the HDS-R and at 6 months for the MMSE.

Sub-populations. The study did not evaluate the differential effects of omega-3 FA on distinct subpopulations.

Covariates. The study did not evaluate covariates.

Effects of source, dose, and exposure duration.
Source: The source assessed was DHA.
Dose: A single dose of 4.3 g of DHA was administered; dose effect was not assessed.
Exposure Duration: The duration of exposure was 12 months. Significant differences between study groups were observed after 3 months and after 6 months, but not after 12 months.

Sustainment of effect. Sustainment of effect was not assessed in either report.

Quality and applicability. Although this trial is described as randomized, the randomization is not described as double-blind, and there is no description regarding blinding or withdrawals/dropouts. The study[24] had an applicability rating of II with a summary quality score of C (Jadad score = 1; concealment of allocation was not reported); thus it can be considered of poor quality (Table 3.4).

Table 3.3.The effect of omega-3 fatty acids on the treatment of dementia in one randomized controlled trial stratified by outcome.*

Author, Year	Results				
Terano, 1994[24]	Total n	Before	After 3 months	After 6 months	After 12 months
Mean scores of HDS-R					
Standard nursing home diet	10	16.3	16.7	16.7	15.3
Standard nursing home diet PLUS DHA 4.3 grams/day	10	17.2	20.6†	19.9†	20.2
Mean scores of MMSE					
Standard nursing home diet	10	19.7	19.4	19.6†	19.1
Standard nursing home diet PLUS DHA 4.3 grams/day	10	20.1	21.3	22.2	21.9

*HDS-R = Hasegawa's Dementia rating scale; MMSE = Mini Mental Status Exam; † $p < 0.05$ for comparisons between groups with paired t-test.

Table 3.4. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on treatment of dementia in randomized controlled trials (RCTs).

		Methodologic Quality		
Applicability		A	B	C
	I			
	II			Terano[24]
	III			

Incidence of Neurological Diseases

Overall effect. We identified four studies[34, 43, 60, 61] that specifically addressed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia: two assessed the incidence of MS,[43, 61] one assessed the risk of Parkinson's disease,[34] and one assessed the risk of cerebral palsy[60] (Table 3.6).

The relationship between dietary intake of omega-3 FA and incidence of MS was assessed in two reports; one pooled data from two large cohorts of women from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II),[61] and the other used a case-control design.[43] The prospective cohort study assessed the effect of omega-3 fatty acids in terms of fish consumption, fish omega-3 FA, ALA, EPA, and DHA (Table 3.6). ALA was associated with a reduced risk of MS in both cohorts that did not reach statistical significance (pooled RR = 0.3; 95% C.I. 0.1 – 1.1) (Table 3.6). Intakes of omega-3 FA, EPA, or DHA were not associated with MS incidence. Relative risk estimates pooled for both NHS and NHS II cohorts for omega-3 FA intake (fish) were 1.1 (95% C.I. 0.9 - 1.3), for EPA intake, 1.3 (95% 0.9 -1.9), and 1.1 (95% C.I. 0.9-1.5) for DHA intake (Table 3.6). The case-control study[43] evaluated 197 incident MS cases and 202 age-, sex- and neighborhood-matched controls and found no significant association between fish consumption and risk of MS overall (OR = 0.91, 95% C.I. 0.78 - 1.05). However, fish consumption was significantly associated with a lower risk of MS in females only (OR = 0.83, 95% C.I. 0.69 - 1.00; $p<0.05$) (Table 3.6).

The relationship between dietary intake of omega-3 FA and incidence of Parkinson's disease was assessed in one report that pooled data from two large prospective cohorts, the Health Professionals Follow-up Study and the Nurses' Health Study. This study assessed the effect of omega-3 FA in terms of omega-3 fats from fish, ALA, EPA, and DHA over a six- to eight-year period (Table 3.6). There was no significant association between fish omega-3 FA, ALA, EPA, or DHA intake and risk of Parkinson's disease (p for trend = 0.9, 0.9, 0.9 and 0.8, respectively).

In a pooled analysis of men and women across two cohorts, ALA was associated with a reduced risk of developing Parkinson's disease (RR = 0.65, 95% CI 0.46, 0.91 for comparison of highest to lowest quintiles of risk). Among women, there was a significant trend but no significant risk reduction for any individual quintile of consumption. This finding is particularly noteworthy given the statistical power of the Health Professionals Follow-up Study and the Nurses' Health Study and the longitudinal analysis of dietary intake in these studies.

One study[60] evaluated the effects of maternal dietary intake on the risk of cerebral palsy in offspring in a case-control study of 91 cases of cerebral palsy identified from statistics of hospitals and rehabilitation centers in Greece and 246 neighborhood controls. Mothers of cases and controls were interviewed about their dietary habits during pregnancy using a food-frequency questionnaire. Consumption of fish once a week throughout pregnancy was associated with a lower risk of cerebral palsy (OR= 0.63, 95% C.I. 0.37-1.08; $p < 0.09$) compared with no fish intake.

Sub-populations. Two studies[34, 43] stratified the effects of omega-3 FA by gender. The study that investigated the relationship between dietary intake of fat and Parkinson's disease found no apparent association between omega-3 FA intake and risk of Parkinson's disease for either males or females (p for trend = 0.9 for males and 0.8 for females).

In the other study,[43] which used a case-control design, fish consumption was associated with a reduced risk of MS among females, (OR = 0.83, 95% C.I. 0.69 - 1.00) but not males (OR = 1.08, 95% C.I. 0.84-1.40) (Table 3.6).

Covariates. Effects of any specific covariates on the observed omega-3 associations were not reported in any of the studies.

Effects of source, dose, and exposure duration.

Source: The effect of fish consumption on the incidence of two different neurological diseases was assessed in three different reports. Fish consumption was associated with a reduced risk of cerebral palsy;[60] it had no overall effect on the incidence of MS in two studies,[43, 61] but was associated with a reduced risk for women in one.[43] Omega-3 FA from fish had no effect on the incidence of MS[43] or Parkinson's disease.[34] ALA was associated with a reduced risk of MS in one study[61] and had no effect on the incidence of Parkinson's disease in another.[34] EPA and DHA had no effect on the incidence of MS[61] or Parkinson's disease.[34]

Dose: Dose effect was assessed in two studies.[34, 61] One study[34] assessed the effect of fish dose on the incidence of MS and found no dose (or other) effect. A dose effect for ALA on the incidence of MS was reported in one study,[34] but no dose effect for ALA on the incidence of Parkinson's disease was found in the other study.[61] There was no dose effect for EPA or DHA in either study.

Exposure Duration: None of the studies assessed the effect of exposure duration.

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

Quality and applicability. Parameters of methodologic quality are detailed in Table 3.5. All four of the studies[34, 43, 60, 61] had an applicability rating of II.

Table 3.5. Parameters of methodological quality.*

Parameters	Chen, 2003[34]	Ghadirian, 1998[43]	Petridou, 1998[60]	Zhang, 2000[61]
Adjustment for confounders	Y	Y	Y	Y
Blinding of exposure/outcome	Y	Y	Y	Y
Valid ascertainment of outcome	Y	Y	Y	Y
Valid ascertainment of exposure	Y	Y	Y	Y
Exposure before outcome	Y	Y	Y	Y
Selection bias	N	N	Y	N
Description of withdrawals and dropouts	NR	Y	Y	Y

* NR = not reported.

Table 3.6 Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		Multivariable Adjustors, Matching parameters
						Multivariable adjusted RR (95% CI)		
Fish								
Multiple sclerosis	Zhang, 2000[61] Cohort Study: The Nurses' Health Study I and II		Dose Groups					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
			1	81	< 1/week	1.0		
			2	77	1-2.9/week	1.0	(0.8-1.4)	
			3	37	3-4.9/week	0.9	(0.6-1.3)	
						p = 0.79‡		
Multiple sclerosis	Ghadirian, 1998,[43] Case control study	Men	Control	64	-	1.0		*Multivariable adjustors:* Total energy, body mass index *Matching:* Age, sex, phone number
		Men	Case	61	-	1.08§	(0.84-1.40)	
		Women	Control	138	-	1.0		
		Women	Case	136	-	0.83§	(0.69-1.00)	
		All	Control	202	-	1.0		
		All	Case	197	-	0.91§	(0.78-1.05)	
Cerebral palsy	Petridou, 1998,[60] Case control study		Control	166	1/week	1.0		*Multivariable adjustors:* 'Core' variables‖ plus total energy intake, body mass index *Matching:* Age, neighborhood or age, physician
			Case	58	1/week	0.63	(0.37-1.08)	

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. ‖ Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes; § Risk of MS per 100 grams of fish per day (log transformation).

Table 3.6 (continued). Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design	Study arm (quartile; quintile; dose group; case or control)	n†	Median dose	Estimates of effect: Multivariable adjusted RR (95% CI)		Multivariable Adjustors, Matching parameters
Omega-3 fat from fish							
Parkinson's Disease	Chen, 2003[34] Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study	Men	Quintiles				*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
			1	NR	0.03 % of energy	1.0	
			2	NR	0.07% of energy	0.84	(0.52-1.37)
			3	NR	0.1% of energy	1.08	(0.69-1.69)
			4	NR	0.2% of energy	0.88	(0.55-1.40)
			5	NR	0.3 % of energy	0.99	(0.63-1.55)
			Total 47,331		p = 0.9‡		
		Women	Quintiles				
			1	NR	0.03 % of	1.0	
			2	NR	0.05 % of energy	0.70	(0.41-1.19)
			3	NR	0.08 % of energy	0.76	(0.45-1.29)
			4	NR	0.1% of energy	0.75	(0.45-1.26)
			5	NR	0.2 % of energy	0.90	(0.55-1.47)
			Total 88,653			p = 0.9‡	
		Pooled men and women	Quintiles				
			1	NR	NR	1.0	
			2	NR	NR	0.77	(0.54-1.11)
			3	NR	NR	0.93	(0.66-1.31)
			4	NR	NR	0.82	(0.58-1.16)
			5	NR	NR	0.94	(0.68-1.32)
			Total 135,894			p = 0.9‡	

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. || Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes; § Risk of MS per 100 grams of fish per day (log transformation).

Table 3.6 (continued). Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design		Study arm (quartile; quintile; dose group; case or control)	n†	Median dose	Estimates of effect: Multivariable adjusted RR (95% CI)	Estimates of effect: Multivariable Adjustors
ALA							
Multiple Sclerosis	Zhang, 2000[61] Cohort Study: The Nurses' Health Study I and II		Groups				*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
			1	NR	< 1% of energy	1.0	
			2	NR	≥ 1% of energy	0.3 (0.1-1.1)	
Parkinson's Disease	Chen, 2003[34] Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study	Men	Quintiles				*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
			1	NR	0.05 % of energy	1.0	
			2	NR	0.06% of energy	0.54 (0.34-0.87)	
			3	NR	0.08% of energy	0.75 (0.49-1.15)	
			4	NR	0.09% of energy	0.88 (0.58-1.32)	
			5	NR	0.1 % of energy	0.69 (0.45-1.07)	
			Total 47,331			p = 0.4‡	
		Women	Quintiles				
			1	NR	0.04 % of energy	1.0	
			2	NR	0.06 % of energy	0.83 (0.51-1.34)	
			3	NR	0.07 % of energy	0.71 (0.43-1.17)	
			4	NR	0.09% of energy	0.68 (0.41-1.13)	
			5	NR	0.1 % of energy	0.60 (0.35-1.01)	
			Total 88,563			p = 0.04‡	
		Pooled men and women	Quintiles				
			1	NR	NR	1.0	
			2	NR	NR	0.67 (0.47-0.93)	
			3	NR	NR	0.73 (0.53-1.01)	
			4	NR	NR	0.79 (0.57-1.09)	
			5	NR	NR	0.65 (0.46-0.91)	
			Total 135,894			p = 0.05‡	

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. || Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes; § Risk of MS per 100 grams of fish per day (log transformation).

Table 3.6 (continued). Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design		Study arm (quartile; quintile; dose group; case or control)	n†	Median dose	Estimates of effect: Multivariable adjusted RR (95% CI)		Multivariable Adjustors
EPA								
Parkinson's Disease	Chen, 2003[34] Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study	Men	Quintiles					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
			1	NR	0.009 % of energy	1.0		
			2	NR	0.02 % of energy	0.77	(0.48-1.25)	
			3	NR	0.04 % of energy	0.88	(0.56-1.39)	
			4	NR	0.06 % of energy	0.92	(0.59-1.44)	
			5	NR	0.1 % of energy	0.91	(0.59-1.42)	
			Total 47,331			p = 0.9‡		
		Women	Quintiles					
			1	NR	0.007 % of energy	1.0		
			2	NR	0.01 % of energy	0.67	(0.39-1.16)	
			3	NR	0.02 % of energy	0.80	(0.48-1.34)	
			4	NR	0.04 % of energy	0.74	(0.44-1.24)	
			5	NR	0.07 % of energy	0.91	(0.56-1.49)	
			Total 88,563			p = 0.8‡		
		Pooled men and women	Quintiles					
			1	NR	NR	1.0		
			2	NR	NR	0.73	(0.51-1.04)	
			3	NR	NR	0.84	(0.60-1.19)	
			4	NR	NR	0.84	(0.60-1.18)	
			5	NR	NR	0.91	(0.66-1.27)	
			Total 135,894			p = 0.9‡		

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. || Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes; § Risk of MS per 100 grams of fish per day (log transformation).

Table 3.6 (continued). Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design		Study arm (quartile; quintile; dose group; case or control)	n†	Median dose	Estimates of effect		
						Multivariable adjusted RR (95% CI)		Multivariable Adjustors
DHA								
Parkinson's Disease	Chen, 2003[34] Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study	Men	Quintiles					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
			1	NR	0.02 % of energy	1		
			2	NR	0.05 % of energy	0.79	(0.49-1.28)	
			3	NR	0.07 % of energy	1.05	(0.67-1.64)	
			4	NR	0.1 % of energy	0.90	(0.57-1.42)	
			5	NR	0.2 % of energy	0.92	(0.58-1.44)	
			Total 47,331			p = 0.9‡		
		Women	Quintiles					
			1	NR	0.02 % of energy	1		
			2	NR	0.04 % of energy	0.62	(0.36-1.07)	
			3	NR	0.06 % of energy	0.65	(0.38-1.09)	
			4	NR	0.08 % of energy	0.81	(0.49-1.32)	
			5	NR	0.1 % of energy	0.76	(0.46-1.26)	
			Total 88,563			p = 0.8‡		
		Pooled men and women	Quintiles					
			1	NR	NR	1		
			2	NR	NR	0.71	(0.49-1.02)	
			3	NR	NR	0.86	(0.61-1.21)	
			4	NR	NR	0.86	(0.61-1.20)	
			5	NR	NR	0.84	(0.60-1.18)	
			Total 135,894			p = 0.8‡		

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. || Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes; § Risk of MS per 100 grams of fish per day (log transformation).

Progression of Multiple Sclerosis

Overall effect. We identified three studies that evaluated the effect of omega-3 FA on the treatment and progression of MS. Among these, one study was an RCT[40] and two were single arm, open-label clinical trials.[62, 63] The RCT assessed the effect of treatment with an omega-3 FA supplement (MaxEPA) on disability and relapse rates (Table 3.7). There were no significant differences in disability or relapse rates between the treatment and placebo groups. Results for disability did not differ on subgroup analyses of patients with disease duration of 5 years or less and baseline Kurtzke disability scores of 2 or less (Table 3.7).

The one-arm open-label studies[62, 63] described the effects of supplementation with omega-3 FA on disability and progression among patients with MS (Table 3.8). Both studies reported a significant reduction on the Expanded Disability Status Scale (EDSS) after treatment with the omega-3 supplement; one also reported improvement on an index of disease progression.[62]

Sub-populations. The effects of omega-3 FA on subpopulations were not assessed.

Covariates. The effects of covariates on omega-3 FA effects were not assessed.

Effects of source, dose, and exposure duration.

Source: The source of omega-3 FA was fish oil in one study[63] and fish oil capsules in the other.[62]

Dose: A single dose was assessed in each study; hence, dose effect was not assessed.

Exposure Duration: The effect of exposure duration was not assessed.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. The RCT[40] had an applicability rating of II-B and a summary quality score of B (Jadad score = 3); concealment of allocation was not reported. This study is applicable to the general population of adult patients with multiple sclerosis (Table 3.9). The two open label one-arm trials[62, 63] were both of poor methodologic quality: there was no comparison group or blinding; additionally there was no description of withdrawals or dropouts. Both of these trials had a Jadad score of 0. The applicability rating of these studies was II-B.

Table 3.7. The effect of omega-3 fatty acids on progression of multiple sclerosis reported in one randomized controlled trial (RCT).*

Author, Year	Treatment Group	Disability, number (%)of patients						Mean relapse rates			
Bates, 1989[40]		Overall		Kurtzke ≤ 2		Duration ≤ 5 years		Kurtzke ≤ 2		Kurtzke > 2	
		Better/ same	Worse	Better/ same	Worse	Better/ same	Worse	Better/ same	Worse	Better/ same	Worse
	Max EPA 10 grams/day for 24 months	79 (51)	66 (43)	50 (59)	35 (41)	30 (57)	23 (43)	0.44	0.15	0.55	0.05
	Olive oil 10 grams/day for 24 months	65 (42)	82 (52)	41 (46)	49 (54)	24 (42)	33 (58)	0.55	0.16	0.63	0.70

*No significant difference between groups for any comparisons.

Table 3.8. The effect of omega-3 fatty acids on progression of multiple sclerosis in open-label trials stratified by outcome.

Author, Year	Intervention	Mean EDSS Scores*	Mean Progression Index			
		n, clinical diagnosis	Before	After	Before	After
Cendrowski, 1986[62]	MaxEPA (4.2 g/day EPA; 2.8 g/day DHA)	5, acute remitting MS	3.30	2.70	0.59	0.44†
Cendrowski, 1986[62]	MaxEPA (4.2 g/day EPA; 2.8 g/day DHA)	7; slowly progressive MS	6.92	7.07	0.35	0.36
Nordvik, 2000[63]	Fish oil supplement (0.4 g/day EPA; 05 g/day DHA)	16; MS	2.16	1.63‡	NA	NA

NA = Not Applicable; * EDSS = Expanded Disability Status Scale; † $p < 0.05$; ‡ = $p = 0.005$.

Table 3.9. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on progression of multiple sclerosis in randomized controlled trials (RCTs).

		Methodologic Quality		
Applicability		A	B	C
	I			
	II		Bates[40]	
	III			

Chapter 4. Discussion

Overview

We screened 5,868 titles, from which we reviewed 500 full-text articles. Among these, 62 articles met our inclusion criteria for further review. Fifty were rejected and 12 met our inclusion criteria and were reviewed further for data abstraction. Among these, two articles were randomized controlled trials, six articles were prospective cohort studies, two articles were case-controls, and two were one-arm open label trials.

Main Findings

Effects of omega-3 fatty acids.

Cognitive function in normal aging. In a single prospective cohort study[59] that evaluated the effects of omega-3 fatty acid on cognitive function in normal aging, there was no significant association between omega-3 FA intake in the form of fish consumption and cognitive decline.

Incidence of dementia. Among three prospective cohort studies[21, 23, 67] that assessed the effects of omega-3 FA on the incidence of dementia, fish consumption was associated with a statistically and clinically significant reduction in the incidence of non-Alzheimer's dementia in all three.[67] Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies; the association was statistically significant in one[67] and nearly so in the other two[21, 23] (Table 3.2). Total omega-3 FA consumption and consumption of DHA were associated with a significant reduction in the incidence of Alzheimer's disease for the general population; consumption of ALA and EPA were not.[23] Among individuals who were APOE-4 positive, ALA was associated with a reduced risk.

Treatment of dementia. One RCT[24] assessed omega-3 fatty acids as a treatment for dementia. This study demonstrated statistically significant improvements on both Hasegawa's Dementia rating scale and the MMSE scores with omega-3 supplementation. However, the sample size was small and the methodologic quality was poor.

Incidence of neurological diseases. We identified four studies that assessed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia: two assessed the incidence of MS,[43, 61] one assessed the risk of Parkinson's disease,[34] and one assessed the risk of cerebral palsy.[60] Overall, there was no significant association between omega-3 FA and the incidence of MS in either a study that pooled data across two cohort studies[61] or in a case-control study.[43] However, the case-control study did demonstrate a reduced risk of MS with fish consumption, but only among women. A single observational cohort study[34] found that ALA was associated with a reduced risk of Parkinson's disease when comparing highest and lowest quintile of intake in a pooled analysis of men and women; among women, but not men, there was a trend for risk reduction. There was no significant association between dietary intake of other omega-3 FAs and Parkinson's disease. A single case-control

study[60] found a reduced risk of cerebral palsy in offspring of women who consumed fish at least once a week throughout pregnancy, relative to women who did not.

Progression of multiple sclerosis. We identified one RCT[40] and two single arm, open-label clinical trials[62, 63] that assessed the effect of omega-3 fatty acids on the progression of MS.[63-66] There were no significant differences in disability or relapse rates between the treatment and placebo groups in the RCT.[40] The one-arm open label trials both reported a significant reduction on the Expanded Disability Status Scale (EDSS) after treatment with the omega-3 supplement; one also reported improvement on an index of disease progression.[62]

Dose, source, duration effects and sustainment of effect. Data were insufficient to draw conclusions about source or duration effects or about sustainment of effect.

Quality and applicability. The quality of the clinical trials was generally poor. Among the two RCTs that met our inclusion criteria, one[33] was of good quality with an overall summary quality of B (Jadad score 3, no concealment of allocation), and the other[24] was of poor quality with an overall summary quality of C (Jadad score1, no concealment of allocation). The two open-label one-arm trials[62, 63] were both of poor methodologic quality: there was no comparison group or blinding; additionally there was no description of withdrawals or dropouts. The applicability ratings for all four of these clinical trials were II, meaning that the study populations were representative of a subgroup of the general population; these subjects had either MS or dementia.

The quality of the eight observational studies was generally good. Among these six prospective observational cohort and two case-control studies, all eight adjusted for confounders, reported using valid methods to ascertain outcomes, and confirmed that the exposure occurred prior to the outcome. The methods used to enroll subjects in one study would be expected to introduce selection bias.[60] All but one study described withdrawals and dropouts[34] or a valid method to ascertain dietary intake[21] (method used was not described). Only three of the studies explicitly described whether the investigators were blinded to information on exposure when obtaining data on outcome or on outcome when obtaining data on exposure.[23, 34, 61] For the two case-control studies, we also assessed whether the case and control groups were comparable, and they were in both studies.[43, 60] The applicability ratings were I (representative of the US population) for one study[23] and II for all other studies. The studies with applicability ratings of II either had subjects that were part of a subpopulation[34, 43, 60, 61] and/ or were population-based, but the populations were not from the United States.[21, 59, 67]

Limitations

It is important to point out that a major limitation of studies of omega-3 FA and disease is the lack of standardized methods to measure nutrient intakes.[68] Thus, it is possible to overestimate or underestimate true associations with outcomes, because of errors in measurement of nutrients.

Furthermore, the studies we reviewed lacked a uniform or consistent approach to quantifying the type of omega-3 FA. For example, some measured nutrient intake from food frequency questionnaires without reporting type of fish or method of preparation; other studies defined

omega-3 fatty acid supplements. This issue will increasingly become important in the design of future studies of omega-3 fatty acids and disease.

Another major limitation with respect to studies relating omega-3 FA interventions to dementia, particularly Alzheimer's disease, is that the majority of studies have been done in subjects aged 60 and older. Since the length of the latency period for AD is unknown and may precede the presentation of any symptoms by several decades, the potential effect of implementing dietary interventions aimed at prevention at an advanced age may be limited. Furthermore, in studies that assessed the effects of omega-3 fatty acids on cognitive function in normal aging or dementia, standard measures often are not used or the instruments used to assess cognitive function lack uniformity.

It is also important to note that in observational studies, it is not possible to control exposure,[69] which can lead to confounding.[70]

An additional limitation is the possibility of publication bias. For large observational studies, this issue is slightly different than that observed for randomized trials. Publication bias for the latter generally means that no results of the trial are published at all. For the former, which are the main source of evidence for this report, findings may be published, but only for outcomes that achieve statistical significance, with no regard for whether such outcomes were secondary in nature. Results for primary outcomes may not be published. We must interpret our findings in light of such possible publication bias.

It is possible that additional information that would change our conclusions is available in reports that we were unable to locate or for which we were unable to find a translator. However, among 505 requested articles, only five were not found, and we were able to screen all 500 articles retrieved.

Conclusions

For each of the conditions assessed in this report, conclusions can be drawn from a few studies on the effects of Omega-3 FA. Additionally, the strength of evidence for effects of omega-3 FA on outcomes in the conditions assessed varies greatly. The evidence suggests a possible association between omega- 3 FA and reduced risk of dementia. However, due to the small number of studies that inform this topic, further research is necessary before a strong conclusion can be drawn. Data are insufficient to draw conclusions about the effects of omega-3 FA on incidence of Parkinson's disease, cerebral palsy, or MS. In addition, the evidence regarding the progression of MS is inconsistent and inconclusive. There was insufficient evidence in the studies that met our systematic inclusion criteria to draw any substantive conclusions on omega-3 fatty acid intake. The paucity of evidence in this area suggests that further epidemiological and clinical research remains to be done before any conclusions can be drawn or policy recommendations can be made in this area.

Future Research

We offer the following observations and recommendations regarding future research on the effects of omega-3 FA on the various neurological conditions reviewed.

1. Additional research on the effects of omega-3 FA needs to be performed on all of the conditions reviewed in this report before recommendations regarding the use of omega-3 FA can be made for these conditions.

2. Of particular importance, properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g. three to five years of follow-up) need to be conducted for dementia, especially Alzheimer's disease, as distinct from vascular dementia.

3. Given the concern described above regarding the possible difficulty of conducting valid studies on dementia, due to a lengthy presymptomatic latency period, it would be of interest to conduct intervention clinical trials of omega-3 fatty acids in middle-aged adults as well as in populations of cognitively-impaired adults prior to a dementia diagnosis, such as individuals with various sub-types of mild cognitive impairment (MCI).

4. Properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g. three to five years of follow-up) need to be conducted for multiple sclerosis.

5. Studies should address the effects of different types of omega-3 fatty acids (i.e. DHA, EPA, ALA, and total omega-3 FA) as well as the ratio of omega-3 to omega-6 FA.

6. Studies that assess the effects of omega-3 FA should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 FA consumption.

7. Trials of omega-3 FA should include a baseline assessment of dietary omega-3 and omega-6 FA intake.

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

9. All studies that assess the effects of omega-3 FA should use standard validated instruments to assess clinical outcomes.

10. Studies that investigate the effects of omega-3 FA on cognition should include repeated measures of cognitive function using standard validated instruments to evaluate within-person cognitive change.

11. All studies that assess the effects of omega-3 FA should use standard validated dietary assessment instruments to assess nutritional intake.

12. Observational studies should report data about type of fish consumed and method of preparation.

13. Observational studies focused on repeated measures of diet for long-term intake, and sub-group analysis among persons with cardiovascular conditions (including history of stroke or myocardial infarction) also need to be performed in order to determine whether change in diet among these sub-groups results is confounding.

U.S. Department of Health and Human Services
Mike Leavitt, *Secretary*

Office of Public Health and Science
Richard H. Carmona, M.D., M.P.H., F.A.C.S., *Surgeon General of the United States*

Agency for Healthcare Research and Quality
Carolyn M. Clancy, M.D., *Director*

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Acronyms

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

Appendices for the Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases

Preliminary Research Questions

Table A.1.1. Preliminary research questions.

GENERAL QUESTIONS: Questions posed for all three participating EPCs, for years 1 and 2.
1. What is the evidence that variable clinical effects may reflect differences in: • Serving size (fish vs. dietary supplement); • Source (fish, food, plant) vs. dietary supplement (fish oil, plant oil); • Specific type(s) of omega-3 fatty acids (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA), fish, fish oil), or the ratio of omega-6/omega-3 fatty acids used; • Manufacturer (different purity, presence of other potentially active agents)? 2. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acids (DHA, EPA, DPA, ALA, fish oil, fish)? 3. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations such as diabetics? 4. What are the mean and median intakes of DHA, EPA, DPA, ALA, fish, fish oil, omega-6, omega-6/omega-3 ratio in the US population? 5. What is the evidence that omega-3 fatty acids influence overall energy balance? 6. What is the evidence that accurate interpretation of the results of clinical studies is dependent on knowing the absolute fatty acid content of the baseline data, the relative fatty acid content of the baseline diet, or the tissue ratios of fatty acids (omega-6/omega-3) during the investigative period?
DISEASE-SPECIFIC QUESTIONS: questions posed to the SCEPC for Year 2 of the project:
Neurology:
1. What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function with aging? 2. What is the evidence that the level of brain or retinal DHA levels affect the incidence of neurological diseases?

Technical Expert Panel

The members of our technical expert panel are listed in Table A.2.1. We conducted our TEP meetings via teleconference on December 18, 2003. Dr. Beth Collins-Sharp, the Task Order Officer, and Jacqueline Besteman, Director of the Evidence-Based Practice Center Program, represented AHRQ on these calls; Dr. Anne Thurn, Director of the Evidence-Based Review Program, represented ODS; and Dr. Catherine MacLean, the Task Order Director, and Rena Hasenfeld, the Project Manager, represented the SCEPC. The key comments and recommendations of the TEP are summarized in Table A.2.2. The TEP continued to advise the SCEPC throughout the project via mail, fax, e-mail, and phone calls.

Table A.2.1 Technical expert panel members.

Neurology		
Name	**Area of Expertise**	**Institution**
Alberto Ascherio, M.D., M.P.H., Dr. P.H.	Neurology	Harvard Medical School
Julie Conquer, M.S., Ph.D.	Neurological Disorders/Nutrition	University of Guelph
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Irwin Rosenberg, M.D.	Nutrition/Aging	Tufts University
Paul Sheehy, Ph.D.	Neurology	National Institute of Neurological Disorders and Stroke
Molly Wagster, Ph.D.	Neurology/Aging	Neuroscience and Neuropsychology of Aging Program

Table A.2.2. Key TEP comments and recommendations.

Neurology
1. What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function with aging?
• This question pertains to 1) both maintenance and gains in cognitive functioning with normal aging, and 2) the prevention of dementia..
• The literature primarily includes studies on Alzheimers' disease, but other forms of dementia are also of interest..
• Normative data should be used to measure cognitive function.
• Focus on domains of cognitive function rather than specific tests. Domains of function include 1) general memory, 2) working memory, and 3) executive function.
• Part B of the Trail Making Test and praxis components of the ADAS-Cog are scales that can be used to define normal cognitive function.
• The following instruments can be used to screen for or assess cognitive function in dementia: the Folstein Mini Mental Status Exam, the Alzheimer's Disease Assessment Scale, the Modified Mini-Mental State Examination, and the Telephone Interview of Cognitive Status.
• Look at cognitive domains that are likely to change with aging: executive function, concentration, perceptual/motor processing, verbal learning and memory, verbal and spatial working memory and semantic memory.
• There is no single answer regarding the time frame within which an improvement or decline in cognitive function would occur. Most studies range from 6 months to 1-2 years. To determine the impact of a treatment, you would need to look at the impact over a period of years.
• To determine an effect over time, it may be necessary to look at large observational studies.
• There is more likely to be data on decline over time than on improvement.
• For mild cognitive impairment where there is a significant problem with memory only, look for a change in the conversion rate and at historical cohort studies.
• Look at whether omega-3 fatty acids are both preventing and staving the course of dementia.
• A new set of measurements was published two years ago to assess the rate of change. Do not restrict to these criteria, however, since all of the data should be examined.
• The minimum age limit to assess cognitive function with aging should be 50 years. Other neurological diseases have earlier onset so the age limit should be 45 years for those diseases.

Table A.2.2 (continued). Key TEP comments and recommendations.

Neurology
2. What is the evidence that the level of brain or retinal DHA levels affect the incidence of neurological diseases?
• Do not restrict the review to studies that assess brain or retinal levels of DHA.
• Look at brain levels separate from blood levels
• This question is marginal compared to Question #1 and could be limited.
• The mechanisms that affect DHA levels are unknown.
• It would be helpful to have data on blood levels to show the link between dietary intake of omega-3 fatty acids and blood levels.
• If a study doesn't report blood levels, it should not be included.
• The accuracy of dietary intake data is not as effective as blood levels, but dietary intake studies should not be excluded.
• It is critical to include information on studies that have negative results.
• For studies that compare supplements versus placebo, it is important to get information on dose effect.
• The evidence available for dementia is disproportionate to other neurological diseases. Other diseases to consider include Attention Deficit Disorder and non-verbal learning disabilities.
• This question is not necessarily restricted to adults.
• Focus on the effects of omega-3 fatty acids on disease incidence rather than on the effects of omega-3 fatty acids on prevalent disease, except for multiple sclerosis. For multiple sclerosis, the effects of omega-3 fatty acids is of interest.
• Revise the key questions as follows: o What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function in normal aging? o What is the evidence that omega-3 fatty acids affect the incidence of dementia including Alzheimer's disease? o What is the evidence that omega-3 fatty acids are effective in the treatment of dementia including Alzheimer's disease? o What is the evidence that omega-3 fatty acids affect the incidence of neurological diseases? o What is the evidence that omega-3 fatty acids prevent the progression of multiple sclerosis?

Industry Experts

Table A.3.1. Industry experts that were contacted for data about efficacy of omega-3 fatty acids.

Name	Affiliation
Ian Newton	Roche Vitamins
Herb Woolf, PhD	BASF Corporation
Annette Dickinson	Council for Responsible Nutrition

Figure A.3.1. Letter sent to industry experts.

Date

Name
Address
City, State, Zip Code

Dear XXX,

I am writing on behalf of the Evidence Based Practice Centers at RAND, New England Medical Center and the University of Ottawa. We are conducting a systematic review of the efficacy and toxicity of omega-3 fatty acids in the prevention and treatment of a number of different diseases/conditions. This review is being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ).

We are contacting you to see if there is any evidence, including unpublished evidence, that you want considered. Our focus is on clinical trials of omega-3 fatty acids in humans, so animal and chemical studies are not necessary.

The specific questions that all the EPCs will address are detailed in the attachment to this letter.

Please contact me with any information that you might have.

Best regards,

Catherine MacLean, M.D., Ph.D.
RAND
1700 Main Street, M 23-C
Santa Monica, CA 90407-2138
Voice: 310 393-0411, x6364
Fax: 310-451-6930

Search Strategies

Table A.4.1. Core search strategy.

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31

Table A.4.2. Literature searches by disease category.

Neurology
1. exp fatty acids, omega-3/ 2. fatty acids, essential/ 3. Dietary Fats, Unsaturated/ 4. linolenic acids/ 5. exp fish oils/ 6. (n 3 fatty acid$ or omega 3).tw. 7. docosahexa?noic.tw,hw,rw. 8. eicosapenta?noic.tw,hw,rw. 9. alpha linolenic.tw,hw,rw. 10. (linolenate or cervonic or timnodonic).tw,hw,rw. 11. menhaden oil$.tw,hw,rw. 12. (mediterranean adj diet$).tw. 13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw. 14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 15. (fish adj2 oil$).tw. 16. (cod liver oil$ or marine oil$ or marine fat$).tw. 17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 18. (fish consumption or fish intake or (fish adj2 diet$)).tw. 19. diet$ fatty acid$.tw. 20. or/1-19 21. dietary fats/ 22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 23. random$.tw. 24. exp clinical trials/ or evaluation studies/ 25. follow-up studies/ or prospective studies/ 26. or/22-25 27. 21 and 26 28. exp Aging/ 29. Aged/ 30. (aging or aged or geriatric$).tw. 31. or/28-30 32. 27 and 31 33. limit 27 to "all aged <65 and over>" 34. 32 or 33 35. exp Nervous System Diseases/ 36. Alzheimer Disease/ 37. exp Dementia/ 38. parkinson disease/ or Parkinson disease, secondary/ 39. parkinson disease/ or Parkinson disease, secondary/ 40. exp Multiple Sclerosis/ 41. exp Guillain-Barre Syndrome/ 42. (alzheimer or parkinson or dementia or multiple sclerosis or guillain barre).tw. 43. (neurological disease$ or neurological disorder$).tw. 44. (neurological disease$ or neurological disorder$).tw. 45. exp Optic Nerve Diseases/ 46. (myopathy or neuropathy).tw. 47. Cognition Disorders/ 48. exp Cognition/ 49. (cognition or cognitive).tw. 50. or/35-49 51. 27 and 50 52. exp fatty acids, omega-3/ 53. fatty acids, essential/

Table A.4.2 (continued). Literature searches by disease category.

Neurology
54. Dietary Fats, Unsaturated/ 55. linolenic acids/ 56. exp fish oils/ 57. (n 3 fatty acid$ or omega 3).tw. 58. docosahexa?noic.tw,hw,rw. 59. eicosapenta?noic.tw,hw,rw. 60. alpha linolenic.tw,hw,rw. 61. (linolenate or cervonic or timnodonic).tw,hw,rw. 62. menhaden oil$.tw,hw,rw. 63. (mediterranean adj diet$).tw. 64. ((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$).tw. 65. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw. 66. (fish adj2 oil$).tw. 67. (cod liver oil$ or marine oil$ or marine fat$).tw. 68. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw. 69. (fish consumption or fish intake or (fish adj2 diet$)).tw. 70. diet$ fatty acid$.tw. 71. or/52-70 72. dietary fats/ 73. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt. 74. random$.tw. 75. exp clinical trials/ or evaluation studies/ 76. follow-up studies/ or prospective studies/ 77. or/73-76 78. 72 and 77 79. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw. 80. (omega 3 or n 3).mp. 81. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp. 82. 80 and 81 83. 71 or 78 or 79 or 82 84. 83 and 50 85. 84 not 51 86. 83 and 31 87. 86 not 34 88. limit 87 to "all aged <65 and over>"

Inclusion/Exclusion Criteria

Table A.5.1. Inclusion/Exclusion Criteria at Screening Stage for Neurology.*

Assessed the effect of omega-3 fatty acids on neurology
Presented research on human subjects
Reported the results of randomized or controlled clinical trials or controlled clinical trials or case-control trials or case series or prospective cohort studies†
Exclusion criteria: cross-sectional studies, case reports

* Language was not a barrier to inclusion; † We defined a randomized controlled trial (RCT) as one in which the participants were assigned to one of two (or more) study groups using a process of random allocation (e.g., random number generation, coin flips); we defined a controlled clinical trial (CCT) as one in which participants were either: (1) assigned to one of two (or more) study groups using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier), or (2) possibly assigned to one of two (or more) study groups using a process of random or quasi-random allocation.

Evidence Grading System

Table A.6.1. Summary Score for Methodologic Quality.

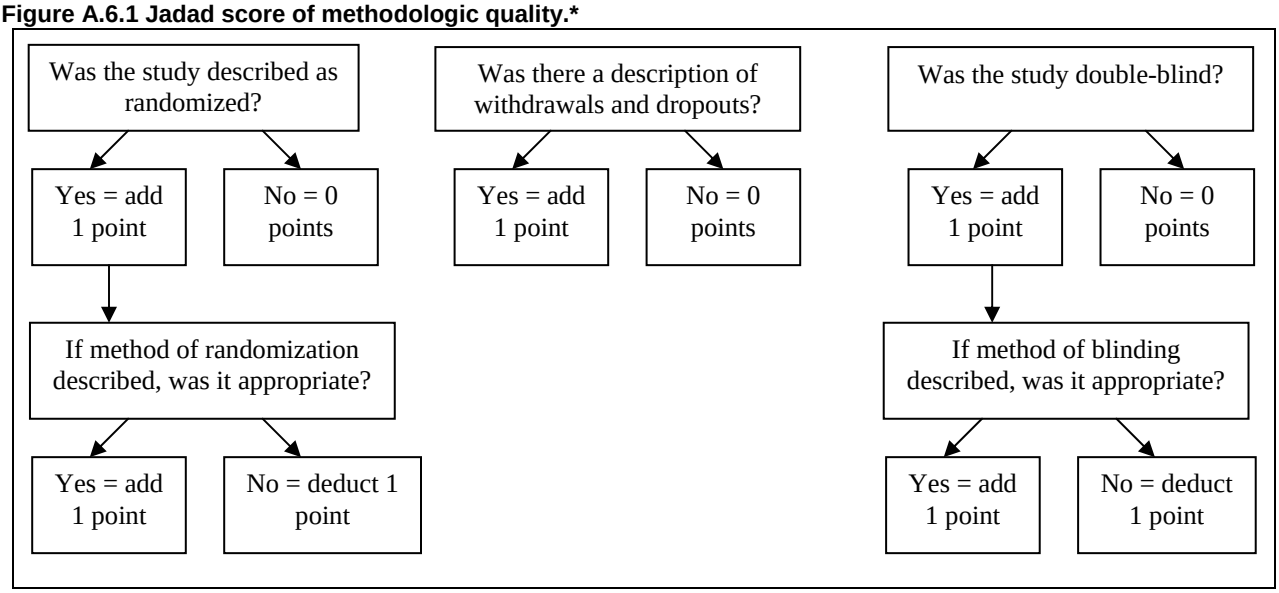
Summary Score	Jadad Score	Concealment of Allocation
A	5	Performed
B	5	Not performed, or Not reported
	3 or 4	Performed, Not performed, or Not reported
	0,1, or 2	Performed
C	0, 1, or 2	Not performed or not reported

Even though a study may focus on a specific target population, limited study size, eligibility criteria and patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To capture this parameter, we categorize studies into the applicability scale described in Table A.6.1.

Table A.6.2 Applicability ratings.

Applicability		**Health state**
I	Sample is representative of the U.S. population.	A General population. Typical healthy people similar to Americans without known neurological diseases/conditions.
II	Sample is representative of a relevant sub-group of the target population, but not the entire population. For example, a study that is restricted to women or a fish oil study in Japan where the background diet is very different from that of the US would fall into this category.	B Diseased population. Subjects with neurological disease/condition.
III	Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups. For example, a study of oldest old men or a study of a population on highly controlled diet.	

Figure A.6.1 Jadad score of methodologic quality.*



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

External Peer Reviewers

Table A.7.1. Peer Reviewers.

Peer Reviewer	Area of Expertise	Affiliation
Judith Ashley, Ph.D., M.S.P.H., R.D.	Nutrition	University of Nevada, Reno
Mona Baumgarten, Ph.D.	Epidemiology	University of Maryland
Graham Colditz, M.D., DR.P.H.	Neurology	Harvard
David Heber, M.D., Ph.D.	Nutrition	UCLA
Martha Clare Morris, Sc.D.	Neurology	Rush Institute for Healthy Aging
Lon Schneider, M.D.	Geriatric Psychiatry/ Clinical Neuroscience	University of Southern California
Philip A. Wolf, M.D.	Neurology	Boston University
Christina Wolfson Ph.D.	Neurology	McGill University

Appendix B. Coding/Data Abstraction Forms

B.1 Literature Screener Form.

Article ID

Reviewers: Assigned on:

2. **Author:**
Title:
Cite:

3. Reviewer: _____

4. Research Topic: (**circle one**)
Omega 3 or synonymous topic 1
Unclear, no English abstract 8
(**If unclear, skip to question 10 on language**)
None of the above ..... 9 (**STOP**)

5. Condition(s)/Subject(s) studied: (**check all that apply**)
- Cancer ..... □
- Cognitive function (>=45) ..... □
- Neurological disease ..... □

None of the above ..... □ (**STOP**)

6. Study population: (**check all that apply**)
Human ..... □
Animal ..... □ (**STOP**)
Unclear ..... □ (**STOP**)
Other ..... □ (**STOP**)

7. Study design: (**circle one**)
Descriptive (historical, editorial, etc.) ..... 1 (**STOP**)
Review/meta-analysis ..... 2 (**STOP**)
Randomized clinical trial 3
Controlled clinical trial (quasi-randomization) 4
Non-randomized clinical trial 5
Cohort/Case control 6
Case series (≥ 10) 7
Case report (≥ 10) ..... 8 (**STOP**)
Other (specify: _____) ..... 9 (**STOP**)

8. Type of disease: (**check all that apply**)
CANCER:
Skin □
Oral cavity and pharynx ..... □
Colorectal ..... □
Other gastrointestinal ..... □
Lung and bronchus ..... □
Other respiratory ..... □
Bone and soft tissue ..... □
Breast ..... □
Female genital ..... □
Urinary system ..... □
Lymphoma ..... □
Leukemia ..... □
Pre-cancerous ..... □
Other cancer ..... □

NEURO: (**check all that apply**)
Amyotrophic lateral sclerosis (ALS) ..... □
Dementia: Alzheimer's Disease ..... □
Dementia: Multi-Infarct ..... □
Dementia: Vascular ..... □
Dementia: NOS ..... □
Epilepsy ..... □
Guillain-Barré Syndrome ..... □
Huntington's Disease ..... □
Multiple sclerosis ..... □
Neuromyelitis optica (Devic's syndrome) ..... □
Optic Neuritis ..... □
Parkinson's Disease ..... □
Peroxisomal Biogenesis Disorders/Leukodystrophies ..... □
(Zellweger Syndrome, Metachromatic Leukodystrophy, Alexander Disease, Infantile Refsum Disease)
Other neuro ..... □

9. Does the study describe the effects of Omega-3 FA on:
CANCER:
Cancer incidence ..... □
Tumor growth ..... □
Tumor differentiation ..... □
Apoptosis ..... □
Chemotherapy ..... □
Mortality/Survival ..... □
Other cancer outcomes ..... □
NEURO:
Incidence of neuro disease ..... □
Outcomes of neuro disease ..... □
Cognitive function ..... □
NONE OF THE ABOVE ..... □

10. Language of article: (**circle one**)
English 1
German 2
French 3
Italian 4
Danish 5
Russian 6
Spanish 7
Other (specify: _____) 8

11. Do you think this article might be a duplicate or include the same data as another study?
No 1
Yes 2
If yes, which one(s)? _____
(enter article ID, author, or 9999 for "don't know.")

12. Is there a reference that needs to be checked?
No 1
Yes 2
If yes, which one(s)? _____
(enter article ID, author, or 9999 for "don't know.")

Notes:

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (CIRCLE ONE)

RCT.....1
RXT 2
CCT.....3
Cohort 4
Case control (**STOP** if Cancer) 5
Case series ≥ 10 (**STOP** if Cancer) 6
Other design .....7 (STOP)

2. Is there a difference in Omega-3 content between arms: (CIRCLE ONE)

Yes 1
Not applicable (Case control & case series) 2
No.....3 (STOP)
Unclear.....8 (STOP)

3. Is Omega-3 measured in any of the following ways? (CIRCLE ONE)

Diet.....1
Tissue 2
Diet and Tissue 3
None of the above.....4

4. If the study reports on cognitive function, is the age of the population 45 or older? (CIRCLE ONE)

Yes 1
Study not on cognitive function.....2
No.....3 (STOP)
Unclear.....8 (STOP)

IF THE STUDY DESIGN IS COHORT, CASE CONTROL, OR CASE SERIES PLEASE SKIP TO QUESTION 12.

5. Is the study described as randomized? (CIRCLE ONE)

Yes 1
No.....2

6. If the study was randomized, was method of randomization appropriate? (CIRCLE ONE)

Yes 1
No.....2
Method not described.....8
Not applicable (not randomized).....9

7. Is the study described as: (CIRCLE ONE)

Double blind.....1
Single blind, patient 2
Single blind, outcome assessment 3
Open.....4
Blinding not described 8
Not applicable 9

8. If reported, was the method of double blinding appropriate? (CIRCLE ONE)

Yes 1
No.....2
Double blinding method not described 8
Not applicable 9

9. If study was randomized, did the method of randomization provide for concealment of allocation? (CIRCLE ONE)

Yes 1
No.....2
Concealment not described 8
Not applicable (not randomized).....9

10. Are withdrawals (W) and dropouts (D) described? (CIRCLE ONE)

Yes, reason described for **all** W and D 1
Yes, reason described for **some** W and D..... 2
Not described 8
Not applicable 9

11. If the design is crossover, please note the duration of the following periods:

Please enter the number and code in the appropriate box.

Period	Number	Unit	Units
X-Over			1. Hour 2. Day 3. Week 4. Month 5. Year 8. ND 9. NA
Run-In			
Wash-Out			

12. Does the study population represent any of the following characteristics? (CHECK ALL THAT APPLY)

	Healthy	Diseased
Typical people	❑	❑
Atypical people (in terms of diet, SES, other factors)	❑	❑
Narrow, atypical people (including highly controlled diet)	❑	❑
Cannot categorize (incomplete data)	❑	❑

13. What was the study's funding source? (CHECK ALL THAT APPLY)

Government..... ❑
Hospital..... ❑
Industry ..... ❑
Private (non-industry) ..... ❑
Unclear ..... ❑
Not described ..... ❑

Other (code(s): _____) ..... ❑

14. What was the number of sites involved in the study?
(Enter number or 99 if not reported)

___ ___

15. In what country was the study conducted? (CHECK ALL THAT APPLY)

Australia..... ❑
Denmark..... ❑
Germany..... ❑
Italy ..... ❑
Japan ..... ❑
Netherlands ..... ❑
Russia..... ❑
UK..... ❑
US ..... ❑
Other (enter code) ..... ❑

____ ____, ____ ____, ____ ____, ____ ____

Not specified ..... ❑

16. What was the racial/ethnic population studied?
(Check all that apply)

Caucasian ..... ❑
African Ancestry ..... ❑
Hispanic ..... ❑
Asian ..... ❑
Native American ..... ❑
Eskimo/Intuit ..... ❑
Other (enter code): ..... ❑

_____ _____ , _____ _____ , _____ _____
Not described ..... ❑

17. What was the percent of male participants?
(Enter number or 999)

___ ___ ___ %

18. What was reported for the following questions regarding subjects ages? (Enter number 99 for not reported)

Mean Age..... ____ ____
Median Age..... ____ ____
Age Range..... ____ ____ to ___ ____

19. What were the study's inclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

20. What were the study's exclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

21. Was a validated dietary assessment method described?
(CIRCLE ONE)

Yes 1
No..... 2
Not described 8
Not applicable 9

22. Was the omega 3 fatty acid content described in the baseline diet?
(CIRCLE ONE)

Yes (please answer Q23)..... 1
No (please SKIP Q23)..... 2
Not applicable (not RCT or CCT, SKIP Q23) 9

23. If the omega 3 content was described in the baseline diet, please specify the quantification:

(Example: Fish 8 grams per week, please use codes for source and units.)

Source (code)	Number (Enter #)	Source Unit (code)	Time Unit (code)

Source Units
1. grams 6. tabs
2. oz 7. ml
3. mg 8. other
4. servings 9. ND
5. caps

Time Units
1. hour 5. year
2. day 6. ND
3. week
4. month

Interventions (for all study designs)

24. Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.

For observational studies answer only columns denoted with asterisks (*):

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
1	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
2	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
3	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
4	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control CASES Cases	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter code(s) Bioactive markers begin at code 100.

Interventions (continued)

24. See instructions on previous page.

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
5	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
6	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
7	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
8	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control CASES Cases	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter code(s) Bioactive markers begin at code 100.

Interventions (continued)

24. See instructions on previous page.

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
9	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
10	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
11	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
12	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND	Enter code(s) Bioactive markers begin at code 100.

	CASES Cases							9. NA	

Case report /Case series/Cohort specific questions

Instructions: For case report, case series, and cohort studies ONLY, please fill out this page (Q25-Q29), otherwise SKIP to Q30.

25. Were case controls identified from any of the following locations:

(CHECK ALL THAT APPLY)

Community ..... ☐
Hospital ..... ☐
Health care system (non-hospital) ..... ☐
Nursing home ..... ☐
Not described ..... ☐
Not Applicable (cohort studies) ..... ☐

26. Was there blinded assessment of the following:

(CIRCLE ONE FOR EACH ROW)

	YES	NO	N/A
Eligibility of cases and controls/ Or exposed vs. unexposed	1	2	3
Assessment of outcome	1	2	3
Assessment of exposure	1	2	3

27. In the analysis, was any attempt made to adjust for known confounders, not included in matching?

(CIRCLE ONE)

Yes 1
No 2

28. Were cases and controls matched by any of the following characteristics?

(CHECK ALL THAT APPLY)

Age ..... ☐
Sex ..... ☐
Underlying neurological disease ..... ☐
Cognitive function ..... ☐
Educational level ..... ☐
Other characteristics ..... ☐
Not matched ..... ☐
Not applicable ..... ☐

29. Was ascertainment of cases valid? (CIRCLE ONE)

Yes 1
No..... 2

Outcomes

30. Please enter the type of outcomes measured. For case series, case report, or cohort enter the outcome that defines the study:

Enter code for each outcome measured:	Enter code(s) for each set of adjustments made for each outcome measured.: (Please separate with commas)		

31. Overall, was a validated method used for ascertainment of clinical outcomes?

(CIRCLE ONE)

Yes.....1
No.....2
Not applicable.....9

Evaluation

32. When, relative to the start of the intervention or exposure, were outcomes reported?

(Enter the number/code in the appropriate box)

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups		

Units

1. Hour	5. Year
2. Day	8. ND
3. Week	9. NA
4. Month	997. Variable

33. What was the total duration of the study?

_____ (Number) _____ (Units: use codes from above)

Adverse Events

34. Were any of the following adverse events mentioned?

(Check all that apply)

Clinical bleeding..... ❑
Dermatological..... ❑
Diarrhea..... ❑

GI complaint or nausea..... ❑
Headaches..... ❑
Withdrawal due to adverse event..... ❑
Other adverse events..... ❑
No Adverse events..... ❑
Not described..... ❑
Not applicable..... ❑

For CANCER studies only, answer Q35-37.

If not a cancer study then SKIP.

35. Is the state of the immune system described?

(CIRCLE ONE)

Yes.....1
No.....2

36. Are the effects of omega 3 fatty acids on the outcomes of any of the following reported?

(Check all that apply)

Cancer surgery..... ❑
Chemotherapy..... ❑
Radiation..... ❑
None of the above..... ❑

37. Does the study describe genes involved in omega 3 fatty acid transport or metabolism?

(CIRCLE ONE)

Yes.....1
No.....2

Appendix C. Evidence Tables

Table C.1.1.Part A. Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies.*

First Author, Year Cohort	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability Funding source Quality
Barberger-Gateau, 2002[21] PAQUID (Personnes Agées QUID) Study	Sample size (people/person years): 1,416/NR Age (mean/range): NR/68-99 Race: NR % male: NR # sites: 1 Location: France	Duration: 7 years	Inclusion: Age = 68/Normal cognition/Living at home Exclusion: Dementia	Disease: Dementia Ascertainment: MMSE; neurological exam	Applicability: II Funding source: Industry and private Quality: Adjustment for confounders: Y Blinding of exposure/outcome: N Valid ascertainment of outcome: Y Valid ascertainment of exposure: NR Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: Y
Kalmijn, 1997[59] Zutphen Elderly Study	Sample size (people/person years): 818/NR Age (mean/range): NR/69-89 Race: NR % male: 100 # sites: 1 Location: Netherlands	Duration: 3 years	Inclusion: NR Exclusion: NR	Disease: cognitive function, normal aging and incidence of dementia Ascertainment: Clinical exam; MMSE	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinding of exposure/outcome: N Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: Y

*NR = not reported.

Table C.1.1.Part A (continued). Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies.*

First Author, Year Cohort	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability Funding source Quality
Kalmijn, 1997[67] Rotterdam Cohort	Sample size (people/person years): 5,386/NR Age (mean/range): 67.7/NR Race: NR % male: 41 # sites: 1 Location: Netherlands	Duration: 2.1 years	Inclusion: Residents of a suburb in Rotterdam, age ≥ 55 Exclusion: Cambridge Mental Disorders of the Elderly Examination (CAMDEX) score below 80; illogical answers to food pattern questionnaire	Disease: Dementia Ascertainment: Medical records or medical examination	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinding of exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: Y
Morris, 2003[23] Chicago Health and Aging Project	Sample size (people/person years): 815/NR Age (mean/range): 73/NR Race: Caucasian and Black % male: 39 # sites: 1 Location: U.S.	Duration: 3.9 years	Inclusion: Normal cognition Exclusion: NR	Disease: Alzheimer's disease Ascertainment: NINCDS criteria, neurological exam	Applicability: I Funding source: Government Quality: Adjustment for confounders: Y Blinding of exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: Y

*NR = not reported.

Table C.1.1.Part B. Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies by category of omega-3 consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariable RR (95% CI)	Multivariable Adjustors
FISH							
Barberger-Gateau, 2002[21] PAQUID (Personnes Agées QUID) Study	Dementia	1	NR	NR	1.0	1.0	Age, sex, education
		2	1122	At least once a week	0.66† (0.47-0.93)	0.73† (0.52-1.03)	
	Alzheimer's disease	1	NR	NR	1.0	NR	
		2	1122	At least once a week	0.69† (0.47-1.01)	NR	
		Total 1122					
Kalmijn, 1997[67] Rotterdam Study	Total dementia	1	1807	≤ 3 g/day	NR	1.0	Age, sex, education, total energy intake.
		2	1773	3.0-18.5 g/day	NR	0.8 (0.4-1.4)	
		3	1806	> 18.5 g/day	NR	0.4 (0.2-0.9)	
						p = 0.03‡	
	Alzheimer's disease without vascular component	1	1807	≤ 3 g/day	NR	1.0	
		2	1773	3.0-18.5 g/day	NR	0.9 (0.4-1.8)	
		3	1806	> 18.5 g/day	NR	0.3 (0.1-0.9)	
						p = 0.005‡	
	Dementia with a vascular component	1	1807	≤ 3 g/day	NR	1.0	
		2	1773	3.0-18.5 g/day	NR	0.6 (0.2-2.5)	
		3	1806	> 18.5 g/day	NR	0.7 (0.2-2.8)	
		Total 5386				p = 0.39‡	
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	121	never	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	250	1-3 servings/months	0.7 (0.3-1.6)	0.6 (0.3-1.3)	
		3	296	1 serving/ week	0.5 (0.2-1.0)	0.4 (0.2-0.9)	
		4	148	≥ 2 servings/week	0.6 (0.2-0.9)	0.4 (0.2-0.9)	
		Total 815			p = 0.18‡	p = 0.07‡	

* NR = not reported, g = grams; † hazard ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table C.1.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies by category of omega-3 consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Median Amount by category	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariable RR (95% CI)	Multivariable Adjustors
Omega-3 fatty acids							
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	0.9 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	1.13 g/day	1.1 (0.4-2.9)	1.2 (0.5-3.0)	
		3	NR	1.30 g/day	0.5 (0.2-1.4)	0.6 (0.2-1.7)	
		4	NR	1.49 g/day	0.6 (0.2-1.5)	0.7 (0.3-1.6)	
		5	NR	1.75 g/day	0.3 (0.1-0.7)	0.4 (0.1-0.9)	
		Total 815			p = 0.01‡	p = 0.01‡	
ALA							
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	0.72 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	0.92g/day	1.7 (0.7-3.8)	1.8 (0.8-3.8)	
		3	NR	1.06g/day	0.8 (0.4-1.9)	0.8 (0.4-2.0)	
		4	NR	1.23g/day	0.8 (0.4-1.7)	0.9 (0.4-2.0)	
		5	NR	1.46g/day	0.5 (0.2-1.1)	0.7 (0.3-1.6)	
		Total 815			p = 0.01‡	p = 0.10‡	
DHA							
Morris, 2003[23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	0.03 g/day	1.0	1.0	Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	0.05 g/day	0.8 (0.3-2.1)	0.8 (0.3-2.1)	
		3	NR	0.06 g/day	0.4 (0.1-1.1)	0.4 (0.1-1.0)	
		4	NR	0.07 g/day	0.3 (0.1-0.9)	0.2 (0.1-0.8)	
		5	NR	0.10 g/day	0.4 (0.2-1.1)	0.3 (0.1-0.9)	
		Total 815			p = 0.05‡	p = 0.02‡	

* NR = not reported, g = grams; † hazards ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table C.1.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies by category of omega-3 consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Median Amount by category	Estimates of effect				
					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
EPA									
Morris, 2003 [23] Chicago Health and Aging Project	Alzheimer's disease	1	NR	0.0 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
		2	NR	0.0 g/day	NR§	NR§	NR§	NR§	
		3	NR	0.01 g/day	1.0	(0.4-2.4)	1.1	(0.4-2.8)	
		4	NR	0.02 g/day	0.5	(0.2-1.2)	0.5	(0.2-1.2)	
		5	NR	0.03 g/day	0.9	(0.4-2.1)	0.9	(0.4-2.3)	
		Total 815			p = 0.40‡		p = 0.40‡		

* NR = not reported, g = grams; † hazards ratio; ‡ age and sex adjusted; test for trend; § Authors report that 40% of participants had 0 g/day of intake.

Table C.2.1.Part A. Evidence table of the effects of omega-3 fatty acids on the treatment of dementia in RCTs.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Terano, 1994[24]	Sample size (people/person years): 20/NR Age (mean/range): 83/NR Race: NR % male: NR # sites: 1 Location: Japan	Design: RCT Duration: 12 months	Inclusion: Other dementia Exclusion: NR	NR	1	Intervention: Standard hospital diet Dosage: NR
					2	Intervention: DHA Dosage: 4.3 grams/day for 12 months

* NR = not reported.

Table C.2.1.Part B. Evidence table of the effects of omega-3 fatty acids on the treatment of dementia in RCTs.*

First Author, Year	Outcomes Results					Quality Applicability Funding Source
Terano, 1994[24]	**Study arms**	**Results**				**Quality** Jadad: 1 Concealment of Allocation: NR **Applicability:** II-B **Funding Source:** NR
		Before	After 3 months	After 6 months	After 12 months	
	Mean scores of HDS-R					
	Standard nursing home diet	16.3	16.7	16.7	15.3	
	Standard nursing home diet PLUS DHA 4.3 grams/day	17.2	20.6†	19.9†	20.2	
	Mean scores of MMSE					
	Standard nursing home diet	19.7	19.4	19.6†	19.1	
	Standard nursing home diet PLUS DHA 4.3 grams/day	20.1	21.3	22.2	21.9	

* NR = not reported, HDS-R = Hasegawa's Dementia rating scale; MMSE = Mini Mental Status Exam. † $p < 0.05$ with paired t-test.

Table C.3.1. Part A. Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

First Author, Year Cohort	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability Funding source Quality
Chen, 2003[34] Health Professionals Follow-up Study Cohort and The Nurses' Health Study Cohort	Study Design: Cohort Sample size (people/person years): 135,894/NR Age (mean/range): NR/30-75 Race: NR % male: 35 # sites: 1 Location: US	Duration: Variable years	Inclusion: NR Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake	Disease: Parkinson's Ascertainment: neurological exam	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinding of exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: NR
Ghadirian, 1998[43]	Study Design: Case-Control Sample size (people/person years): 399/NR Age (mean/range): NR/NR Race: NR % male: 31 # sites: 1 Location: Canada	Duration: NR	Inclusion: Multiple sclerosis Exclusion: NR	Disease: MS Ascertainment: Neurological exam, Kurtzke/EDSS	Applicability: II Funding source: NR Quality: Adjustment for confounders: Y Blinding of exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Groups comparable: Y Selection bias: N Description of withdrawals and dropouts: Y

* NR = not reported.

Table C.3.1.Part A (continued). Evidence table of the effects of omega-3 fatty acids on neurological diseases in cohort and case control studies.*

First Author, Year Cohort	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability Funding source Quality
Petridou, 1998[60]	Stdy Design: Case-Control Sample size (people/person years): 337/NR Age (mean/range): 5/4-8 Race: NR % male: 53 # sites: 1 Location: Greece	Duration: NR	Inclusion: NR Exclusion: NR	Disease: CP Ascertainment: Clinical exam; registry	Applicability: II Funding source: Government and private Quality: Adjustment of confounders: Y Blinding of exposure/outcome: Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Groups comparable: Y Selection bias: Y Description of withdrawals and dropouts: Y
Zhang, 2000[61] Nurses' Health Study Cohort	Study Design: Cohort Sample size (people/person years): 187,811/NR Age (mean/range): NR/25-55 Race: NR % male: NR # sites: 1 Location: US	Duration: 14 years	Inclusion: NR Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake	Disease: MS Ascertainment: neurological exam; Poser criteria	Applicability: II Funding source: Government Quality: Adjustment of confounders: Y Blinding of exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Exposure before outcome: Y Selection bias: N Description of withdrawals and dropouts: Y

* NR = not reported.

Table C.3.1. Part B. Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect Multivariable RR (95% CI)		Multivariable Adjustors, Matching parameters
Fish							
Zhang, 2000[61] The Nurses' Health Study I and II Multiple Sclerosis		1	81	< 1/week	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
		2	77	1-2.9/week	1.0	(0.8-1.4)	
		3	37	3-4.9/week	0.9	(0.6-1.3)	
						p = 0.79‡	
Ghadirian, 1998,[43] Multiple sclerosis	Men	Control	64		1.0		*Multivariable adjustors:* Total energy, body mass index *Matching:* Age, sex, phone number
		Case	61		1.08	(0.84-1.40)	
	Wome	Control	138		1.0		
		Case	136		0.83	(0.69-1.00)	
	All	Control	202		1.0		
		Case	197		0.91	(0.78-1.05)	
Petridou, 1998,[60] Cerebral palsy		Control	166	1/week	1.0		*Multivariable adjustors:* 'Core' variables§ plus total energy intake, body mass index *Matching:* Age, neighborhood or age, physician
		Case	58	1/week	0.63	(0.37-1.08)	

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend. § Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of Fe during pregnancy, intention al physical exercise during pregnancy, painless delivery classes.

Table C.3.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile: quintile: dose group; case or control)	n†	Median dose	Estimates of effect		
					Multivariable RR (95% CI)		Multivariable Adjustors, Matching parameters
Omega-3 fat from fish							
Chen, 2003[34] Health Professional Follow-up Study and The Nurses' Health Study, Parkinson's Disease	Men	1	NR	0.03 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
		2	NR	0.07% of energy	0.84	(0.52-1.37)	
		3	NR	0.1% of energy	1.08	(0.69-1.69)	
		4	NR	0.2% of energy	0.88	(0.55-1.40)	
		5	NR	0.3 % of energy	0.99	(0.63-1.55)	
		Total 47,331		p = 0.9‡			
	Women	1	NR	0.03 % of energy	1.0		
		2	NR	0.05 % of energy	0.70	(0.41-1.19)	
		3	NR	0.08 % of energy	0.76	(0.45-1.29)	
		4	NR	0.1% of energy	0.75	(0.45-1.26)	
		5	NR	0.2 % of energy	0.90	(0.55-1.47)	
		Total 88,563			p = 0.9‡		
	Pooled men and women	1	NR	NR	1.0		
		2	NR	NR	0.77	(0.54-1.11)	
		3	NR	NR	0.93	(0.66-1.31)	
		4	NR	NR	0.82	(0.58-1.16)	
		5	NR	NR	0.94	(0.68-1.32)	
		Total 135,894			p = 0.9‡		

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend.

Table C.3.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile: quintile: dose group; case or control)	n†	Median dose	Estimates of effect: Multivariable RR (95% CI)	Multivariable Adjustors, Matching parameters
ALA						
Chen, 2003[34] Health Professional Follow-up Study and The Nurses' Health Study, Parkinson's Disease	Men	1	NR	0.05 % of energy	1.0	*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA
		2	NR	0.06% of energy	0.54 (0.34-0.87)	
		3	NR	0.08% of energy	0.75 (0.49-1.15)	
		4	NR	0.09% of energy	0.88 (0.58-1.32)	
		5	NR	0.1 % of energy	0.69 (0.45-1.07)	
		Total 47,331			p = 0.4‡	
	Women	1	NR	0.04 % of energy	1.0	
		2	NR	0.06 % of energy	0.83 (0.51-1.34)	
		3	NR	0.07 % of energy	0.71 (0.43-1.17)	
		4	NR	0.09% of energy	0.68 (0.41-1.13)	
		5	NR	0.1 % of energy	0.60 (0.35-1.01)	
		Total 88,563			p = 0.04‡	
	Pooled men and women	1	NR	NR	1.0	
		2	NR	NR	0.67 (0.47-0.93)	
		3	NR	NR	0.73 (0.53-1.01)	
		4	NR	NR	0.79 (0.57-1.09)	
		5	NR	NR	0.65 (0.46-0.91)	
		Total 135,894			p = 0.05‡	

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend.

Table C.3.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile, quintile or dose group)	n†	Median dose	Estimates of effect		Multivariable Adjustors
					Multivariable RR (95% CI)		
EPA							
Chen, 2003[34] Health Professional Follow-up Study and The Nurses' Health Study Parkinson's Disease	Men	1	NR	0.009 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
		2	NR	0.02 % of energy	0.77	(0.48-1.25)	
		3	NR	0.04 % of energy	0.88	(0.56-1.39)	
		4	NR	0.06 % of energy	0.92	(0.59-1.44)	
		5	NR	0.1 % of energy	0.91	(0.59-1.42)	
		Total 47,331			p = 0.9‡		
	Women	1	NR	0.007 % of energy	1.0		
		2	NR	0.01 % of energy	0.67	(0.39-1.16)	
		3	NR	0.02 % of energy	0.80	(0.48-1.34)	
		4	NR	0.04 % of energy	0.74	(0.44-1.24)	
		5	NR	0.07 % of energy	0.91	(0.56-1.49)	
		Total 88,563			p = 0.8‡		
	Pooled men and women	1	NR	NR	1.0		
		2	NR	NR	0.73	(0.51-1.04)	
		3	NR	NR	0.84	(0.60-1.19)	
		4	NR	NR	0.84	(0.60-1.18)	
		5	NR	NR	0.91	(0.66-1.27)	
		Total 135,894			p = 0.9‡		

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend.

Table C.3.1.Part B (continued). Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile, quintile or dose group)	n†	Median dose	Estimates of effect		
					Multivariable RR (95% CI)		Multivariable Adjustors
DHA							
Chen, 2003[34] Health Professional Follow-up Study and The Nurses' Health Study Parkinson's Disease	Men	1	NR	0.02 % of energy	1		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
		2	NR	0.05 % of energy	0.79	(0.49-1.28)	
		3	NR	0.07 % of energy	1.05	(0.67-1.64)	
		4	NR	0.1 % of energy	0.90	(0.57-1.42)	
		5	NR	0.2 % of energy	0.92	(0.58-1.44)	
		Total 47,331			p = 0.9‡		
	Women	1	NR	0.02 % of energy	1		
		2	NR	0.04 % of energy	0.62	(0.36-1.07)	
		3	NR	0.06 % of energy	0.65	(0.38-1.09)	
		4	NR	0.08 % of energy	0.81	(0.49-1.32)	
		5	NR	0.1 % of energy	0.76	(0.46-1.26)	
		Total 88,563			p = 0.8‡		
	Pooled men and women	1	NR	NR	1		
		2	NR	NR	0.71	(0.49-1.02)	
		3	NR	NR	0.86	(0.61-1.21)	
		4	NR	NR	0.86	(0.61-1.20)	
		5	NR	NR	0.84	(0.60-1.18)	
		Total 135,894			p = 0.8‡		

* NR = Not Reported; † Number of people included in analysis; ‡ test for trend.

Appendix C. Evidence Tables (continued)

Table C.4.1. Part A. Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Bates, 1989[40]	Sample size (people/person years): 312/NR Age (mean/range): 34/16-35 Race: NR % male: 32 # sites: 3 Location: UK	Design: RCT Duration: 24 months	Inclusion: MS defined by specific criteria/Acute relapsing/Kurtzke Disability Scale=6 Exclusion: Chronic disease history	Vitamin E, N6 polyunsaturated fat, Dodecylgallate	1	Intervention: Olive oil Dosage: 10 grams/day for 24 months
					2	Intervention: Max EPA Dosage: 10 grams/day for 24 months

* NR = not reported.

Table C.4.1. Part A (continued). Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Cendrowski, 1986[62]	Sample size (people/person years): 12/NR Age (mean/range): NR/33-64 Race: NR % male: 50 # sites: 1 Location: UK	Design: Single arm open label trial Duration: Variable months	Inclusion: MS defined by specific criteria Exclusion: NR	None	1	Intervention: w-3 and w-6 polyunsaturated fatty acids (MaxEPA) Dosage: 20-30 ml/day
Nordvik, 2000[63]	Sample size (people/person years): 16/NR Age (mean/range): 32/22-37 Race: NR % male: 35 # sites: 1 Location: Norway	Design: Single arm open label trial Duration: 2 years	Inclusion: Relapsing/remitting MS/Stable neurological status Exclusion: Immunosuppressive medications use/Vitamins use/Fish supplements/Steroids use/Change in diet	None	1	Intervention: Long-chain marine fatty acids and vitamins Dosage: 0.9 g/day

*NR = not reported.

Table C.4.1. Part B. Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Bates, 1989[40]	Outcome 1: Kurtzke Disability Scale scores Arm 1 = Olive oil 10 grams/day for 24 months Arm 2 =Max EPA 10 grams/day for 24 months Reported testing: p = 0.07 (not statistically significant) for comparison between groups Outcome 2: Duration and number of relapses Arm 1 = Olive oil 10 grams/day for 24 months Arm 2 =Max EPA 10 grams/day for 24 months Reported testing: Not statistically significant for comparison between groups; statistics not reported Outcome 3: Fatty acid analysis Arm 1 = Olive oil 10 grams/day for 24 months Arm 2 =Max EPA 10 grams/day for 24 months Reported testing: Significant increases in EPA and DHA in arm 2 subjects in comparison with controls (arm 1) but point estimates not reported.	**Quality** Jadad: 3 Concealment of Allocation: NR **Applicability:** II-B **Funding Source:** Private
Cendrowski, 1986[62]	Outcome 1:Mean EDSS Scores† Arm 1: MaxEPA (4..2 g/day EPA; 2.8 g/day DHA) Reported testing: p<0.05 significant for reduction on EDSS Outcome 2: Mean Progression Index Arm 1: MaxEPA (4..2 g/day EPA; 2.8 g/day DHA) Reported testing: p<0.05 significant for improvement on index of disease progression	**Quality** Comparison groups: None Blinding: NR Description of withdrawals/dropouts: NR **Applicability:** II-B **Funding Source:** NR

*NR = not reported.

Table C.4.1. Part B (continued). Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Outcomes Results	Quality Applicability Funding Source
Nordvik, 2000[63]	Outcome 1:Mean EDSS Scores† Arm 1: Fish oil supplement (0.4 g/day EPA; 05 g/day DHA) Reported testing: p<0.05 significant for reduction on EDSS	**Quality** Comparison groups: None Blinding: NR Description of withdrawals/dropouts: NR **Applicability:** II-B **Funding Source:** Government and Private

* NR = not reported. †EDSS = Expanded Disability Status Scale.