Evidence Report/Technology Assessment
Number 116

Effects of Omega-3 Fatty Acids on Mental Health

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0021

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AHRQ Publication No. 05-E022-2
July 2005

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Suggested Citation:
Schachter H, Kourad K, Merali Z, Lumb A, Tran K, Miguelez M, et al. Effects of Omega-3 Fatty Acids on Mental Health. Evidence Report/Technology Assessment No. 116. (Prepared by the University of Ottawa Evidence-based Practice Center, Under Contract No. 290-02-0021.) AHRQ Publication No. 05-E022-2. Rockville, MD: Agency for Healthcare Research and Quality. July 2005.

Preface

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

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

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

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

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Acknowledgments

The authors would like to thank numerous individuals for their support of the present project: Isabella Steffensen and Christine Murray for their ability to clarify the meaning of our words, figures and tables; Pieter Oosthuizen and Robin Emsley for responding affirmatively to our request for data; Malcolm Peet for trying to facilitate the sharing of data he collected yet which are now held by one of his studies' funding sources; Bill Hodge for arranging timely help with assessors of study quality; Samantha Fulton for helping check some of our work; Vladimir Fox for arranging the expert and timely translation of non-English language articles; Herb Woolf for responding with substance to our request of industry for evidence; Peter O'Blenis for assuring that the Internet-based software we used for all aspects of the review process was adapted to our needs; our collaborators at SC-RAND and Tufts-NEMC EPCs; Beth Collins-Sharp, Rosaly Correa-de-Araujo and Jacqueline Besteman who, as our Task Order Officers, provided steady support and guidance on behalf of AHRQ; and, Anne Thurn of the Office of Dietary Supplements for her thoughtful direction on behalf of the Federal Partners. Sections of Chapter 1 were developed in collaboration with Tufts-NEMC EPC, and with contributions from SC-RAND EPC.

Structured Abstract

Context: One popular view holds that psychiatric problems reflect disorders of brain functioning. Fifty percent to 60% of the adult brain is composed of lipids (dry weight), of which 35% are phospholipids comprised of unsaturated fatty acids. Of these, the polyunsaturated fatty acids docosahexaenoic acid (an omega-3 fatty acid) and arachidonic acid (an omega-6 fatty acid) are found in the highest concentrations. Thus, it has been proposed that omega-3 fatty acids could play an important role in mental health.

Objectives: The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise and synthesize the evidence for the effects of omega-3 fatty acids in mental health. Evidence was sought to permit the investigation of three basic questions: the efficacy and safety of omega-3 fatty acids as (primary or supplemental) treatment of psychiatric disorders or conditions (e.g., symptoms alone); the association between intake of omega-3 fatty acids and the onset, continuation or recurrence of psychiatric disorders or conditions; and, the association between the fatty acid content of biomarkers and the onset, continuation or recurrence of psychiatric disorders or conditions. The latter two questions examined the protective value of omega-3 fatty acid content in the diet and/or blood lipid biomarkers. The impact of effect modifiers was examined as well. The results will be used largely to inform a research agenda.

Data Sources: A comprehensive search for citations was conducted using five databases (Medline, Embase, Cochrane Central Register of Controlled Trials, PsycInfo, and CAB Health). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH term "dietary fats," which was limited by study design to increase its specificity. Search elements included: scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid [EPA]; fish oil); and, relevant population terms (e.g., mental disorders). Additional published or unpublished literature was sought through manual searches of references lists of included studies and key review articles, and from the files of content experts.

Study Selection: Studies were considered relevant if they described live human populations of any age, investigated the use of any foods or supplements known to contain omega-3 fatty acids, and utilized mental health outcomes. Studies examining the questions concerning treatment efficacy or the fatty acid content of biomarkers had to employ a controlled research design, whereas any type of design other than a case series or case study was permitted to address the possible association of the intake of omega-3 fatty acids and clinical outcomes. Three levels of screening for relevance, and two reviewers per level, were employed. Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Extraction: All data were abstracted by one reviewer, then verified by another. Data included characteristics of the report, study, population, intervention/exposure, comparator(s), cointerventions, discontinuations (and reasons), and outcomes (i.e., clinical, biomarkers, safety). Study quality (internal validity) and applicability (external validity) were appraised.

Data Synthesis: Question-specific qualitative syntheses of the evidence were derived. Meta-analysis was conducted with data concerning the supplemental treatment of schizophrenia. Limited numbers of studies addressing the other research questions precluded further meta-analysis. Eighty-six reports, describing 79 studies, were deemed relevant for the systematic review, with each of 6 studies described by more than one report.

Conclusions: A notable safety profile for any type or dose of omega-3 fatty acid supplementation was not observed. Overall, other than for the topics of schizophrenia and depression, few studies were identified. Only with respect to the supplemental treatment of schizophrenia is the evidence even somewhat suggestive of omega-3 fatty acids' potential as short-term intervention. However, these meta-analytic results exclusively pertaining to 2 g/d EPA require replication using design and methods refinements. Additional research might reveal the short-term or longterm therapeutic value of omega-3 fatty acids. One study demonstrating a significant placebo-controlled clinical effect related to 1 g/d E-EPA given, over 12 weeks, to 17 patients with depressive symptoms—rather than depressive disorders—cannot be taken to support the view of the utility of this exposure as a supplemental treatment for depressive symptomatology or disorders. Nothing can yet be concluded concerning the clinical utility of omega-3 fatty acids as supplemental treatment for any other psychiatric disorder or condition, or as a primary treatment for all psychiatric disorders or conditions, examined in our review. Primary treatment studies were rare. Much more research, implementing design and methods improvements, is needed before we can begin to ascertain the possible utility of (foods or supplements containing) omega-3 fatty acids as primary prevention for psychiatric disorders or conditions. Overall, almost nothing is known about the therapeutic or preventive potential of each source, type, dose or combination of omega-3 fatty acids. Studies of their primary protective potential in mental health could be "piggybacked" onto longitudinal studies of their impact on general health and development. Because of limited study designs, little is known about the relationship between PUFA biomarker profiles and the onset of any psychiatric disorder or condition. Studies examining the possible association between the intake of omega-3 fatty acids, or the PUFA content of biomarkers, and the continuation or recurrence of psychiatric disorders or conditions were virtually nonexistent. If future research is going to produce data that are unequivocally applicable to North Americans, it will likely need to enroll either North American populations or populations exhibiting a high omega-6/omega-3 fatty acid intake ratio similar to what has been observed in the diet of North Americans. Furthermore, if a reasonable view is that omega-3 fatty acids may play a role in mental health, then given the observed or proposed inter-relationships between omega-3 and omega-6 fatty acid contents both in the regular diet and in the human biosystem, it may behoove researchers to investigate the possible therapeutic or preventive value of the dietary omega-6/omega-3 fatty acid intake ratio.

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Effects of Omega-3 Fatty Acids on Mental Health

Summary

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Introduction

The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise, and synthesize the human evidence for the effects of omega-3 fatty acids on mental health. The review was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It was undertaken as part of a consortium involving three Evidence-based Practice Centers (EPCs), which investigated the value of omega-3 fatty acid supplementation across 11 health/disease areas. The three EPCs are Southern California-RAND, Tufts-New England Medical Center, and the University of Ottawa. To ensure consistency of approach, the three EPCs collaborated on selected methodologic elements, including literature search strategies, rating of evidence, and data table design.

While the intention was to evaluate the spectrum of psychiatric disorders or conditions (i.e., behavior or symptoms which, while their consequences could be serious, do not warrant receipt of a formal psychiatric diagnosis), certain foci were beyond the scope of the review (see Methods). At the same time, a mental health disorder or condition did not require extant animal or basic science data or models to justify the investigation of their evidence. Nevertheless, justification for the study of two disorders exists in the literature: depression and schizophrenia.

The mechanism by which diet may affect health, including depression or cardiovascular disease, has been thought to involve low levels of omega-3 fatty acid content in biomarkers (e.g., red blood cells [RBCs]).[1,2] An omega-3 fatty acid deficiency hypothesis of depression has been put forward, which has helped justify treatment with omega-3 fatty acid supplementation.[3] The membrane phospholipid hypothesis of schizophrenia has been proposed in an attempt to develop a model explaining its etiology.[4] It describes the presumed biochemical dynamics underpinning a neurodevelopmental theory. Some of the evidence used to support this perspective suggests the existence of phospholipid and polyunsaturated fatty acid (PUFA) metabolic abnormalities in schizophrenia.[4-6] It has been posited that modifications to diet could mitigate or even aggravate an underlying abnormality of phospholipid metabolism.[4]

However, the present review was not conducted to test these hypotheses. Rather, the rationale for this 2-year project investigating the possible health benefits of omega-3 fatty acids was to systematically review the evidence to aid in the development of a research agenda. Nevertheless, these emerging models regarding depression and schizophrenia do suggest plausible bases for the use of omega-3 fatty acids to treat or prevent these psychiatric disorders.

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Evidence-Based Practice

Key Questions

Four basic questions were investigated with respect to each psychiatric disorder or condition for which evidence meeting eligibility criteria could be identified. To illustrate, the questions pertaining to depression were:

- Are omega-3 fatty acids efficacious as (primary or supplemental) treatment for depression?
- Is omega-3 fatty acid intake, including diet and/or supplementation, associated with the onset, continuation, or recurrence of depression (i.e., primary or secondary prevention)?
- Is the onset, continuation, or recurrence of depression associated with omega-3 or omega-6/omega-3 fatty acid content of biomarkers (i.e., primary or secondary prevention)?
- What is the evidence in review-relevant studies concerning mental health that adverse events (e.g., side effects) or contraindications are associated with the intake of omega-3 fatty acids?

Where data permitted, the impact of effect modifiers (e.g., covariates) was investigated with respect to the following study characteristics:

- Population (e.g., primary diagnosis, disorder severity, smoker status, alcohol consumption).
- Intervention/exposure (e.g., source, type, dose or serving size, and method to deliver the omega-3 fatty acids; intervention length; dietary omega-6/omega-3 fatty acid content).
- Comparator/control (e.g., type of placebo material, a "gold standard" medication).
- Cointerventions (e.g., concurrent psychotropic medication, other supplement use).

Methods

A Technical Expert Panel (TEP) consisting of nine members was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Several electronic databases were searched: MEDLINE®, EMBASE®, the Cochrane Library including the Cochrane Central Register of Controlled Trials, PsycINFO, and CAB Health®. Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search elements included: scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid (EPA), omega-3 fatty acids, MaxEPA®); and relevant population terms (e.g., depression). Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts. A final set of 1,212 unique references was identified and posted to an Internet-based software system for review.

Studies were considered relevant if they described live human populations of any age with any or no comorbidity, exhibiting a psychiatric status consistent with one of the above-noted research questions concerning treatment or prevention (i.e., with or without [a known elevated risk to develop] a psychiatric diagnosis or condition). Studies also had to investigate at least one pertinent clinical outcome (e.g., symptom improvement, incidence of a disorder).

As markers of omega-3 fatty acid metabolism, the following fatty acid compositions or concentrations, from any source (e.g., plasma phospholipids), were considered relevant as possible predictors of the onset, continuation, or recurrence of psychiatric disorders or conditions: EPA, docosahexaenoic acid (DHA), arachidonic acid (AA)/EPA, AA/DHA, and AA/EPA+DHA. Studies exclusively evaluating the role of other biomarkers (e.g., cytokine production, eicosanoid levels) were not included. Populations with degenerative (e.g., Alzheimer's) and peroxisomal (e.g., Zellweger's) disorders were excluded since each was addressed in Southern California-RAND's year-2 review of the evidence concerning omega-3 fatty acids in neurology.

Treatment studies, as well as those investigating the possible association between omega-3 fatty acid intake and the onset, continuation, or recurrence of psychiatric disorders or conditions, had to investigate foods or supplements known to contain omega-3 fatty acids of any type (e.g., EPA), from any source (e.g., walnuts), any serving size or dose, delivered in any

fashion (e.g., capsules, PUFA-rich diet), and for any length of time. In all studies, some method had to have been employed to suggest the presence of omega-3 fatty acid content in the exposure, if not its actual amount (e.g., g/d). Studies investigating "PUFAs" or " long-chain PUFAs," or even types of diet one might presume would contain marine or land sources of omega-3 fatty acids (e.g., "Mediterranean diet") at minimum had to highlight at least one source of the omega-3 fatty acid content (e.g., oily fish servings). No restrictions were placed on the types or doses of pre- or on-study cointerventions (e.g., psychotropic medication, omega-6 fatty acid intake).

Controlled studies employing any control were required to address questions of intervention efficacy (or effectiveness), with randomized controlled trials (RCTs) being the gold standard method to investigate these questions.[7] Any type of research design other than noncomparative case series or case studies was deemed appropriate for questions concerning the possible association between the intake of omega-3 fatty acids and the onset, continuation, or recurrence of psychiatric disorders or conditions. A special interpretative emphasis was placed on results from prevention RCTs and other controlled prospective designs. Controlled studies involving any control were required to address the questions of the possible association between the fatty acid content of biomarkers and the onset, continuation, or recurrence of psychiatric disorders or conditions. These decisions were made with the assistance of our TEP.

Two initial levels of screening for relevance, and two reviewers per level, were directed at bibliographic records and then full articles. A third dual-assessor relevance screening identified and thereby excluded uncontrolled studies with respect to questions of intervention efficacy or the possible protective role of lipid biomarker content. Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[8] Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Abstraction

Following a calibration exercise, seven reviewers independently abstracted the contents of each included study using an electronic data abstraction form. A second reviewer verified these data. Data included the characteristics of the report (e.g., publication status), study (e.g., research design), population (e.g., diagnosis), intervention/exposure (e.g., omega-3 fatty acid type), comparator group(s), cointerventions (e.g., medications), withdrawals or dropouts, and outcomes (i.e., symptom improvement, biomarker status, adverse events).

After calibration exercises, each study's quality (internal validity) and applicability (external validity) were formally assessed. Dual-review appraised RCTs' quality while only single-assessor evaluations could be conducted for other research designs. For the RCTs, disagreements were resolved by forced consensus and, if necessary, third party intervention. RCTs' reporting of randomization, double blinding, withdrawals and dropouts, and the concealment of allocation, were evaluated using Jadad's[9] and Schulz's validated instruments.[10] The validated Newcastle-Ottawa Scale (NOS) assessed case-control and cohort study designs, while all other designs were evaluated using modifications of the NOS,[11] Jadad's instrument,[9] or items from Downs and Black's validated 27-item tool.[12] Applicability was defined as the extent to which a given study's sample population was representative of a "typical" North American population. The method of diagnosis and the omega-6/omega-3 fatty acid ratio in the background diet were the key variables defining the reference population of North Americans identified with a psychiatric disorder. The omega-6/omega-3 fatty acid ratio in the background diet defined the reference population of North Americans who did not exhibit a psychiatric disorder.

Data Synthesis

A summary table provided a question-specific overview of included studies' relevant data presented in greater detail in evidence tables. A question-specific summary matrix situated each study in terms of its quality and applicability ratings. Question-specific qualitative syntheses of the evidence were derived. A dearth of studies best suited to address a particular kind of question (i.e., RCTs, prospective and controlled observational studies), as well as limitations on, or the strong clinical heterogeneity of, available studies (e.g., divergent intervention-comparator contrasts, use of complex interventions where it was impossible to tease out the possible specific benefit of omega-3 fatty acids, failure to control for key confounders), made it impossible to perform meta-analysis for any question other than the supplemental treatment for schizophrenia.

Results

Literature Search

Of 1,212 records entered into the initial screening for relevance, 955 were excluded. All but seven of the remaining 257 reports were then retrieved and subjected to a more detailed relevance assessment.[13-21] A second relevance screening then excluded 137 reports. A third screening excluded 27 reports of uncontrolled studies. In total, 86 reports, describing 79 unique studies, were deemed relevant for the systematic review, with six studies each described by more than one report. To simplify matters, only one report per study is referred to in this summary. Yet, data from all of a study's documents were included in qualitative and quantitative syntheses. Some studies addressed more than one question.

Of the included studies, only one failed to be described by at least one published report.[22] It was reported in abstract format. Sixteen relevant studies were identified by manual search. One report required translation from Chinese.[23] All the other included reports were written in English.

Overall, depression (n=22 studies) and schizophrenia (n=28) were the most frequently studied disorders. Only the 10 studies investigating attention-deficit/hyperactivity disorder (AD/HD) enrolled pediatric populations. Many of the studies exhibited poor quality or weak applicability to North American populations. Synopses of evidence are presented according to seven cross-cutting topics:

Adverse Events

A number of study reports explicitly stated that no exposure-related adverse events had been observed.[24-32] Ten RCTs described at least one mild adverse event associated with an omega-3 fatty acid intervention/exposure.[2,33-41] Results from these studies suggest that the exposures were well tolerated. In spite of a small number of discontinuations presumed to have been instigated by an adverse event, it is unlikely that moderate or severe side effects were ever observed in relation to an omega-3 fatty acid exposure. Reported difficulties tended to be mild and transient, often involving gastrointestinal upset or nausea. Occasionally, adverse events were linked to the intake of oily substances, rather than to the omega-3 fatty acid contents in the oils. Aside from the mild adverse effects associated with Stoll et al.'s very high dose of 9.6 g/d EPA+DHA (i.e., three patients had to decrease the number of capsules swallowed per day, yet none were required to discontinue),[38] no other patterns were discerned regarding the impact of dose, type (e.g., DHA, EPA) or source (e.g., marine, plant) of omega-3 fatty acids on safety. In one study, a child with AD/HD in the active treatment group had to leave the study due to problems swallowing the capsules.[41] Few of the events described in two trials by Hamazaki et al., which enrolled healthy volunteers, suggested that the adverse effects had been directly related to the exposure.[39,40]

Primary Treatment

One RCT examined omega-3 fatty acids as primary treatment for depression.[34] It found no benefit for 2 g/d DHA as primary treatment despite an increase in the absolute RBC levels of DHA in the active treatment group.[34] Reasons for this null result could include the use of too small a dose, too short an intervention period, the "wrong" omega-3 fatty acid, broken blinding, low power, or failure to modify the on-study background intake of omega-6 fatty acids.

Notwithstanding the noncomparability of interventions, comparators, and populations (i.e., with[32,42,43] or without a formal diagnosis of AD/HD,[41] with[32] or without significant comorbidity[41,43]), the complex definitions of the intervention where it was impossible to tease out the possible specific benefit of omega-3 fatty acids,[41] evidence for selection bias,[43] or the failure to specify study enrollees' specific diagnostic subtype of AD/HD (e.g., inattentive),[44] the results of the three RCTs[32,41,42] and the comparative before-after study[43] addressing the question about the primary treatment of AD/HD were inconsistent. Thus, no definitive conclusions can be drawn about the value of omega-3 fatty acids as primary treatment for AD/HD.

One RCT examined ethyl (E)-EPA as primary treatment for borderline personality disorder and observed significant clinical effects, as the E-EPA group had, at study end, significantly lower mean scores on both clinical outcomes compared with the placebo group.[31] Despite its strong applicability to the North American population, this is a small study requiring replication.

While the results of Peet et al.'s trial[37] indicate placebo-controlled benefits accruing to omega-3 fatty acids as primary treatment for schizophrenia, this was a small, albeit methodologically adequate, pilot trial with little applicability to a North American population. More work is required before we can determine omega-3 fatty acids' promise in this context.

Supplemental Treatment

Peet et al.'s dose-ranging RCT of E-EPA as supplemental treatment for depression found that only 1 g/d for 12 weeks had a significant impact on various clinical outcomes.[2] Two RCTs of shorter duration also showed significant benefits associated with 2 g/d E-EPA and 6.6 g/d of EPA+DHA, respectively;[27,33] the significant clinical effect reported by Su et al. was associated with a significant increase in RBC EPA exclusively in the active treatment group.[33] However, we decided to forego meta-analysis due to study differences on the basis of the intervention (i.e., type, dose, followup length) and comparator (i.e., placebo source). Also, unlike the other two trials, Peet et al.'s did not formally identify patients with a depressive disorder.[2] This may account for their finding that 1 g/d E-EPA had a beneficial effect on depressive symptomatology.[2] A low dose might not have helped the treatment-resistant depressive disorders investigated in the other RCTs. Yet, this likely cannot explain why Peet et al.'s higher doses (2 g/d, 4 g/d) did not likewise ameliorate depressive symptoms, or why more responders (i.e., 50 percent improvement) were found in the placebo group than in the 2 g/d E-EPA group. Su et al.'s trial may have been confounded by uncontrolled combinations of medication.[33] The question of omega-3 fatty acids as supplemental treatment for depression requires additional investigation.

Two studies, one a RCT[38] and one defined merely as "controlled,"[45] evaluated the supplemental treatment of bipolar disorder. Only the RCT report gave us an opportunity to assess its study parameters and results.[38] While it had to be stopped prematurely, their very high dose of 9.6 g/d EPA+DHA produced a significantly longer period of remission in the active treatment group compared with controls. This study's limitations (i.e., loss of power due to its stoppage, broken blind) require its replication. Therefore, the evidence base is too limited to allow us to conclude anything about the value of omega-3 fatty acids as supplemental therapy for bipolar disorder. Likewise, one underpowered and flawed crossover RCT, which failed to show that E-EPA is effective as supplemental treatment for obsessive-compulsive disorder, is insufficient to permit drawing a definitive conclusion.[25]

Inconsistencies in the results produced by three RCTs, the occasional use of a complex intervention making it impossible to tease out the possible specific benefit of omega-3 fatty acids,[46] the confirmation by parents—but not by professionals—of an AD/HD diagnosis,[46] interventions that did not last long enough,[30,42,46] and failures to weight-adjust doses of omega-3 fatty acids prevent us from identifying clear conclusions about their value as supplemental treatment for AD/HD.[30,42,46]

Three of four good quality placebo-controlled RCTs investigating the supplemental treatment of schizophrenia[26,35-37] reported significant clinical effects in favor of EPA using total Positive and Negative Syndrome Scale (PANSS) scores,[26,36,37] although Peet et al.'s study observed this effect only for those receiving clozapine as primary treatment.[36] Yet, the Emsley et al. study found a nonsignificant trend towards greater reduction in total PANSS scores in participants taking typical antipsychotic medication, compared with those receiving clozapine.[26] Results of our meta-analysis of two studies' PANSS total data revealed that dose influenced outcome. A or significant placebo-controlled effect was identified for 2 g/d EPA yet not for doses of at least 3g/d EPA.[36,37] However, these results might have been different had we been able to analyze data by type of psychotropic medication, had both studies used either the purified or unpurified form of EPA as well as the same placebo oils, had their intervention periods lasted longer, or had both trials employed capsules to deliver the omega-3 fatty acids. While the findings are suggestive, they remain inconclusive given that the data subjected to meta-analysis were derived from two small trials exhibiting certain limitations.

Primary Prevention (i.e., Onset) Via Omega-3 Fatty Acid Intake

Inconsistent results, in addition to too few studies exhibiting sound methodologies or research designs that are ideally suited to investigate this question (e.g., prospective, controlled, with subject-level data), suggest that it is too early to conclude whether or not the intake of omega-3 fatty acids protects against the onset of depressive disorders or symptomatology.[1,24,28,47-55] The same issues prevent us from concluding whether or not the intake of omega-3 fatty acids protects against the onset of suicidal ideation or behavior.[51,55] Given the inability of any cross-national ecological analysis to provide meaningful subject-level data, and the failure to control for key confounders (i.e., socioeconomic status, urban/rural ratio, educational level, marital status, alcohol consumption, smoker status, or family history), we cannot conclude anything about the value of seafood consumption as protection against the onset of bipolar disorder.[56]

Two RCTs failed to clarify the protective value of omega-3 fatty acid intake with respect to the onset of symptoms, not disorders, of anxiety.[28,47] However, these small studies do not constitute optimal tests of this potential. Based on one cross-sectional study, which controlled for age, income, smoking, alcohol consumption, and eating patterns, mental health difficulties were more prevalent in those consuming no fish.[57] However, this design precludes inferring a causal link between fish consumption and the onset of mental health difficulties.

Four RCTs,[28,39,40,58] three of which enrolled healthy volunteers, one single population cross-sectional survey[59] and one cross-national ecological analysis[60] studied the possible association between omega-3 fatty acid intake and the onset of tendencies or behavior with the potential to harm others. Overall, their findings are too inconsistent and involve too few research designs permitting the drawing of causal inferences or too many different definitions of the exposure, population, or outcome to permit us to draw a consistent, individual/patient-level conclusion regarding the value of omega-3 fatty acid intake to protect against tendencies or behavior with the potential to harm others.

We could not identify the research designs which, due to their prospective and controlled nature, are most appropriate for addressing the question of the possible relationship between intake of omega-3 fatty acids (e.g., via breastfeeding) and the onset of schizophrenia. Five case-control designs,[22,61-64] one single prospective cohort,[65] and three cross-national ecological analyses[50,56,66] were found. The only prospective study was not controlled, and its followup was very short.[65] Moreover, failure to control for confounders was common (e.g., maternal feeding patterns, sex of children, maternal age, socioeconomic status, early mother-infant contact). Thus, nothing definitive can be asserted about a reliable association between omega-3 fatty acid intake and the onset of schizophrenia.

Secondary Prevention (i.e., Continuation, Recurrence) Via Omega-3 Fatty Acid Intake

One small, multiple-group cross-sectional study revealing that, relative to healthy controls, AD/HD children consumed significantly lesser amounts of linoleic acid and alpha linolenic acid (ALA) is insufficient to permit us to conclude anything definitive regarding the potential of these PUFAs to alter the course, or continuation, of AD/HD.[23] Likewise, a single RCT demonstrating that a complex intervention including omega-3 fatty acids—whose independent effect could not be ascertained—provided young adult prisoners with some protection against committing new offences[29] is insufficient to determine its capacity to prevent the recurrence of tendencies or behavior with the potential to harm others (i.e., antisocial behavior).[29]

Primary Prevention (i.e., Onset) Via Lipid Biomarker Content

Inconsistent results as well as too few studies exhibiting sound methodologies (e.g., protection against selection bias; control for smoking, alcohol use, and psychotropic medication) or research designs (e.g., prospective, controlled) that are ideally suited to investigate this question suggest that it is too early to conclude whether or not omega-3 fatty or omega-6/omega-3 acid content in biomarkers protects against the onset of depressive disorders or symptomatology. One RCT[24] and seven multiple-group cross-sectional studies[1,67-72] were included.

The inconsistency in findings across two multiple-group cross-sectional studies,[73,74] which is potentially attributable to the fact that the studies obtained their PUFA samples from different biomarker sources, in addition to the recognition that this type of research design is less than an ideal test of the research question, and the observation that the studies failed to control for different key confounders together indicate that nothing definitive can be concluded about the ability of specific lipid biomarker content to protect against the onset of bipolar disorder. Irrespective of the limited agreement in observing that both ALA and total omega-6 fatty acid levels in plasma phospholipids were significantly lower in anorexic patients compared with controls, the use of cross-sectional designs in two small studies prevent the drawing of causal inferences regarding the role of lipid biomarker content in the onset of anorexia nervosa.[75,76] Inconsistent findings from three multiple-group cross-sectional studies whose designs are of limited use in investigating the research question,[77-79] the failures to control for dietary intake,[77] to formally rule out the presence of psychopathology in the control subjects, or to employ formal diagnostic criteria (i.e., DSM-III) to identify their hyperactive subjects,[78] made it impossible to draw causal inferences about the role of omega-3 or omega-6/omega-3 fatty acid content in biomarkers to prevent the onset of AD/HD.

Three multiple-group cross-sectional studies examined the possible association of the onset of tendencies or behavior with the potential to harm others with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[80-82] Inconsistent results, small sample sizes, and the exclusive use of cross-sectional designs preclude deriving clear inferences regarding

etiology. Two multiple-group cross-sectional studies investigated the possible association of the onset of alcoholism with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[83,84] However, conflicting results and the use of cross-sectional designs do not allow us to draw conclusions regarding this possible etiology of alcoholism.

Medication status may have had somewhat of an influence on between-group differences in RBC or plasma phospholipid fatty acid content when the comparison group was healthy controls. However, because these data were obtained exclusively from twelve multiple-group cross-sectional studies[74,85-95] or two single prospective cohort studies with methodologic flaws,[96,97] no meaningful possibility exists to permit drawing causal inferences regarding patterns of lipid biomarker content and the onset of schizophrenia. The same criticism relating to cross-sectional designs applies to the single study examining biomarkers data with respect to the onset of autism.[98]

Secondary Prevention (i.e., Continuation, Recurrence) Via Lipid Biomarker Content

This question could not be evaluated since studies meeting eligibility criteria were not identified.

Discussion

A notable safety profile (i.e., beyond occasional and mild discomfort) for any type or dose of omega-3 fatty acid supplementation was not observed. Overall, other than for the topics of schizophrenia and depression, few efficacy or safety studies were identified.

Only with respect to the supplemental treatment of schizophrenia is the evidence even somewhat suggestive of omega-3 fatty acids' potential as short-term intervention. However, these meta-analytic results exclusively pertaining to 2 g/d EPA require replication using design and method refinements. Additional research might reveal the short-term or long-term therapeutic value of omega-3 fatty acids.

One study demonstrating a significant placebo-controlled clinical effect related to 1 g/d E-EPA given over 12 weeks to 17 patients with depressive symptoms—rather than depressive disorders—cannot be taken to support the view of the utility of this exposure as a supplemental treatment for depressive symptomatology or disorders. Nothing can yet be concluded concerning the clinical utility of omega-3 fatty acids as supplemental treatment for any other psychiatric disorder or condition, or as a primary treatment for all psychiatric disorders or conditions examined in our review. Primary treatment studies were rare.

Much more research, implementing design and methods improvements, is needed before we can begin to ascertain the possible utility of (foods or supplements containing) omega-3 fatty acids as primary prevention for psychiatric disorders or conditions. Studies of omega-3 fatty acids' primary protective potential in mental health could be "piggybacked" onto longitudinal studies of their impact on general health and development.

Overall, almost nothing is known about the therapeutic or preventive potential of each source, type, dose, or combination of omega-3 fatty acids. Likewise, limitations within the evidence base prevented us from identifying the influence of key covariables (e.g., smoking, alcohol use, psychotropic medication) on the relationship between omega-3 fatty acid content and clinical outcomes.

Because of limited study designs, little is known about the relationship between PUFA biomarker profiles and the onset of any psychiatric disorder or condition. Studies examining the possible association between the intake of omega-3 fatty acids, or the PUFA content of biomarkers, and the continuation or recurrence of psychiatric disorders or conditions were virtually nonexistent.

If future research is going to produce data that are unequivocally applicable to North Americans, it will need to enroll either North American populations or populations exhibiting a high omega-6/omega-3 fatty acid intake ratio similar to what has been observed in the diet of North Americans. Furthermore, if a reasonable view is that omega-3 fatty acids may play a role in mental health, then given the observed or proposed inter-relationships among omega-3 and omega-6 fatty acid contents both in the human diet and metabolism, researchers should likely consider taking into account the possible therapeutic or preventive influence of the dietary omega-6/omega-3 fatty acid intake ratio.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021. It is expected to be available in July 2005. At that time, printed

copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 116, *Effects of Omega-3 Fatty Acids on Mental Health*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

Schachter HM, Kourad K, Merali Z, Lumb A, Tran K, Miguelez M, et al. Effects of Omega-3 Fatty Acids on Mental Health. Summary, Evidence Report/Technology Assessment No. 116. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021.) AHRQ Publication No. 05-E022-1. Rockville, MD: Agency for Healthcare Research and Quality. July 2005.

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www.ahrq.gov
AHRQ Pub. No. 05-E022-1
July 2005
ISSN 1530-440X

Evidence Report

Chapter 1. Introduction

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

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

The focus of this report is on mental health outcomes in humans. In this chapter, the metabolism, physiological functions, and sources of omega-3 fatty acids are briefly discussed. This constitutes background material, placing in context the data presented in the evidence report. As well, the description of the U.S. population's intake of omega-3 fatty acids is provided in response to a general question posed within the task order (i.e., project). This introductory material is then complemented by a brief review of the epidemiology and descriptions of mental health disorders or conditions, in addition to some of their treatment options. The brief review is intended as an overview rather than a comprehensive description. The terms "mental health" and "psychiatric" are used interchangeably, as in "psychiatric" or "mental health" disorders or conditions. "Conditions" refer to behavior or symptoms (e.g., dysphoric feelings, suicidal ideation, anger, aggressiveness), which are necessary yet insufficient to warrant a formal diagnosis of psychiatric disorder despite their potentially serious consequences.

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

Metabolism and Biological Effects of Essential Fatty Acids

Dietary fat is an important source of energy for biological activities in human beings. It encompasses saturated fatty acids (SFAs), which are usually solid at room temperature, and unsaturated fatty acids (UFAs), which are liquid at room temperature. UFAs can be further divided into monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs). PUFAs can

be classified, on the basis of their chemical structure, into two groups: omega-3 (n-3) fatty acids and omega-6 (n-6) fatty acids. The omega-3 or *n-3* notation means that the first double bond in this family of PUFAs is 3 carbons from the methyl end of the molecule. The same principle applies to the omega-6 or *n-6* notation. Despite their differences in structure, all fats contain the same amount of energy (i.e., 9 kcal/g or 37 kJ/g).

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

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

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

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

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

Omega-3 and omega-6 fatty acids share the same pools of enzymes and go through the same oxidation pathways while being metabolized (Figure 1). Once ingested, the parent of the omega-3 fatty acids, ALA, and the parent of the omega-6 fatty acids, LA, can be elongated and desaturated into LC PUFAs. LA is converted into gamma-linolenic acid (GLA; 18:3 n-6), an

omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the long-chain omega-6 fatty acid, AA, while ALA can be converted, to a lesser extent, to the long-chain omega-3 fatty acids, EPA and DHA. However, the conversion from parent fatty acids into LC PUFAs occurs slowly in humans, and conversion rates are not well understood. Because of the slow rate of conversion, and the importance of LC PUFAs to many physiological processes, humans must augment their level of LC PUFAs by consuming foods rich in these important compounds. Meat is the primary food source of AA, and fish is the primary food source of EPA.

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

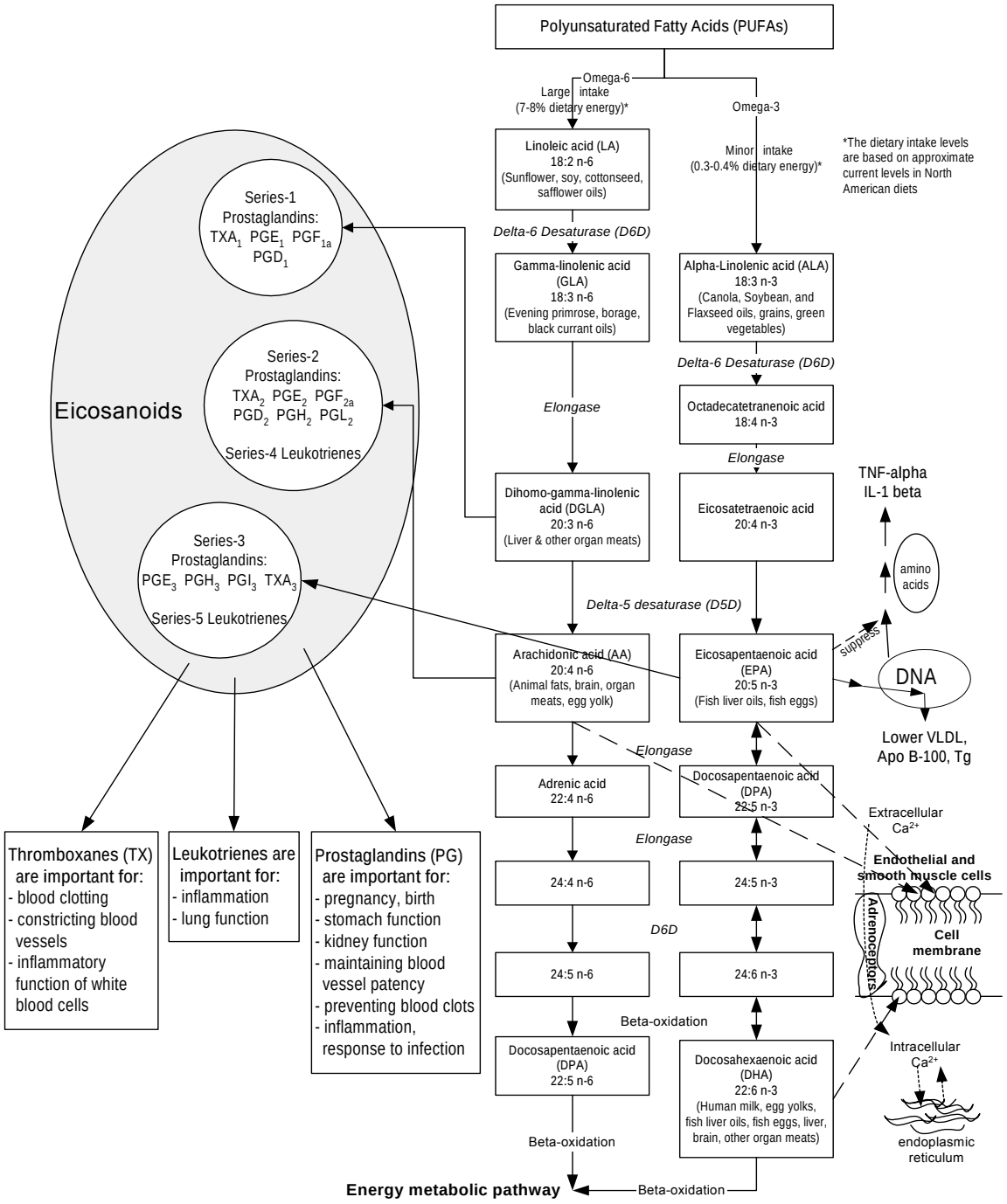
As shown in Figure 1, the long-chain omega-6 fatty acid, AA, is the precursor of a group of eicosanoids including series-2 prostaglandins (PG_2) and series-4 leukotrienes (LT_4). The omega-3 fatty acid, EPA, is the precursor to a group of eicosanoids including series-3 prostaglandins (PG_3) and series-5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

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

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

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

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



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

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

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

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

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

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

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

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

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

Dietary Sources of Omega-3 Fatty Acids

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

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

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

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

Disorders of Mental Health: an Overview

Disorders of mental health are becoming increasingly common in the US. It is estimated that in a given year, 22%, or one in five American adults, suffers from a diagnosable mental health disorder.[11] These disorders, including major depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder, account for four of the ten leading causes of disability in the US and other developed countries.[12] Many people suffer from more than one mental disorder at a given time. The *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV), published by the American Psychiatric Association, is the reference guide currently used particularly in North America to diagnosis psychiatric disorders.

The DSM approach, with its diagnostic criteria often embodied as various methods (e.g., structured interviews), has been updated several times over the past decades, an observation suggesting the need to recognize that individuals diagnosed using the different versions of DSM may actually be exhibiting varying clusters or intensities of clinical features (e.g., symptoms/behaviors).[13] Other classification systems (e.g., ICD-10), employing diagnostic criteria which are potentially different from the DSM approach, have also been used to identify psychiatric disorders. Together, these two observations highlight the importance of considering how the ways in which psychiatric populations are identified may account for varying responses to the same interventions within clinical or research contexts.[13] The following sections introduce the psychiatric disorders or conditions for which evidence pertinent to this systematic review was identified.

Affective Disorders

Affective, or mood, disorders include depression (major and dysthymic) and bipolar disorder (manic depression). In a given year, it is estimated that 18.8 million American adults, or 9.5% of the population aged 18 years and older, exhibit the characteristics of a depressive disorder.[11] Twice as many women (12%) as men (6.6%) are affected.(National Institute of Mental Health, 2001) The World Health Organization (WHO) has estimated that major depressive disorder may become the second leading cause of diability by 2020, positioning it second only to ischemic heart disease, and making it the leading cause in developing regions.[14]

The mainstay of depressive symptoms are feelings of unhappiness, loss of energy and interest, fatigue, poor concentration, altered appetite, sleep disturbances, diminished cognitive function, weight gain/loss, anxiety, agitation or irritability, chronic indecisiveness, and often, suicidal ideation.[15,16] Individuals with dysthymic disorder (chronic, mild depression) have depressive symptoms of lesser severity than what is seen in individuals with major depression. Dysthymic disorder can begin in childhood, adolescence or early adulthood. Symptoms must persist for a minimum of two years in adults, or one year in children, in order to meet criteria for a DSM-IV diagnosis. Individuals with dysthymic disorder are usually able to manage their life, although symptoms may be severe enough to cause distress and interfere with important life responsibilities. In a given year, approximately 40 percent of adults with dysthymic disorder may end up meeting the criteria for major depressive disorder or bipolar disorder.[11]

Major depression (clinical depression, unipolar depression) is characterized by severe symptoms of depression. WHO has determined that major depression is the third leading cause of vocational disability worldwide.[12] According to DSM-IV, major depression is defined as two or more weeks of low mood or diminished interest in usual activities, combined with four or more of the following symptoms: sleep alteration (increased or decreased); inappropriate guilt or loss of self-esteem; altered appetite (increased or decreased); diminished energy; diminished concentration; psychomotor symptoms (either agitation or retardation); or suicidal ideation. The average age of onset is the mid-twenties, and for most people, episodes of major depression last from six to nine months.[11]

Bipolar disorder (manic depression) is characterised by extreme mood swings, that is, alternating between periods of mania and periods of depression. According to DSM-IV, mania is defined as a distinct change in mood and functioning, lasting at least one week, and is characterized by a euphoric or irritable mood accompanied by symptoms such as increased energy, decreased need for sleep, rapid thinking and speech, grandiosity, poor judgement and impulsivity, and in some cases, psychosis (i.e., delusions and/or hallucinations). For patients with bipolar disorder, episodes of mania are followed by periods of major depression. Patients may also have "mixed" mood states in which the symptoms of mania and depression occur simultaneously, or "rapid cycling," where continuous or frequently shifting mood states occur.[16] Unlike dysthymia and major depression, where the incidence is higher in women, bipolar disorder tends to affect men and women equally. The average age of a first manic episode is the early twenties.[11] It has been estimated that 20% to 30% of individuals with bipolar disorder will die as a direct consequence of their illness, usually by suicide.[17]

Treatment Options

Treatment options for patients diagnosed with depression include psychotherapy, pharmacotherapy, and in some instances, electroconvulsive therapy. For individuals with severe depression, antidepressant medication is the treatment of choice, whereas psychotherapy alone may be sufficient to treat individuals with mild to moderate depression.

The most commonly used antidepressant medications include the selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. The monoamine oxidase inhibitors (MAOIs) are used less frequently. Herbal therapy, including St. John's wort, has also been suggested as being helpful in the treatment of depression. The treatment of choice for bipolar disorder remains lithium or divalproex. The SSRIs and tricyclics act by slowing the reuptake of neurotransmitters, thus making them more available. The SSRIs work specifically on the neurotransmitter serotonin, whereas the tricyclics and MAOIs work on both serotonin and norepinephrine. In general, the SSRIs appear to demonstrate fewer side effects than do the tricyclics or MAOIs.

In spite of the availability of these medications, it has been estimated that 29% to 46% of patients are treatment-resistant, that is, they show no clinical response or only a partial response to the antidepressant medications. One approach to dealing with treatment-resistant depression is the use of combination therapy or the addition of a "booster drug" to augment the effects of the primary medication(s). Natural compounds, including omega-3 fatty acids, have recently been touted as potential augmentors of antidepressants' effects in treatment-resistant depression.[18,19]

Anxiety Disorders

Anxiety disorders typically include panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobias (social phobia, agoraphobia). Anxiety disorders often coexist with other disorders (e.g., depressive disorders), with an estimated 75% of individuals with an anxiety disorder also meeting criteria for at least one other psychiatric illness. The NIMH estimates that within a given year, 19 million American adults between the ages of 18 and 54 years exhibit evidence of an anxiety disorder. Although equal numbers of men and women suffer from obsessive-compulsive disorder and social phobia, approximately twice as many women than men suffer from panic disorder, post-traumatic stress disorder, generalized anxiety disorder, and agoraphobia.[11]

Obsessive-compulsive disorder is estimated to afflict 2% to 3% of the world's population,[20] including approximately 3.3 million American adults or 2.3% of the population.[11] It is characterized by obsessive thoughts and compulsive actions (e.g., cleaning, ordering, counting) that are associated with, and often are behavioral attempts to deal with, marked anxiety or distress (DSM-IV). While it can range from mild to severe in intensity, severe obsessive-compulsive disorder can interfere with a person's ability to function.

Treatment Options

As with other mental health disorders, treatment for anxiety disorders, including obsessive-compulsive disorder, typically involves pharmacologic and psychotherapy treatment approaches. Pharmacologic treatment options have included benzodiazepines, tricyclic antidepressants and MAOIs, but more recently include antidepressant medications such as the SSRIs. Psychotherapeutic strategies that help patients cope with their anxiety include the cognitive-behavioural therapies. For individuals with obsessive-compulsive disorder, complete remission is rare, with most people requiring longterm medication.

Anorexia Nervosa

Anorexia nervosa is an eating disorder that more commonly afflicts females. An estimated 0.5% to 3.7% of American females suffer from anorexia during their lifetime.[21] According to DSM-IV, criteria for the diagnosis of anorexia nervosa include an individual's refusal to maintain their body weight at or above a minimally normal weight for their age and height, an intense fear of gaining weight or becoming fat, and a refusal to acknowledge weight loss. Amenorrhea is a common concomitant because of the impact of weight loss on the endocrine system. Other potential problems include heart rhythm disturbances, abdominal abnormalities and anemia. The mortality rate for individuals with anorexia has been estimated to be 0.56% per year.[22]

Treatment Options

The goal of treatment of individuals with anorexia is weight gain. To achieve this, physicians must restore healthy eating patterns and to address thoughts and feelings concerning body image. This usually requires individual and/or family psychotherapy, and in some instances the use of antidepressant medications.

Attention Deficit/Hyperactivity Disorder

Attention deficit/hyperactivity disorder (AD/HD) is the most commonly diagnosed mental health disorder in children and adolescents. According to the American Academy of Pediatrics, 4% to 12% of all school-age children are estimated to be affected by AD/HD. Although traditionally associated with school-age children, its prevalence in adults and in preschoolers is being increasingly recognized. Individuals with AD/HD are often unable to focus on assigned tasks, are easily distracted, and are often impulsive and/or hyperactive (DSM-IV). AD/HD is two to three times more common in boys than in girls. DSM-IV recognizes three main subtypes, that is, where clinical features indicate AD/HD predominantly characterized by problems of inattention, hyperactivity/impulsivity, or both.

Treatment Options

According to the American Academy of Pediatrics, children with AD/HD should be treated with a stimulant medication such as methylphenidate (Ritalin®), dextroamphetamine and/or behavior therapy.[23] A relatively recent complementary or alternative approach, called EEG-centered biofeedback, aims to teach the child to modulate their own attentional states so that they may adapt more readily to varying environmental expectations regarding behavior.

Tendencies or Behaviors With the Potential to Harm Others: the Spectrum of Anger/Hostility, Aggression and Violence

Numerous forms of behavior have the potential to harm others. While not always correlated with or culminating in physical action, verbally manifested anger and hostility can be quite disruptive to others. Aggression—any action that causes injury to oneself, others, or objects—is a common feature of many psychiatric disorders. According to the NIMH, more than 90% of individuals who commit suicide have a diagnosable mental health disorder, most commonly a depressive disorder or a substance abuse disorder. In a review of 28 studies, Flannery found that patients who were found to be repetitively violent more frequently than not had received a diagnosis of schizophrenia or a personality disorder; both males and females were equally represented and patients tended to be younger.[24] Underlying factors that relate to aggression include genetics, environment (i.e., childhood experiences of aggression, parental dysfunction), structural brain abnormalities, and neurotransmitter dysfunction. The focus here is on the broad

spectrum of externalizing tendencies (e.g., angry outbursts) or behaviors (e.g., physical aggression) with the potential to harm others.

Treatment Options

Pharmacological treatment for aggression includes the full spectrum of psychotropic medications including antidepressant medications, neuroleptics, and mood stabilizers. Although these agents have been used successfully in the clinic or in clinical trials, the Food and Drug Administration (FDA) has yet to approve any agent specifically for the treatment of aggression. Approaches to dealing with anger, hostility or violence have also ranged from psychotherapy to incarceration.

Alcoholism

According to DSM-IV, alcoholism is defined as a destructive pattern of alcohol use leading to significant social, occupational or medical impairment. Alcohol dependence and alcohol abuse are among the most common psychiatric disorders in the general population, with an estimated 8% of adults suffering from alcohol dependence and 5% from alcohol abuse. There appears to be a strong genetic predisposition toward alcoholism—the risk is three to four times higher in a close relative of individuals with alcohol dependence. Alcoholism is sometimes seen as a component of general maladaptive functioning that may include tendencies or behavior with the potential to harm others.

Treatment Options

Treatment options for individuals with alcoholism include self-help programs and psychosocial therapy. Pharmacotherapy is often used as an adjunct to psychosocial therapy, with the former including medications such as naltrexone that block the alcohol-brain interaction(s).

Borderline Personality Disorder

Borderline Personality Disorder, according to DSM-IV, is characterized by a pervasive pattern of unstable interpersonal relationships, self-image, and behavior. This instability often interferes with family, work and long-term planning. Although less well known than bipolar disorder or schizophrenia, borderline personality disorder is actually more common, affecting an estimated 2% of adults, including mostly young women. Unlike depression or bipolar disorder where a person can experience the same mood for weeks, a person with borderline personality disorder can exhibit intense periods of anger, depression and anxiety that each last only hours, or maybe a day. The risks of self-injury without suicidal intent or of suicide are both elevated for individuals with this disorder.[25]

Treatment Options

Borderline personality disorder does not appear to respond well to existing pharmacotherapy approaches. In general, antidepressants and mood stabilizers are used to treat some of the defining symptoms, such as depression or psychosis. A new form of psychotherapy called dialectical behavior therapy, developed specifically to treat patients with borderline personality disorder, has shown promising results.[26]

Schizophrenia

Schizophrenia is a debilitating condition characterized by perceptual and behavioral disturbances, conceptual disturbances, impaired ability to communicate, and social/occupational dysfunction. According to the NIMH, approximately 2.2 million American adults experience schizophrenia in a given year. Although it afflicts men and women with equal frequency, symptoms usually appear earlier in men (late teens to early twenties) than in women (twenties or early thirties). In general, diagnostic criteria for schizophrenia include at least two of the following "active phase" symptoms that persist for a significant portion of time during a one-month period: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms (i.e., affective flattening, alogia, or avolition). Only one of these symptoms is required if it is accompanied with a voice that keeps a running commentary on the person's behavior or thoughts, or if two or more voices are talking with each other.

Treatment Options

The hallmark of schizophrenia treatment remains antipsychotic medications. These help to reduce symptoms, thus allowing patients to function better and improve their quality of life. Although these medications have been available since the mid-1950's, many have demonstrated significant side effects. A new class of antipsychotic, the atypical antipsychotics, have been available since the late 1980's. These medications, which include clozapine, risperidone, olozapine, quetiapine, ziprasidone and aripiprazole, may be somewhat more effective while producing fewer side effects than the earlier neuroleptic mediations. However, side effects with these medications still occur and often it is necessary to alter dosages or add additional drugs to find the most effective approach.

Autism

Autism is one of a spectrum of Pervasive Developmental Disorders. It is characterized by severe and pervasive impairment in thinking, feeling, language, and the ability to relate to others. Autism affects an estimated one to two per 1000 individuals, and is generally apparent by the age of three. Although autism is four times more likely to affect boys than girls, girls with autism tend to have more severe symptoms and greater cognitive impairment.[11]

Treatment Options

There is currently no single treatment approach for individuals with autism. Most healthcare professionals agree that early intervention is important. Pharmacotherapy is sometimes used to treat associated behavioral problems (e.g., aggression, self-injurious behaviour) so that the individual can function more smoothly at home and school. The possible importance of nutrition has also been speculated upon.

Omega-3 Fatty Acids and Mental Health

Approximately 50% to 60% of the adult brain is composed of lipids (dry weight), of which roughly 35% are phospholipids comprised of UFAs.[27] Of the UFAs, AA and DHA are found in the highest concentrations. These components of phospholipids have important functions in maintaining nerve cell membrane integrity and fluidity, as well as contributing to neuronal signal transduction. DHA has been shown to be especially important in prenatal brain development, where it appears to play a key role in synaptogenesis.[28,29] DHA deficiency has been linked to a number of neurophysiological deficits including cognitive impairment,[30] decreased visual acuity,[31] and decreased cerebellar function.[32]

In the adult biosystem, an optimal balance between omega-3 and omega-6 fatty acids is likely essential for normal neuronal function, and it has been suggested that the current imbalance in the omega-6 to omega-3 fatty acid ratio in the North American diet may be in small or large part responsible for the observed increases in disorders of all kinds.[33-45] This imbalance has likewise suggested an etiologic mechanism by which psychiatric disorders may develop (i.e., abnormalities in PUFA metabolism), and in turn, a rationale for ways to treat them (e.g., PUFA supplementation). In both of these regards, depression and schizophrenia have been the two most investigated and speculated upon psychiatric disorders.

The strong variability in the annual prevalence rates for major depressive disorder, expressed as an almost 60-fold variation across countries,[46] parallels the wide cross-national differences in mortality rates from coronary artery disease, suggesting that similar risk factors could be involved in both scenarios.[47] In the 20th century the increasing lifetime risk of depression has co-emerged with a shift in diet involving an increase in omega-6 fatty acid intake and a decrease in the intake of omega-3 fatty acids;[48] and, this change in the dietary omega-6/omega-3 fatty acid intake ratio has been proposed as being responsible for the increased risk of depression.[49] At the same time, it has been suggested that these recent changes in the especially Western diet are responsible for the increase in cardiovascular and inflammatory disorders.[49] To add to this picture, there is some empirical evidence suggesting that major depression is strongly predictive of both coronary heart disease and myocardial infarction;[50,51] and, some physical illnesses, such as coronary heart disease or diabetes, appear to occur with increased frequency in patients with major depression and schizophrenia.[52]

The mechanism by which diet may affect health, including depression or cardiovascular disease, is thought to involve low levels of omega-3 fatty acid content in biomarkers (e.g., red blood cells [RBCs]).[48,53] An omega-3 fatty acid deficiency hypothesis of depression has been put forward, which has helped justify treatment with omega-3 fatty acid supplementation.[54]

These treatment-related data, as well as those reflecting the possible association of the fatty acid content of biomarkers with the risk of depression, are systematically reviewed in this report.

The membrane phospholipid hypothesis of schizophrenia has been proposed in an attempt to develop a model explaining schizophrenia's etiology.[55] It describes the presumed biochemical dynamics underpinning a neurodevelopmental theory. Some of the evidence used to support this perspective is systematically reviewed in this review, and so these data are not presented here. Nevertheless, by way of introducing the topic, at least some of the empirical evidence suggests the existence of phospholipid and PUFA metabolic abnormalities in schizophrenia. Experimental investigations have focused on peripheral tissues, including RBCs and skin fibroblasts. Certain data pertaining to phospholipids, which are not systematically reviewed here, have shown that there are reduced levels of phospholipid subtypes (e.g., phosphatidylcholine, phosphatidylethanolamine) in schizophrenic patients.[56] Since other work has shown increased levels of phosphodiesters (i.e., phospholipid breakdown products) and decreased levels of phosphomonoesters (i.e., used in phsopholipid synthesis) in prefrontal and temporal brain tissue of drug-naïve schizophrenic patients,[57] it has been proposed that there exists increased phospholipid turnover in the brains of schizophrenic patients.[55]

Numerous studies have assessed the PUFA content of membrane phospholipids in schizophrenia, with controlled studies eligible for inclusion in the present review (see Chapter 2). The ensuing discussions in the literature have centered on whether there is evidence for a depletion of omega-6 and omega-3 fatty acid content in the RBCs and the brain tissue of patients with schizophrenia.[58] At the same time, some animal studies have shown that essential and non-essential fatty acids in the diet can have a significant impact on neuronal membrane phospholipid composition.[59] Thus, it has been posited that modifications to diet could mitigate or aggravate an underlying abnormality of phospholipid metabolism.[55]

However, the present review was not conducted specifically to test either of these hypotheses. Rather, the rationale for this two-year project investigating the possible health benefits of omega-3 fatty acids is to systematically review the evidence to aid in the development of a research agenda. Nevertheless, these emerging models regarding depression and schizophrenia do suggest plausible bases for the use of omega-3 fatty acids to treat these two psychiatric disorders. As with depression, treatment-related data, as well as those reflecting the possible association of the fatty acid content of biomarkers with the risk of schizophrenia, are systematically reviewed in this report. Evidence concerning psychiatric disorders and conditions for which there are poorly developed, or no, animal or human models suggesting the use of omega-3 fatty acids as treatment or prevention are also systematically reviewed.

Chapter 2. Methods

Overview

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

Key Questions Addressed In This Report

The purpose of this evidence report was to synthesize information from relevant studies to address the following basic questions:

- Are omega-3 fatty acids efficacious as primary or supplemental treatment for (*some psychiatric disorder or condition*)? (Question 1)

- Is omega-3 fatty acid intake, including diet and/or supplementation, associated with the onset, continuation or recurrence of (*some psychiatric disorder or condition*)? (Question 2)

- Is the onset, continuation or recurrence of (*some psychiatric disorder or condition*) associated with omega-3 or omega-6/omega-3 fatty acid content of biomarkers? (Question 3)

- What is the evidence that, in review-relevant studies concerning mental health, adverse events (e.g., side effects) or contraindications are associated with the intake of omega-3 fatty acids? (Question 4)

The overarching goal was to identify and systematically review whatever evidence exists within the eligibility boundaries established for this review in consultation with our TEP and in light of the topics being addressed by SC-RAND and Tufts-NEMC EPCs. These boundaries are delineated in the Eligibility Criteria section (below). More details concerning the four basic questions are provided in conjunction with the description of the Analytic Framework (below). We were also guided collectively by ODS, our TEP and our UO-EPC review team content

experts to examine, where data permitted, the possible influence on efficacy, association or safety evidence of the following potential effect modifiers:

- intervention/exposure length;
- type(s) of omega-3 fatty acid (e.g., ALA, EPA, DHA);
- source of the omega-3 fatty acids (e.g., marine, plant, nut), including the specific source (e.g., mackerel as an oily fish);
- delivery format (e.g., whole food servings, capsules, pourable or spreadable oils);
- dose/serving size, including the precision/control of its delivery (e.g., per-day specific, minimum, maximum or range of numbers of capsules, whole food servings or bottle-pourable litres);
- type of processing used to purify the intervention/exposure and/or to maintain the experimental blind (e.g., ethyl esterification; adding an anti-oxidant to stabilize/preserve oils; adding flavor to oils; [vacuum] deodorization);
- amount/dose of omega-6 fatty acid intake either added as a separate cointervention or identified as being present in the background diet, thereby establishing a specific, minimum, maximum or range of allowable or mandated on-study omega-6/omega-3 fatty acid intake;
- the identity of the manufacturer and/or certain characteristics of their product(s) (i.e., purity; presence of other potentially active agents that have not been added intentionally: e.g., methylmercury content);
- for questions relating to efficacy or association, the prestudy/baseline or on-study omega-3 or omega-6/omega-3 fatty acid content of blood lipid biomarkers;
- absolute or relative omega-3 fatty acid content of the prestudy/baseline diet;
- omega-6/omega-3 fatty acid content in the prestudy/baseline diet, with the study population's country of origin as a possible surrogate measure of the omega-6/omega-3 fatty acid content of the background diet; and,
- any study subpopulations (e.g., minority; ethnic; genetic, including diabetics).

Furthermore, where data permitted, the following factors with the potential to influence (i.e.., aggravate, control) mental health outcomes (e.g., intensity of symptoms/behaviors) were also investigated:

- severity of the psychiatric disorder or condition;

- psychotropic medication type and dose;
- comorbid conditions and their treatments;
- diagnostic classification system/criteria employed to identify study population;
- age and other sociodemographic factors (e.g., marital status, education, income, employment status);
- general health status;
- stressors;
- other cointerventions (e.g., licit drug use, other supplement use, psychological interventions, use of complementary/alternative [CAM] medicine/products);
- social support;
- current smoker status;
- current alcohol consumption; and,
- influences on vegetative functioning (e.g., exercise, quality of sleep).

Psychotropic medication, current smoker status, and alcohol consumption are especially important effect modifiers in that they have been observed to influence both mental health status and essential fatty acid status, with levels of the latter potentially affecting the former.[60]

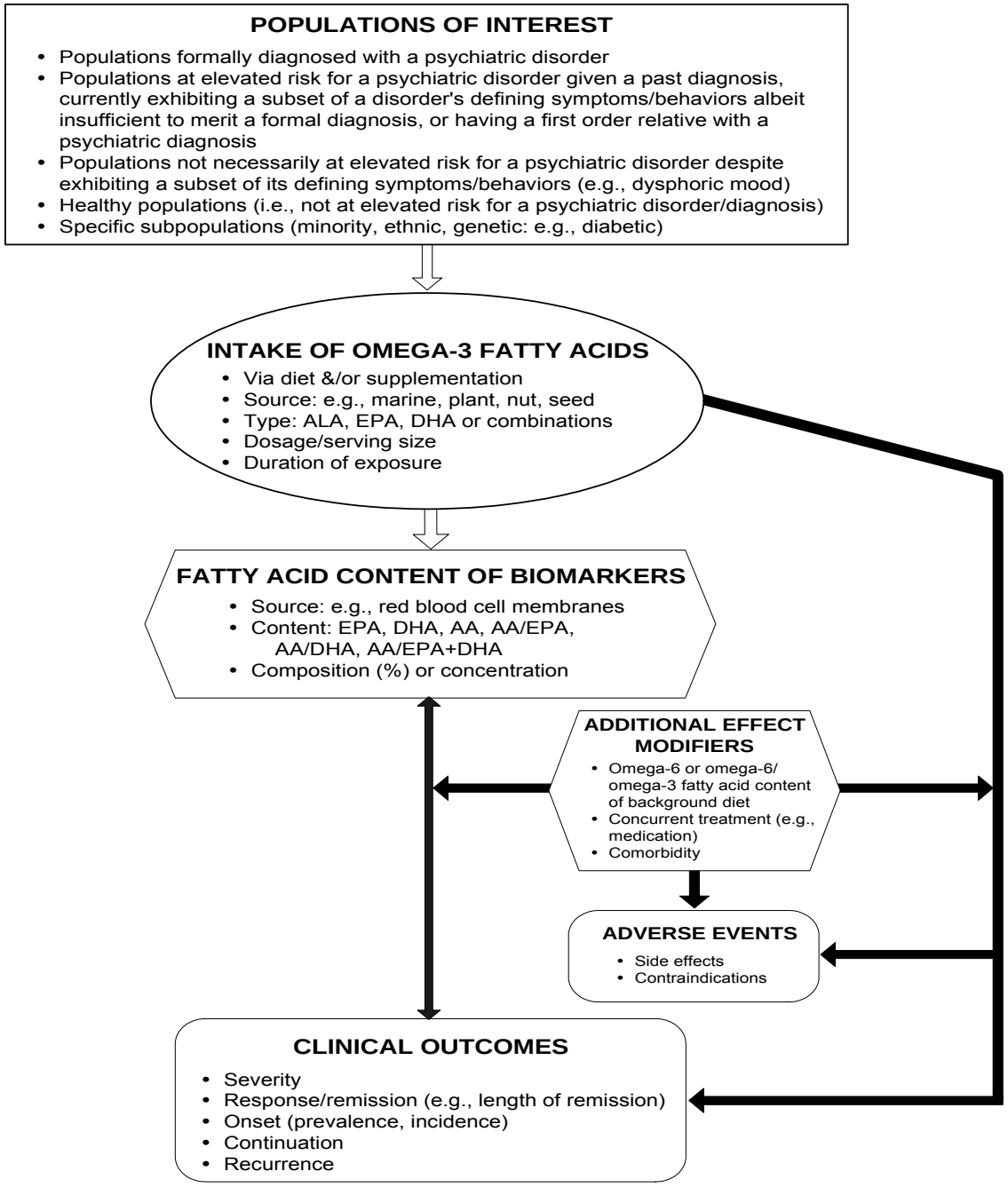
Analytic Framework

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

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

task order is to afford a clinically-relevant research agenda, this decision was judged to be appropriate by both our TEP and our review team. Thus, excluded were studies whose sole focus was to examine the impact of omega-3 fatty acid interventions or exposures on the omega-3 or omega-6/omega-3 fatty acid content of biomarkers, even if the study populations met the other eligibility criteria set for the present review. Each of the four basic questions outlined above is now seen in light of the links identified in the framework.

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



The populations of interest include those:

- with a current psychiatric diagnosis (Population 1);
- at elevated risk to develop a psychiatric disorder or condition by virtue of certain past or present events (i.e., a past psychiatric diagnosis; currently experiencing a subset of symptoms/behaviors with the potential [e.g., intensity] to develop into a full-fledged disorder; having a first order relative with a psychiatric diagnosis) (Population 2);
- who are not necessarily at risk to develop a psychiatric disorder despite currently experiencing a subset of its symptoms/behaviors (Population 3);
- "healthy" individuals who, under certain circumstances (e.g., stress) may exhibit a subset of symptoms/behaviors necessary yet insufficient to indicate a psychiatric disorder (e.g., aggression) (Population 4); and,
- specific subpopulations, some of whose characteristics may predispose them to develop or avoid developing psychiatric difficulties (Population 5).

Our TEP requested that studies investigating the fourth population category be included in the review. As the four basic questions are introduced, and their important linkages are highlighted within the framework, the relevant populations are identified. The fifth category of population, or specific subpopulations, could be examined with respect to each of the four basic questions.

Questions pertaining to the efficacy of omega-3 fatty acids as primary or supplemental treatment (i.e., Question 1) entail a direct investigation of their potentially beneficial influence on clinical outcomes. Pertinent populations include the first three delineated above, that is, those individuals with a psychiatric diagnosis or a psychiatric condition at the time of the study, the latter including symptoms/behaviors insufficient to merit a formal diagnosis (e.g., dysphoric mood). Outcomes could involve changes in symptom severity, time to a treatment failure, or remission of the disorder.

The question regarding the possible association between the intake of omega-3 fatty acids and the onset, continuation or recurrence of a psychiatric disorder or condition (i.e., Question 2) examines whether intake protects individuals from developing, or perhaps predisposes them to develop, a psychiatric disorder or a subset of its symptoms/behaviors (i.e. onset). The question also examines whether omega-3 fatty acid intake influences the clinical course or outcome of a psychiatric disorder or condition insofar as it could facilitate or prevent its continuation (e.g., progression of a condition so that it becomes a disorder; progression of a disorder) or recurrence. Relevant populations for the "onset" subquestion include those in Population 4 (i.e., "healthy" individuals), those belonging to "at risk" Population 2 with a psychiatrically diagnosed first order relative, or those in either Populations 2 or 3 who might be exhibiting a psychiatric condition that could develop into a full-fledged disorder. For the "continuation" subquestion, pertinent populations include Populations 1 (i.e., a current psychiatric disorder), 2 or 3 (i.e., a current psychiatric condition). The "recurrence" focus includes Population 2 (i.e., past diagnosis). Outcomes could include prevalence and incidence, as well as indices of secondary prevention. The latter could be observed where amounts or types of fatty acid intake prevent the intensity of

a psychiatric condition (e.g., dysphoric mood) from increasing and contributing to the development of a full-fledged disorder (e.g., major depression).

Results from relevant studies (see Eligibility Criteria) with respect to Questions 1 and 2, which reflect the possible influence of interventions/exposures on the omega-3 or omega-6/omega-3 fatty acid content of biomarkers (see their definition in Eligibility Criteria section), are highlighted briefly and exclusively with an *exploratory* intention since reliable associations between biological and clinical effects could suggest a mechanism by which omega-3 fatty acid interventions/exposures bring about improved clinical outcomes.

The question regarding the possible association between the omega-3 or omega-6/omega-3 fatty acid content of biomarkers and the onset, continuation or recurrence of a psychiatric disorder or condition (i.e., Question 3) investigates whether certain levels of fatty acid content (i.e., composition, or concentration) in blood lipid biomarkers (e.g., RBCs, plasma phospholipids) protect individuals from developing, or perhaps predispose them to develop, psychiatric disorders or subsets of their symptoms/behaviors (i.e. onset). The question also examines whether certain levels of fatty acid content in blood lipid biomarkers can influence the clinical course or outcome of a psychiatric disorder or condition by facilitating or preventing their continuation (e.g., progression of a condition so that it becomes a disorder; progression of a disorder) or recurrence. Relevant populations for the "onset" subquestion include those in Population 4 (i.e., "healthy" individuals), those belonging to "at risk" Population 2 with a diagnosed first order relative, or those in either Populations 2 or 3 who might have a psychiatric condition that could develop into a full-fledged disorder. For the "continuation" subquestion, pertinent populations are Populations 1 (i.e., a current psychiatric disorder), 2 or 3 (i.e., a current psychiatric condition). The "recurrence" focus includes Population 2 (i.e., a past diagnosis). Outcomes could include prevalence and incidence, although observing that a certain fatty acid composition in biomarkers prevents the intensity of a psychiatric condition (e.g., dysphoric mood) from increasing and contributing to the development of a full-fledged disorder (e.g., major depression) could indicate secondary prevention. Question 4 is addressed using safety data from studies meeting eligibility criteria.

The possible influence of predefined effect modifiers is evaluated in relation to each of the basic questions. Where possible, question-specific sections titled "Impact of Covariates and Confounders" elucidate a) those variables (e.g., omega-3 fatty acid type; comorbid conditions; psychotropic medication) that were consistently observed, across reviewed studies, to influence study outcomes as well as b) those variables (e.g., age, sex), which having been controlled for either experimentally or analytically in reviewed studies, were observed to consistently influence, or consistently fail to influence, study outcomes.

Study Identification

Search Strategy

The search strategy for this project was designed to be comprehensive and achieve the highest possible recall of relevant clinical studies. The electronic search strategy was developed by an information specialist in consultation with clinical content experts in mental health. Because of the number of conditions falling under the rubric of mental health, the mental health

subject tree and index terms for suicidal, aggressive and impulsive behavior was used, rather than terms appearing in free text. For those with less robust subject indexing in the area of mental health, supplemental free text terms were added to the electronic search strategy (CDSR, CAB Health). The mental health search concept was combined with the core omega-3 fatty acids search strategy established in collaboration with the project librarians, biochemists, nutritionists, and clinicians from the three EPCs involved in the 2-year, Health Benefits of Omega-3 Fatty Acids task order. Consultation among these sources provided the biochemical names and abbreviations of omega-3 fatty acids, names of commercial omega-3 fatty acids products, and food sources of omega-3 fatty acids.

The following electronic databases were searched: Medline (1966 – November Week 2 2003 and updated to April Week 3 2004), Embase (1980 to 2003 Week 48 and updated to 2004 Week 18), the Cochrane Library including the Cochrane Central Register of Controlled Trials (3rd Quarter 2003), PsycInfo (1982 to December Week 1, 2003) and CAB Health (1973-Sept 2003). All databases were searched via the Ovid interface using Search Strategy 1 (Appendix A*), except CDSR where we used Search Strategy 2 (Appendix A*) and CAB Health, which was searched through SilverPlatter using Search Strategy 3 (Appendix A*). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH term "dietary fats," which was limited by study design to increase its specificity. A total of 1606 bibliographic records were downloaded, with 410 duplicate records identified and removed using citation management software (Reference Manager®).

Reference lists of included studies, book chapters, and narrative or systematic reviews retrieved after having passed the first level of relevance screening, were manually searched to identify additional unique references. Through contact with content experts, attempts were made to identify both published and unpublished studies. On behalf of the three EPCs investigating the evidence concerning the health benefits of omega-3 fatty acids, a letter was written to industry representatives to obtain additional evidence (Appendix B*). Unsuccessful attempts were made to contact the lead author of a recent Cochrane Collaboration systematic review of PUFA supplementation for schizophrenia to obtain unpublished data they claimed to have received from investigators.[61] These supplementary efforts identified an additional 16 records that were added to the collection for review. A final set of 1,212 unique references was identified.

Eligibility Criteria

Published and unpublished studies, written in any language, were eligible for inclusion. Excluding grey literature from systematic reviews of interventions can lead to the overestimation of effect sizes.[62] Substantial bias in the results of a systematic review pertaining to a complementary/alternative medical (CAM) intervention can ensue from the exclusion of data from reports written in languages other than English.[63] AHRQ and ODS consider omega-3 fatty acids to be a CAM exposure.

Data from live human study populations or subpopulations (e.g., genetic, minority, ethnic: e.g., diabetic) of any age were required to maximize generalizability. Study populations in treatment studies, as well as in those investigating the possible association of the onset, continuation or recurrence of psychiatric disorders or conditions with either the intake of omega-

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

3 fatty acids or the fatty acid content of biomarkers had to have been assessed using any formal psychiatric diagnostic criteria (e.g., DSM-IV) or established psychiatric research instruments (e.g., Hamilton Depression Rating Scale). Our TEP requested that we investigate both psychiatric disorders and psychiatric conditions (i.e., behaviors, symptoms: e.g., dysphoric mood), recognizing that while the latter are necessary to identify a psychiatric disorder, alone they are insufficient to signal the presence of one (e.g., major depression). Any and all types of comorbid condition were eligible. Studies conducted in any era of psychiatric practice were considered candidates for inclusion.

The specific types of population required to address each of the basic research questions are described with reference to the analytic framework and those details are not repeated here. As one point of clarification, our TEP asked that, within the context of assessing the possible association between omega-3 fatty acid intake and psychiatric disorders or conditions (Question 2) we should review studies examining the possible protective effects of omega-3 fatty acid intake on the development of maladaptive behavior in populations presumed to be "healthy" (e.g., college volunteers), yet who might, for example, develop evidence of disrupted well-being when subjected to stressful circumstances. Excluded populations were those with degenerative (e.g., Alzheimer's) and peroxisomal (e.g., Zellweger's) disorders since each was addressed in SC-RAND's year-2 review of the evidence concerning omega-3 fatty acids in neurology.

Treatment studies, as well as those investigating the possible association between omega-3 fatty acid intake and the onset, continuation or recurrence of specific psychiatric disorders or conditions, had to specifically investigate foods or supplements known to contain omega-3 fatty acids of any type (e.g., EPA, ALA), from any source (e.g., fish, walnuts, seed oil), any serving size or dose, delivered in any fashion (e.g., capsules, liquid, PUFA-rich diet), and for any length of time. In all studies, some method had to have been employed to suggest the presence of omega-3 fatty acid content in the exposure, if not its actual amount (e.g., g/d). Studies investigating "PUFAs" or " LC PUFAs," or even types of diet one might presume would contain marine or land sources of omega-3 fatty acids (e.g., "Mediterranean diet") at minimum had to highlight at least one source of the omega-3 fatty acid content (e.g., oily fish servings). No restrictions were placed on the types or doses of pre- or on-study cointerventions (e.g., medication, omega-6 fatty acid intake, other dietary supplements).

Controlled studies were required to address questions of intervention efficacy or effectiveness, with randomized controlled trials (RCTs) being the gold standard method to investigate these questions (Question 1).[64] Any definition of control, or comparator, was permitted. RCTs exhibit a greater inherent potential to deal with potentially serious biasing influences (e.g., selection bias) although a poorly designed or conducted RCT can produce results whose interpretability is no less complicated by the presence of confounding influences, for example, than observations derived from a well-constructed and conducted study employing a design with a lesser intrinsic capacity to control for these biases (e.g., non-RCT; prospective cohort study). For example, not all RCTs succeed, either through an explicit experimental plan or the process of randomization per se, to equally distribute known confounding influences (e.g., background diet; energy/caloric intake from the intervention; types and doses of psychotropic medication) across study arms in intervention studies. That said, our TEP asked that we identify all excluded uncontrolled studies with respect to questions of intervention efficacy/effectiveness so that future synthesis work could begin with these data. We achieved this by adding a third level of screening, which yielded a listing of citations for these excluded studies (see Study Selection Process section for details).

Any type of research design other than noncomparative case series or case studies was deemed appropriate for questions concerning the possible association between the intake of omega-3 fatty acids and the onset, continuation or recurrence of psychiatric disorders or conditions (Question 2). Often, but not exclusively, relevant data were generated by cross-sectional surveys involving a single sample. A special interpretative emphasis was placed on results from prevention RCTs and other controlled prospective designs.

Controlled studies were required to address the questions of the possible association between the fatty acid content of biomarkers and the onset, continuation or recurrence of psychiatric disorders or conditions (Question 3). Evidence of the possible role played by the fatty acid content of biomarkers in the etiology of schizophrenia, for example, requires derivation from controlled designs although not all of these designs are equal in their capacity to generate data directly pertinent to Question 3. A special interpretative emphasis was thus placed on results from prospective controlled designs, with cross-sectional studies yielding the least direct evidence.

Overall, any and all clinical outcomes were considered relevant, including symptom severity or control, response rate, incidence, prevalence or diagnostic status (e.g., case-control or cross-sectional studies). As markers of omega-3 fatty acid metabolism, the following fatty acid compositions or concentrations, from any source (e.g., red blood cell [RBC] membranes, plasma phospholipids), were considered relevant in intervention studies (i.e., exclusively as an exploratory focus on the possible covariation of clinical and biomarker effects, or correlations between these factors) or as possible predictors of the onset, continuation or recurrence of psychiatric disorders or conditions: EPA, DHA, AA/EPA, AA/DHA, AA/EPA+DHA. Studies exclusively evaluating the role of other biomarkers (e.g., cytokine production, eicosanoid levels) were not included. These decisions were made with the assistance of our TEP.

Study Selection Process

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

Following a calibration exercise, which involved screening five sample records using an electronic form developed and tested especially for this review (Appendix C[*]), two reviewers independently screened the title, abstract, and key words from each bibliographic record for relevance by liberally applying the eligibility criteria. A record was retained if it appeared to contain pertinent study information. If the reviewers did not agree in finding at least one unequivocal reason for excluding it, it was entered into the next phase of the review. The

[*]**Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

reasons for exclusion were noted using a modified QUOROM format (Appendix D*).[65] The screening process also aimed to identify the exact mental health question a record addressed, in addition to determining whether it might also or instead pertain to any of the other topics being systematically reviewed by the three EPCs in year 2 of the omega-3 fatty acids project.

Print or electronic copies of the full reports for those citations having passed level one screening were then retrieved. After completing a calibration exercise which involved evaluating five sample reports using the same eligibility criteria (Appendix C*), the rest of the reports were independently assessed by two reviewers. Reports were not masked given the equivocal evidence regarding the benefits of this practice.[66] To be considered relevant at this second level of screening, all eligibility criteria had to be met. Implementing the recommendations of our TEP, a third level of dual-reviewer screening was used to exclude, yet at the same time to identify, studies addressing questions of intervention efficacy/effectiveness employing uncontrolled research designs.

Disagreements arising at either screening levels 2 or 3 were resolved by forced consensus and, if necessary, third party intervention. Excluded studies at each of these levels are noted as to the reason for their ineligibility in listings found at the end of this report.

Data Abstraction

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

- report (e.g., publication status, language of publication, year of publication);
- study (e.g., sample size; research design; number of study arms/groups, cohorts, or phases; funding source);
- population (e.g., age; percent males; diagnosis description, including severity, duration, and comorbid conditions);
- intervention/exposure (e.g., omega-3 fatty acid types, sources, doses, and intervention/exposure length), and comparator(s);
- cointerventions (e.g., concurrent medications, omega-6 fatty acid use);
- withdrawals and dropouts, including reasons;
- clinical outcomes;

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

- fatty acid content of biomarkers; and,
- adverse events (e.g., side effects).

Summarizing the Evidence

Overview

The evidence is presented in three ways. Evidence tables in the Appendices offer a detailed description of the included studies (e.g., study design, population characteristics [e.g., diagnosis], intervention/exposure characteristics [e.g., omega-3 fatty acid types and doses], cointervention [e.g., background diet, concurrent medication]), with a study represented only once. These tables are organized by research design (Table 1: experimental studies [e.g., treatment RCTs]; Table 2: observational studies [e.g., cross-sectional studies examining the possible association of the omega-3 or omega-6/omega-3 fatty acid content of biomarkers with the onset, continuation or recurrence of a specific psychiatric disorder or condition]; Table 3: cross-national ecological analyses [e.g., studies addressing the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of a specific psychiatric disorder or condition), with studies arranged alphabetically within each of the three table/design categories.

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

Study Quality

Study quality refers to the internal validity, or methodological soundness, of a study. A systematic review can be faced with great variability in the quality of its included studies. Our approach is not to use a minimal level of quality as an inclusion criterion since this precludes assessing the possible impact of study quality on study results.

A study with low quality can make it difficult to clearly and meaningfully interpret its results, that is, to unequivocally attribute a significant observed benefit exclusively to an intervention/exposure (as opposed to other factors). Since definitions, or standards, of study quality can depend on the type of research design, different constructs were selected to evaluate, from study reports, the quality of RCTs and studies employing other types of research design. After a calibration exercise involving two studies with an RCT design, two assessors independently evaluated study quality. Disagreements were resolved via forced consensus. In the case of designs other than RCTs, a single experienced quality assessor performed the evaluations. Time did not permit their dual assessment.

Four fundamental quality constructs from two instruments were used to rate the internal validity of RCTs. These tools were chosen collectively by the three EPCs involved in the 2-year

task order because they have been validated. The Jadad items[67] assess the reporting of randomization, double blinding, and, withdrawals and dropouts (Appendix C*). Total scores range from 0 to 5, with a score less than 3 indicating low quality. The reporting of the concealment of a trial's allocation to treatment[68] yields three grades (A = adequate; B = unclear; C = inadequate) (Appendix C*).

The assessment of the quality of studies using designs other than RCTs is complicated by the dearth of validated instruments and the variety of such designs (e.g., non-randomized controlled trials; uncontrolled studies). Nevertheless, a recent systematic review by Deeks et al. identified a number of "best tools" for use with these designs.[69] Among them was a published instrument developed by Downs and Black[70] and an unpublished one derived by experts in Newcastle and Ottawa (NOS).[71] The former validated both design-specific and design-neutral items.

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

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

It was decided by our review team that, given the limitations of space, especially in print-based study reports, and the amount of detail that would likely be required to provide all of the details we needed to fully establish that only appropriate methods had been used to extract, prepare, store and analyze lipid content, it was reasonable to appraise these methods by focusing instead on identifying extant descriptions of inappropriate methods. On occasion, the inappropriateness of methods had to be determined by reference to standard protocols.

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

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* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

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

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

Study Applicability

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

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

With regards to the highest level of applicability (Level I) in the first scheme, the broadest definition of the population of interest is the otherwise "healthy" North American (or similar individual) identified with a psychiatric disorder or condition, diagnosed using a standard North American strategy and methodology/nomenclature (e.g., DSM-IV) or identified using at least one established psychiatric instrument, presenting with or without comorbid psychiatric conditions while possibly receiving "typical" North American medications for the primary

[*] **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

diagnosis, is drawn from a somewhat broad socio-demographic spectrum (i.e., gender, race), and eats a diet "typical" of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio of at least 15: see below for references). For Level I applicability in the second scheme, the broadest definition of the population of interest is the otherwise "healthy" North American (or similar) individual, presenting with or without a known elevated risk for onset of a psychiatric disorder or condition, representing a somewhat broad socio-demographic spectrum (i.e., gender, race), and eating a diet "typical" of a broad spectrum North American population (e.g., with an estimated omega-6/omega-3 intake ratio of at least 15).

Together, these level I definitions represent the respective reference points, with applicability decreasing as the definition of the sample study population narrows in terms of the factors represented in the two schemes. With respect to the scheme applied to studies with diagnosed participants, we identified what are likely the two most important variables as being the method of diagnosis and the background diet of participants leading up to the study, if not also during the study. Each defines the study population. When the second scheme is applied to studies where the participants have not yet been diagnosed with a psychiatric disorder or condition, background diet is the key variable.

The method of diagnosis is an important factor since not all countries employ the diagnostic methods or nomenclatures used most frequently in North America (e.g., DSM). Psychiatric populations identified using different approaches, even when diagnostic labels are the same, can vary in terms of what these labels refer to.[13] At the same time, different labels (e.g., "AD/HD" in North America versus "hyperactivity" in the UK) can refer to the same clinical entity. That said, the most frequently employed approaches employed in North America are considered the reference point.

Operationalized ideally in this review as the omega-6/omega-3 fatty acid ratio, background diet is an important factor in assessing both types of study population (i.e., diagnosed vs undiagnosed participants). Given the competitive relationship between omega-3 and omega-6 fatty acids, both for enzymes to yield key metabolites with specific effects in the human biosystem (see Chapter 1) and for positions in cell membranes from which to have these and other possible influences (e.g., clinical improvement or prevention), the absolute and relative intake of omega-3 and omega-6 fatty acids from all sources, and not just from the identified exposure, likely need to be taken into account when deciding whether populations assessed in different studies are comparable. The likelihood of biological and/or clinical effects in studies may turn out to vary depending on these absolute or relative intake values. A high background dietary omega-6/omega-3 fatty acid intake ratio—potentially reflected in a corresponding differential in these contents in cell membranes—may make it harder for omega-3 fatty acid supplementation to make a clinically meaningful difference,[72] although already having considerable omega-3 fatty acid content in the background diet and in cell membranes because of a low omega-6/omega-3 fatty acid intake ratio may make it difficult for typically small amounts of omega-3 fatty acid supplementation to make a clinically meaningful difference (see Discussion).

Irrespective of which of these hypotheses may be eventually confirmed elsewhere, the fact that national, and sometimes regional, populations can vary in terms of their diet's omega-6/omega-3 fatty acid intake ratio strongly suggests that this potential confounding influence on study outcomes needs to be represented in the applicability schemes whereby the North American value is the reference point. The typical North American diet contains an omega-

6/omega-3 fatty acid intake ratio of at least 15, while urban India and Japan's corresponding values are 38-50 and 4, respectively.[33-45]

UK populations represent somewhat of a special case in that, while they often use the same diagnostic methods and research instruments to identify psychiatric disorders and conditions in populations, respectively, and while they can exhibit socio-demographic pictures similarly broad to the ones seen in North American study populations, their somewhat different lifestyle and background diet recommended an applicability value of "II." However, if participants were drawn from a narrower UK population, then a "III" was assigned. Given their inclusion of multi-national populations, with or without representation from the U.S. or Canada, cross-national ecological analyses necessarily received a "III." One experienced assessor evaluated study applicability.

Summary Matrix

For a given research question, and where possible (e.g., more than one study addressing the question), a summary matrix situates the pertinent studies in terms of their respective study quality (internal validity) and applicability (external validity) values. The Jadad total quality score defined RCTs' internal validity in summary matrices. A three-level format was derived from the range of possible RCT quality scores (A = Jadad total score of 4 or 5; B = Jadad total score of 3; C = Jadad total score of 0, 1 or 2). Given that allocation concealment scores have in the past tended to vary less widely than Jadad total scores, allocation concealment values were entered as superscripts in the summary matrices.[72] A similar approach was taken for the studies employing other research designs. The following cutpoints were established, albeit without benefit of a validational exercise:

- comparative before-after study: A = total quality score of 8-11; B = 5-7; C = 1-4;
- case-control study (NOS): A = 8-10; B = 4-7; C = 1-3;
- (multiple-group) cross-sectional study: A = 8-10; B = 4-7; C = 1-3;
- single prospective cohort study (Modified NOS): A = 8-10; B = 4-7; C = 1-3;
- cross-sectional survey: A = 8-10; B = 4-7; C = 1-3; and,
- cross-national ecological analysis: A = 7-9; B = 4-6; C = 1-3.

The three-level applicability format was established by the 3 EPCs involved in the 2-year project for practical reasons, to permit the incorporation of quality scores within a summary matrix. Studies assigned an "X" (i.e., insufficient information to establish applicability) were excluded from summary matrices.

Qualitative Data Synthesis

An overarching qualitative synthesis describes the progress of each citation, then report, through the stages of the systematic review. It also highlights certain report and study design

characteristics of included studies (e.g., distributions of research design by research question). Then, for each question, a separate qualitative synthesis is derived for included evidence, organized by broad categories of research design (i.e., experimental studies vs observational studies vs cross-national analyses). A brief study-by-study overview typically introduces the synthesis, followed by a narrative summary of the key defining features of relevant studies (e.g., inclusion/exclusion criteria), including their populations (e.g., diagnosis-related), intervention/exposures (e.g., types of omega-3 fatty acid), cointerventions (e.g., psychotropic medication), outcomes, study quality, applicability and results. Whether or not data can be organized according to these subheadings depends on the number of studies addressing a given question and the amount or variety of detail available in the study reports. For example, having identified too few studies per research question that do *and* do not exhibit significant effects for a given clinical outcome can preclude determining the impact of covariables with the potential to modify or confound study results (e.g., type or dose of omega-3 fatty acids).

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

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

Quantitative Data Synthesis

Given its greater potential to control for possible confounding factors, only RCT evidence regarding the question of interventions' efficaciousness was considered for inclusion in meta-analysis. All things being equal, it was also assumed that priority in meta-analysis might be given to clinical outcomes pertinent to the present day practice of psychiatry and psychology.

Providing the result would have a clearly defined population to which to generalize a synthetic result, and that sufficient numbers of prospective controlled studies exist (e.g., RCT; cohort study), meta-analysis was considered with respect to data investigating questions of the possible association of the onset, continuation or recurrence of a psychiatric disorder or condition with either the intake of omega-3 fatty acids or the PUFA content of biomarkers. Prospective controlled designs constitute the most appropriate way to establish these risk-relationships among variables. Decisions regarding statistical models are provided where results of meta-analysis are reported. Reasons to forego meta-analysis are likewise described.

Chapter 3. Results

Results of Literature Search

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

Of 1,212 records entered into the initial screening for relevance, 955 were excluded. Reflecting the specific eligibility criteria, the reasons for exclusion were: a. not a first publication of empirical evidence (e.g., a review; n = 500); b. not involving human participants (n = 216); c. no omega-3 fatty acid focus (i.e., intervention/exposure or biomarkers) (n = 167); and, d. not related to predefined mental health outcomes (n = 72). All but 7[73-79] of the remaining 257 reports were then retrieved and subjected to a more detailed relevance assessment. Of those 7 reports which were not retrieved, one was an abstract[77] whose study results may have been published subsequently as a journal article included in the review.

A second relevance screening then excluded 137 reports for the following reasons: a. not a first publication of empirical evidence (e.g., a review; n = 91); b. not involving human participants (n = 7); c. no omega-3 fatty acid focus (i.e., intervention/exposure or biomarkers) (n = 23); and, d. not related to predefined mental health outcomes (n = 16). Finally, a third relevance screening level excluded 27 uncontrolled studies failing to meet eligibility criteria regarding the questions of the efficacious nature of omega-3 fatty acid interventions or the possible assocation of the fatty acid content of biomarkers with the onset, continuation or recurrence of psychiatric disorders or conditions.

In total, 86 reports, describing 79 unique studies, were deemed relevant for the systematic review, with 6 studies each described by more than one report. The specific relationships between studies and reports are identified in the next paragraph. As stated earlier, the two listings of studies excluded as a result of appraisals of full reports are presented at the end of this document.

When the lead author of the Tanskanen et al. studies was contacted because their two studies appeared to be similar,[80,81] he clarified that the studies, and their study populations, were non-overlapping. As introduced above, on occasion multiple reports published or presented in different places did describe the same study. To afford transparency for those considering replicating or updating our work, we identify these relationships at this time. Hibbeln[47] included Weissman et al.'s[46] data as part of their cross-national ecological analysis. Edwards et al.'s data[48] were first disseminated in an abstract.[82] Likewise, Peet et al.'s publication, describing their study of the primary treatment of schizophrenia,[58] was preceded by an abstract.[83] Peet and Mellor's abstract[84] became available before their data, concerning the supplemental treatment of schizophrenia, were published.[58] Two abstracts[85,86] also reported Peet and Horrobin's data

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

regarding the supplemental treatment of schizophrenia.[87] Two additional analyses[60,88] extended Fenton et al.'s initial work.[89] To avoid confusion in the text, evidence tables, summary tables and figures, only one report is used to refer to a given study and its data. It is typically the first, or "parent," publication. Peet et al.'s report, describing two relevant studies (primary vs supplemental treatment of schizophrenia),[58] is represented twice in Evidence Table 1 (see Appendices*).

Some studies provided data addressing more than one research question. For example, Noaghiul and Hibbeln's cross-national ecological analysis evaluated the possible association of seafood consumption with bipolar disorder and with schizophrenia.[90] Mellor et al.'s study investigated the possible associations of schizophrenia outcomes with the dietary intake of omega-3 fatty acids as well as with the omega-3 and omega-6/omega-3 fatty acid content of biomarkers.[91] However, Mellor et al.'s subsequent intervention study, described in the same report, was not eligible for the present review because it employed an uncontrolled design.

To help guide the reader, a table appears at the end of this report, which lists the studies addressing each question. The questions are organized by the order in which they are addressed in the text. Only the first, or "parent," report is represented in the table.

Report and Study Design Characteristics of Included Studies

Of the included studies, only one failed to be described by at least one published report.[92] It was reported in abstract form. Another included report was a published letter to the editor, which while reporting the use of omega-3 fatty acids for a problem outside the scope of the present review (i.e., lithium-induced psoriasis), it referred to the source of these data as being a placebo-controlled trial investigating the supplemental treatment of bipolar disorder.[93] Of the 16 relevant studies identified by manual search, only one was disseminated in a format other than a journal publication.[92] All but one of the included reports (all published), which required translation from Chinese,[94] were written in English.

As an overview, the number of included studies investigating each of the three basic questions are described, distinguished by psychiatric disorder, or condition, and by research design. A given study may have addressed more than one basic question.

Twenty-two unique studies investigated the first three basic questions concerning depression. Of these, seven were RCTs,[53,95-100] seven were multiple-group cross-sectional studies,[48,101-106] three were single population cross-sectional surveys,[80,81,107] three were cross-national ecological analyses[47,108,109] and two were single prospective cohorts.[110,111] Four RCTs examined omega-3 fatty acids as either a primary[95] or supplemental treatment.[53,96,97] Three RCTs,[98-100] three cross-national ecological analyses,[47,108,109] three single population cross-sectional surveys,[80,81,107] one multiple-group cross-sectional study[48] and two single prospective cohorts[110,111] comprised the twelve studies investigating the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of depression. One RCT[98] and seven multiple-group cross-sectional studies[48,101-106] looked at the possible association of the onset, continuation or recurrence of depression with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.

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Two studies, one a single prospective cohort[111] and the other a single population cross-sectional survey,[80] investigated the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of suicidal ideation or behavior. Five unique studies investigated three basic questions concerning bipolar disorder. Two studies, one RCT[112] and one defined merely as "controlled,"[93] evaluated the supplemental treatment of bipolar disorder. One cross-national ecological analysis[90] examined the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of bipolar disorder. Two multiple-group cross-sectional studies looked at the possible association of the onset, continuation or recurrence of bipolar disorder with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[113,114]

Two RCTs investigated the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of anxiety.[99,100] One crossover RCT studied the supplemental treatment of obsessive-compulsive disorder.[115] Two multiple-group cross-sectional studies examined the possible association of the onset, continuation or recurrence of anorexia nervosa with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[116,117]

Ten unique studies assessed the first three basic questions pertaining to AD/HD. These studies were the only ones in the review that investigated children. Three RCTs,[118-120] with one facet of one of them[118] centered on children not receiving medication, and one comparative before-after study,[121] investigated the primary treatment of AD/HD. One of the same RCTs,[118] this time looking exclusively at children receiving medication, and two other RCTs,[122,123] evaluated the supplemental treatment of AD/HD. One multiple-group cross-sectional study investigated the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of AD/HD.[94] Three multiple-group cross-sectional studies examined the possible association of the onset, continuation or recurrence of AD/HD with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[124-126] One single population cross-sectional survey assessed the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of mental health difficulties.[127]

Ten unique studies investigated two of the three basic questions regarding tendencies or behavior with the potential to harm others. Five RCTs,[99,128-131] one single population cross-sectional survey[132] and one cross-national ecological analysis,[133] studied the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of these tendencies or behavior. Three multiple-group cross-sectional studies examined the possible association of the onset, continuation or recurrence of these tendencies or behavior with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[134-136] Two multiple-group cross-sectional studies investigated the possible association of the onset, continuation or recurrence of alcoholism with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.[137,138] One RCT studied the primary treatment of borderline personality disorder.[139]

Twenty-eight unique studies investigated the first three basic questions concerning schizophrenia. One RCT[58] studied the primary treatment of schizophrenia and four RCTs[58,87,89,140] investigated the supplemental treatment of schizophrenia. Five case-control designs,[92,141-144] one single prospective cohort[91] and three cross-national ecological analyses[90,109,145] assessed the possible association of omega-3 fatty acid intake with the onset, continuation or recurrence of schizophrenia. Twelve multiple-group cross-sectional studies[114,146-156] and two single prospective cohort studies[157,158] investigated the possible association of the onset, continuation or recurrence of schizophrenia with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers.

One multiple-group cross-sectional study[159] examined the possible association of the onset, continuation or recurrence of autism with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers. Ten RCTs described adverse event (e.g., side effects) data associated with an omega-3 fatty acid intervention/exposure (Question 4),[53,58,87,89,95,96,112,119,129,130] with two of these trials involving healthy volunteers.[129,130]

The remainder of this chapter is organized by disorder or condition, with the evidence addressing each of its first three basic questions presented in turn. If a question is not represented in the report, there was no evidence that met eligibility criteria. Safety data are presented last. We begin with mood disorders.

Are Omega-3 Fatty Acids Efficacious as Primary Treatment for Depression?

As observed in Summary Table 1 (below), derived from Evidence Table 1 (Appendix E*), only one controlled study (2003) employing an RCT design met eligibility criteria in investigating the question of omega-3 fatty acids' possible efficaciousness as a primary treatment for depression.

Overview of Relevant Study's Characteristics and Results

Likely at one US site, Marangell et al. randomized 36 adult outpatients (18-65 years; racial/ethnic background unreported) meeting DSM-IV criteria for major depressive disorder (duration unreported), without psychotic features, to receive either 2 grams per day (2 g/d) DHA or placebo (source undefined) in a 6-week parallel design (followups at 2 and 6 weeks).[95] Inclusion criteria were a score of at least 12 on the Montgomery-Asberg Depression Rating Scale (MADRS), a score of at least 17 on the Hamilton Depression Rating Scale (HDRS), no psychotropic medication for at least 2 weeks, and dietary intake of no more than one fish serving per week. Exclusion criteria included any significant comorbid psychiatric or medical conditions, and a lifetime failure of at least two adequate antidepressant trials. Clinical response was the primary outcome, and was defined as a mimimum 50% reduction, from baseline to 6 weeks, on the MADRS. Funding was provided by way of an investigator-initiated grant from Martek Biosciences Corporation.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 1: Omega-3 fatty acids as primary treatment for depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Notable biomarker effects[2,3]	Internal validity	Applicability
Marangell, 2003, US: 6 wk parallel RCT[95]	2g/d DHA (n=18)	pb (source undefined) (n=18)	NS MADRS response rate; NS after adjusting for baseline HDRS score	↑ absolute RBC DHA only in DHA grp;$^{++++}$ RBC DHA (% wt of total FAs) ↑ only in DHA grp	Jadad total: 2 [Grade: C]; Schulz: Unclear	X

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; MADRS = Montgomery-Asberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; RBC = red blood cells; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Response rates were 27.8% and 23.5% in the DHA (n=18 with at least one followup) and placebo groups (n=17), respectively, with the difference failing to reach statistical significance in an intention-to-treat analysis (ITT). This null finding held after an adjustment for baseline HDRS score. The two groups did not vary in terms of age, percent male participants, alcohol intake, or education. The placebo group comprised a significantly greater number of smokers and a lower weight. Both at baseline and at study endpoint the placebo group exhibited a significantly higher HDRS score. Only in the DHA group did the absolute level of RBC DHA content increase in statistically significant fashion from baseline to endpoint, whereas a report of a similar difference in the change in DHA's percent weight of total fatty acids was not accompanied by results of a statistical test of significance. No information was provided regarding the reason one participant in the placebo group did not reach final followup.

A summary matrix is not required for a single study. Study quality assessed via the Jadad total score was low, with insufficient clear information preventing us from concluding that the allocation to study groups had likely been adequately concealed. There were insufficient details reported by Marengell et al. to permit the determination of a level of applicability even though the trial appeared to have been conducted in the US.

This was a single study with a limited sample size and a limited complexity to its design (e.g., no stratification for covariates). Thus, other than the observation that the possible confounding impacts of certain factors (e.g., between-group differences or on-study changes in psychotropic medication type or dose; alcohol intake; education, age, sex) were likely controlled in this primary treatment study, little can be said about the possible impact of additional factors with the potential to influence mental health outcomes. Yet, one factor with the potential to influence these outcomes, current smoker status, was not distributed equally across study groups although the observation that more placebo group members were smokers makes it difficult to see how this may have contributed to a null between-group difference in the primary clinical outcome. This between-group difference could have influenced the observations of a between-group difference in changes in RBC DHA content, however, given the effects of smoking on

EFA status.[60] The restriction on weekly fish intake likely made study groups somewhat more comparable. Meta-analysis was considered unnecessary.

Are Omega-3 Fatty Acids Efficacious as Supplemental Treatment for Depression?

As observed in Summary Table 2 (below), derived from Evidence Table 1 (Appendix E[*]), three RCTs met eligibility criteria in investigating omega-3 fatty acids' possible efficaciousness as supplemental treatment for depression. Studies were published in 2002 or 2003.

Overview of Relevant Studies

Peet and Horrobin conducted a dose-ranging study of the effects of ethyl eicosapentaenoate (E-EPA: i.e., a pure ethyl ester derivative of EPA) in adult outpatients (n=70; 18-70 years) identified with persistent depressive symptomatology despite ongoing treatment with an adequate dose (undefined) of a standard antidepressant (Summary Table 2).[53] Recruited by family physicians, study participants were randomized into a 12-week parallel RCT (followups at 4, 8 and 12 weeks) on a double-blind basis to receive either placebo (liquid paraffin) or total doses of 1 g/d, 2 g/d or 4 g/d E-EPA via 500 mg soft gelatin capsules (taken morning and evening). The primary outcome was HDRS score, with the MADRS and the patient-completed Beck Depression Inventory (BDI) serving as secondary outcome measures.

[*] **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 2: Omega-3 fatty acids as supplemental treatment for depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Notable biomarker effects[2,3]	Internal validity	Applicability
Peet, 2002, England & Scotland: 12 wk parallel RCT[53]	4g/d E-EPA (n=17)/ liquid paraffin pb (n=18)	2g/d E-EPA (n=18)/ 1g/d E-EPA (n=17)	All ITT & PP analyses of HDRS, MADRS & BDI showed ↑ ↓'s only for 1g/d grp at 12 wk$^{+ - +++}$	n/a	Jadad total: 4 [Grade: A]; Schulz: Adequate	II
Nemets, 2002, Israel: 4 wk parallel RCT[97]	2g/d E-EPA (n=10)	pb (source undefined) (n=10)	2g/d E-EPA showed ↑ HDRS ↓'s at 2,$^{+++}$ 3^{+++} & 4 wk^{+++}	n/a	Jadad total: 4 [Grade: A]; Schulz: Unclear	III
Su, 2003, China: 8 wk parallel RCT[96]	4.4g/d EPA + 2.2g/d DHA (n=14)	olive oil ethyl ester pb (n=14)	6.6g/d showed ↑ HDRS ↓'s at 4,$^{+++}$ 6,$^{+++}$ & 8 wk;$^{+++}$ rate of ↓ in HDRS ↑ in EPA grp^{++}	↑ RBC DHA for EPA grp only;$^{+}$ NS ↑ in RBC EPA for both grps	Jadad total: 3 [Grade: B]; Schulz: Unclear	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; MADRS = Montgomery-Asberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; RBC = red blood cells; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ITT = intention-to-treat analysis; PP = per-protocol analysis (e.g., completers); ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Nemets et al. randomized 20 Israeli outpatients (mean age: 53.4 [28-73] years), meeting DSM-IV criteria for a current diagnosis of major depressive disorder, to receive either 2 g/d E-EPA derived from 96% pure fish oil (stabilized with 0.2% vitamin E) or matching placebo (undefined) given in 1 g doses twice daily (via 50 0mg soft gelatin capsules) for 4 weeks.[97] Only one patient did not continue receiving the antidepressant treatment they had been taking for at least 3 months, making this male's trial an evaluation of the impact of E-EPA as a primary treatment. He was exhibiting a 4-month severe depressive disorder that had been resistant to treatment with two different SSRIs. All other study participants had, in the past, suffered relapses when antidepressant doses were reduced or discontinued altogether. The primary outcome measure was the HDRS, with ratings conducted at baseline and weekly thereafter in this double-blind trial.

Su et al. conducted an eight-week, double-blind, placebo-controlled parallel RCT.[96] They compared the impact, on HDRS scores, of 6.6 g/d of omega-3 fatty acids (i.e., 4.4 g/d EPA and 2.2 g/d DHA from menhaden fish) against placebo (i.e., olive oil ethyl ester) in 28 physically healthy outpatients diagnosed with DSM-IV major depressive disorder. Five identical gelatin capsules containing 440 mg EPA and 220 mg DHA were taken twice daily. Inclusion criteria were an HDRS score of at least 18, and no change in medication or psychotherapy 4 weeks prior to enrolment. Participants could not exhibit comorbid Axis I or Axis II psychiatric disorders, or

be receiving antipsychotics or mood stabilizers. Placebo responders (i.e., mimimum 20% decrease in HDRS score) during a pre-randomization, one-week run-in were excluded. One participant in each group was free of medication, indicating that their trials assessed the primary treatment of depression. Followups using the HDRS occurred every 2 weeks. Dietary frequency ratings, recorded food diary data, and blood samples to assess the fatty acid content of RBC membranes were assessed during the run-in and at 8 weeks.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Three parallel RCTs involving adults addressed the question (Summary Table 2; Evidence Table 1: Appendix E).[53,96,97] Only Su et al.[96] and Nemets et al.[97] provided detailed descriptions of both inclusion and exclusion criteria. Only Peet and Horrobin[53] employed a design having more than two study groups (i.e., 4). A total of 118 adult outpatients were randomized. The mean sample size for the three studies was 39.3 (range: 20-70) participants, with the Peet and Horrobin trial being much larger than either of the other two. The studies' participants received the intervention for an average of eight (range: 4-12) weeks, with Peet and Horrobin's intervention period lasting the longest. The RCTs were conducted in three countries outside North America: the UK,[53] Israel,[97] and China.[96] The UK RCT was funded by industry (Laxdale Research Ltd),[53] the study from China was funded by government (National Science Council) and industry (China Chemical & Pharmaceutical Company),[96] and the Israeli trial's funding source was not reported.[97]

Population characteristics. The mean age of study participants across the three trials was impossible to determine given that full sample means were not given for two trials.[53,96] Participants' ages ranged from 18-73 years when two studies' data were combined.[53,97] Participants in the Su et al. study tended to be younger (mean for omega-3 group=35.2 years; placebo group: 42.3 years), on average, than participants in the Peet et al. (means of four groups: 43-48 years)[53] or Nemets et al. studies (omega-3 group mean: 54.2 years; placebo mean: 52.1).[97] Females were consistently more strongly represented in the three trials (82-85%). Racial/ethnic backgrounds included Asian[96] and Middle Eastern,[97] yet no data were provided for a potentially diverse UK population.[53]

Only the Peet and Horrobin RCT[53] did not report having employed any formal diagnostic criteria. The other two studies used DSM-IV to identify populations with major depressive disorder. Rather, the UK study required a score of at least 15 on the HDRS, and thus likely identified their participants as merely experiencing persistent depressive symptomatology. Nemets et al.'s participants had had relapses in the past when medication dosages were reduced or discontinued.[97] All three studies employed the HDRS score to establish the severity of the psychiatric condition. While Peet and Horrobin required a score over 15, Su et al. required a score above 18.[96] Nemets et al. only reported mean actual HDRS scores of 22.3 (placebo group) and 24.0 (EPA group).[97] Based only on completer data subjected to a statistical test, Su et al. noted that HDRS-defined severity was equivalent for study groups.[96] Peet and Horrobin did not present baseline HDRS severity data for study groups.

Peet and Horrobin[53] did not identify or exclude any comorbidity while Nemets et al. required that there be no unstable medical disease, no alcohol or drug abuse, no psychotic features, no history of hypomania or mania, and no comorbid psychiatric diagnosis other than panic disorder (n=2, one per study group), dysthymic disorder (n=2, one per study group), and obsessive

compulsive disorder (n=1, E-EPA group).[97] Su et al. asserted that no one in their sample received any other Axis I or any Axis II psychiatric diagnosis.[96]

Likely because their study participants did not receive a formal diagnosis, Peet and Horrobin did not report data concerning the duration of the current depressive episode, age of onset, the number of previous episodes, or the time since diagnosis.[53] Su et al. reported the study groups' mean current episode duration (omega-3 group: 21.5 weeks; placebo group: 22.8 weeks), age of onset (omega-3 group: 30.6 years; placebo group: 35.1 years), number of previous episodes (omega-3 group: 2.5; placebo group: 2.3), but not the time since diagnosis.[96] Statistical tests of the possible significance of between-group baseline differences exclusively for completers revealed that study groups were comparable on these bases as well as with respect to age, percentage of males, body mass index, HDRS score, and both EPA and DHA levels in RBCs. Nemets et al. reported their sample's mean current episode duration (EPA group: 44.6 days; placebo group: 43.1 days), time since diagnosis (EPA group: 7.6 years; placebo group: 8.0 years), number of previous episodes (EPA group: 2.1; placebo group: 1.9), but not their age of onset.[97] While statistical tests of significance were not employed, notable between-group differences at baseline were not observed for these variables.

Only Nemets et al. controlled for two of these potential confounding influences by excluding participants if they had had substance abuse or unstable medical problems.[97] Only Su et al. reported data reflecting the omega-3 fatty acid content of biomarkers at baseline, which by statistical analysis, were comparable between study groups. They did not, however, report the units of measurement for biomarker data (e.g., absolute level; percent of total fatty acids).[96]

Intervention/exposure characteristics. Both Su et al.[96] and Nemets et al.[97] identified the source of their intervention as fish oil whereas Peet and Horrobin[53] reported no details. Only Su et al. identified the exact type of source: menhaden fish.[96] Nemets et al. compared 2 g/d E-EPA derived from 96% pure fish oil (stabilized with 0.2% vitamin E) and a matching, albeit undefined placebo.[97] Peet and Horrobin employed 1 g/d, 2 g/d, 4 g/d or placebo (liquid paraffin) as their intervention.[53] Su et al.'s participants received 6.6 g/d of omega-3 fatty acids (i.e., 4.4 g/d EPA and 2.2 g/d DHA) or placebo (i.e., olive oil ethyl ester).[96] Only Su et al. used DHA in addition to EPA. Each RCT employed a placebo control and used the appropriate numbers of capsule and amounts of placebo content to equalize the total daily "intervention" across their study groups.

Omega-3 fatty acid contents were delivered by capsule in each study. However, there are few clear data to suggest that all three studies were equally able to eliminate the possible confounding influence of having unequal amounts of calories, as energy, provided for their different study groups. Nemets et al.'s placebo was not defined, making it impossible to know whether participants in each study group received the same number of calories. Although it is possible, ultimately it is unclear whether a unit of Peet and Horrobin's liquid paraffin, an inert lubricant laxative, provided the same caloric/energy content as that received from purified EPA. Given that the typical laxative dose is 15-30 g/d, and that Peet and Horrobin's study, as well as others described in this review, have consistently used much smaller daily doses, it is unlikely that its laxative effect would be any worse than that produced by a similar food oil.[87] Su et al., on the other hand, used olive oil ethyl ester to match their groups for energy/caloric intake.

If, as it was decided in consultation with the TEP working with us on our review of the evidence regarding the effects of omega-3 fatty acids on asthma,[72] and recognizing the FDA view that a 3 g/d dose of EPA and DHA is safe,[160] then two of the standardized doses in the three studies met our criterion that 3 g/d is a high dose of omega-3 fatty acid supplementation: Su et al's 6.6 g/d EPA plus DHA,[96] and Peet and Horrobin's 4 g/d E-EPA.[53]

None of the RCTs provided omega-6 fatty acids or any other supplement as cointervention, and none attempted to implement a specific on-study ratio of omega-6/omega-3 fatty acid intake through diet and/or supplementation. Nemets et al.[97] and Peet and Horrobin[53] did not report whether their study participants were told to maintain their background diet, to alter their background diet in some uniform fashion (e.g., modify omega-6 fatty acid intake and thereby change their omega-6/omega-3 fatty acid intake), or whether participants routinely complied with any such mandates. Only Su et al. established, for example, that study groups did not differ in terms of their on-study dietary frequency of fish intake as reported via 24-hour recall and three-day dietary records.[96] Few compliance data, in general, were provided. Peet and Horrobin used capsule counts to report that at least 90% of the dose had been consumed in each of the four study groups.[53] Even then, this method for determining compliance may not be overly accurate. Moreover, fatty acid content in biomarkers is likely not a perfect methodology either, given that EFA status can be influenced by various factors in addition to intake (e.g., oxidative degradation). Without hard data it is thus difficult to rule out the possibility in at least two studies that notable changes did not occur in the on-study background diet (i.e., Nemets et al., Peet et al.) or that protocol violations with respect to the number of capsules ingested did not occur, leaving unknown the extent of possible confounding with regards to clinical outcomes (i.e., from unplanned changes in the study groups' equivalence of energy/caloric intake from the "exposure" or related to unplanned changes in the between-group difference in the amount of omega-3 fatty acid received from supplementation).

Of the three trials, only Peet and Horrobin[53] failed to report having stabilized their omega-3 fatty acid doses with some form of anti-oxidant. Su et al. attempted to maintain blinding by having all capsules vacuumed to deodorize any odour, and having their contents blended with an orange flavor.[96] Anti-oxidant tertiary butylhydroquinone (0.2 mg/g) and tocopherols (2 mg/g) were added to all capsules both to maintain blinding, by preventing oxidation and rancidity, and to avoid possible confounding that could occur if these were added only to active treatment capsules and actually produced psychotropic effects,. In spite of no effort to deodorize their intervention, Nemets et al.'s participants were unable to reliably guess which capsules they had taken.[97]

For all three RCTs, the manufacturer of the omega-3 intervention was reported. Purity data were provided for two of the trials' exposures.[53,97] In the one study that evaluated the fatty acid content of biomarkers, no notable inappropriate methods to extract, prepare, store or analyze lipids were described.[96] No study report included details as to whether, or how, the presence of methylmercury was tested or eliminated from the omega-3 fatty acid exposure.

Cointervention characteristics. Given the focus of the present question is supplemental treatment, it could be argued that the omega-3 fatty acids are the cointervention. Nevertheless, to simplify matters, "cointervention" is defined as those other treatments or interventions that are provided concurrently, even if their initiation predated the omega-3 fatty acids intervention.

Peet and Horrobin reported similar distributions of background treatment by type of antidepressant (i.e., tricyclics, serotonin selective reuptake inhibitors [SSRIs], and others) in each study group.[53] They did not present data regarding whether or not this antidepressant use remained constant, by type or dose, over the study for any of their study groups. Nemets et al. described their participants as having received their antidepressants for at least three weeks at the current dose.[97] However, antidepressant medication was not distributed equally by type or dose across study groups. There was similar fluoxetine and mirtazapine use and doses, but five placebo and one E-EPA participant received paroxetine, usually at 20 mg/d. As well, the E-EPA

study group included the only three users of fluvoxamine and the only recipient of citalopram. Moclobernide was given to a single participant in the placebo group. Participants on prestudy medication in Su et al.'s trial maintained their dosages on-study, with only oral sedatives/hypnotics (loazepam or zolpidem) permitted as additional therapy for possible anxiety or insomnia.[96] They did report statistically-tested between-group baseline comparability for completers' duration of antidepressant use prior to enrollment or their (fluoxetine equivalent) dose of antidepressants while being enrolled.

Certain population characteristics have the potential to influence mental health outcomes if, in controlled investigations, study groups diverge significantly at baseline on these bases, or if unplanned on-study changes unrelated to the exposure occur in their status that vary notably across study groups (or within a single study group). Some cointerventional factors may exhibit a similar potential to confound clinical outcomes (e.g., psychological interventions, other licit drug use, use of complementary/alternative medicine/products, other supplement use with psychotropic potential). Not reported in the three included RCTs were data regarding the between-group comparability at baseline, or data regarding the on-study change in the status of these factors, making it difficult to rule out the possibility that these variables influenced clinical outcomes.

Outcome characteristics. All three RCTs employed the validated HDRS as the primary outcome.[53,96,97] While Peet used the validated MADRS and BDI as well, Su et al. assessed the omega-3 fatty acid content of biomarkers.

Study quality and applicability. The three RCTs received a mean Jadad total quality score of 3.6, indicating sound internal validity (Summary Matrix 1). The trials conducted by Peet and Horrobin[53] and Nemets et al.[97] each received a score of 4, while Su et al.'s score was 3.[96] The latter two studies[96,97] each received an applicability rating of III, and a II was assigned to Peet and Horrobin's UK trial.[53] Overall, these studies' individual or collective results were not readily generalizable to a North American population.

Summary Matrix 1: Study quality and applicability of evidence regarding the supplemental treatment of depression

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author Peet[A]	Year 2002	n 70	Author	Year	n	Author	Year	n
	III	Author Nemets[U]	Year 2002	n 20	Author Su[U]	Year 2003	n 28	Author	Year	n

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

Qualitative Synthesis of Individual Study Results

Peet and Horrobin's trial conducted both ITT (last observation carried forward) and per-protocol (PP) analyses, the latter assessing study completer data.[53] Analyses of variance

(ANOVA) compared data reflecting change from baseline to study endpoint for each active treatment group with comparable data from participants receiving placebo. All of the ITT and PP analyses involving each of the 3 scales showed that participants in the 1 g/d group improved significantly more than did those in the placebo group. For the 2 g/d and 4 g/d groups no comparison reached a level of statistical significance, with only the 4 g/d results for the PP population approaching statistical significance. For the 1 g/d versus placebo contrast, the HDRS and MADRS differences were already statistically significant at 4 weeks; only the BDI scores failed to show statistically significant changes at 4 weeks. Eight-week data regarding 1g/d supplementation was only provided for the BDI, and changes in these scores at 8 weeks only approached statistical significance. Analyses of specific items from the rating scales (i.e., the three main components of the HDRS [items 1-3: depression; 4-6: sleep; 9-11: anxiety] and the ten MADRS items) demonstrated that, for the comparison involving the PP population, there were no significantly greater improvements in the 1 g/d group compared with the placebo group. Statistically significant differences in favor of the 1 g/d dose were observed on the BDI-defined items pertaining to sadness, pessimism, inability to work, sleep disturbance and libido. These results suggest improvements defined by both patient and clinician assessments. While results of tests of statistical significance were not reported, the number of participants exhibiting a 50% improvement was always higher, when compared with placebo rates, in the 1 g/d and 4 g/d groups for all three scale scores assessed in both the ITT and PP populations. Yet, response rates for placebo participants consistently exceeded those from participants receiving the 2 g/d dose.

Analyses of covariance (ANCOVA) of Peet and Horrobin's data for each of the rating scales at each of the followups assessed overall differences between study groups.[53] They revealed that center (exact number unreported) and background medication, by class (i.e., tricyclic, selective serotonin reuptake inhibitor [SSRI], or either norepinephrine or mixed reuptake inhibitors), had no significant effects on any rating scale scores in the ITT and PP populations. Baseline HDRS score had no effect on the HDRS and MADRS outcomes in either of the ITT or PP populations yet had a significant effect on BDI outcome only in the ITT population. Treatment had a significant overall effect on all three rating scale scores for both the ITT and PP populations yet the p-value for the HDRS comparison in the ITT population barely missed indicating statistical significance.

Nemets et al.'s multivariate analysis of covariance (MANCOVA), with baseline HDRS score as covariate, described a statistically significant treatment-by-time interaction in the ITT population (i.e., last value at week three carried forward, n=1).[97] This observation was maintained after the week three HDRS score from the sole placebo dropout was excluded. Compared to placebo, E-EPA yielded significantly improved HDRS scores at each of weeks 2, 3 and 4. The mean reduction in HDRS score in the E-EPA group (12.4 points) was greater than that in the placebo group (1.6), and was considered clinically meaningful. Only one of ten patients in the placebo group and six of 10 in the E-EPA group achieved a 50% reduction in HDRS score. Item analysis showed that E-EPA influenced core symptoms such as depressed mood, feelings of guilt, feelings of worthlessness and insomnia. The investigators did not remove from any analyses the one study patient who was receiving E-EPA as monotherapy.

Su et al. observed, by week 4, and likewise for weeks 6 and 8, a statistically greater HDRS-defined improvement in the active treatment group.[96] By repeated measures ANOVA it was found that the rate of reduction in HDRS scores was also significantly greater in the omega-3 fatty acids group. Pre- and post-intervention RBC fatty acid status data were limited, with a significantly increased level of DHA seen at post-treatment for the EPA group (n=7) but not the

placebo group (n=6). No statistically significant increases in EPA levels were observed for either study group.

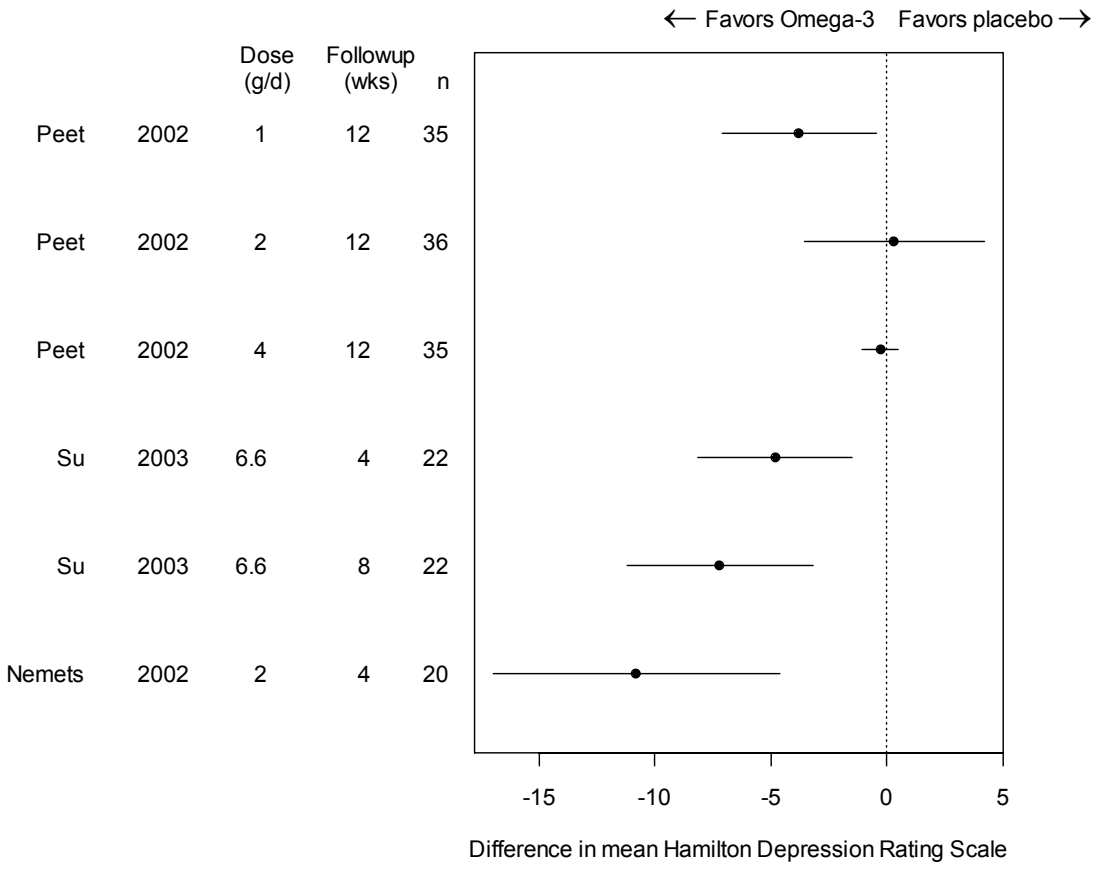
Nemets et al. reported a single study dropout, from the placebo group, by week 3 because of worsening depressive symptoms.[97] Six of 28 participants dropped out prior to week 8 in Su et al.'s trial; two had been receiving active treatment (one lost to followup, and one lost due to noncompliance), and four were in the placebo group (three lost to followup, one lost due to noncompliance).[96] Ten participants left Peet and Horrobin's trial,[53] with four from the placebo group (one lost to followup, one withdrew consent during study, one violated protocol, one had an adverse event presumed to be unrelated to treatment) and two from each of the E-EPA groups (no data by group: three withdrew consent, one left due to lack of efficacy, one violated protocol, one had gastrointestinal adverse event).

Quantitative Synthesis

We decided it was reasonable to explore the possibility of conducting meta-analysis for this question. HDRS was chosen as the primary outcome measure. We aimed to extract the mean change from baseline in HDRS, together with the standard deviation of this change, for each study group. The goal was to focus on the ITT population. We requested data to afford this analysis from the lead investigators of the Peet and Horrobin[53] and the Su et al. trials.[96] Only the former replied, passing on our request to the company now holding their data. A representative of the company stated they would consider the request yet no further reply was received.

In order to help decide on the possibility and appropriateness of meta-analysis, we created a forest plot of all possible combinable results. Length of follow-up varied notably between studies, so from each study we considered the longest followup data reported in addition to 4 week and 8 week results where they were provided. Su et al.'s study[96] used capsules containing EPA together with DHA to yield a very high total dose (6.6 g/d). The other two studies[53,97] employed capsules exclusively containing E-EPA. The study by Peet et al.[53] reported change in HDRS after 12 weeks of treatment for four different study groups (placebo, 1 g/d, 2 g/d, and 4 g/d). Although the standard deviation of change from baseline was not reported, p-values for change from baseline relative to placebo were reported for each dose so that the standard error for each contrast could be inferred. Su et al.[96] reported mean HDRS scores at baseline and post-treatment, but not the standard deviation in the change from baseline. We were nevertheless able to extract estimates from one of their graphs.

Figure 3. Estimates of the change in HDRS score between omega-3 fatty acid and placebo groups from studies evaluating the supplemental treatment of depression



The Peet et al.[53] and Nemets et al.[97] studies reported ITT analyses (using a last observation carried forward strategy). Yet, it was unclear whether Su et al.[96]had also employed an ITT approach. In addition, their data concerning loss to followup at 4 weeks and 8 weeks were unclear.

After a careful appraisal of the estimates and key study parameters, however, it was decided not to conduct meta-analysis. No pooled estimate was derived because of the variations in dose both within and among studies, and in view of variations in the length of followup. It should also be noted that, in the Peet and Horrobin study[53] the estimates for the different doses involving placebo shared the same placebo group. As well, Su et al.'s intervention was the only one including DHA in addition to EPA,[96] as the other trials employed purified forms of E-EPA.[53,97] All three RCTs employed different types of placebo. Finally, unlike the other two studies wherein patients had been formally (DSM-IV) diagnosed with major depression, Peet and Horrobin's use of a HDRS cut-off score to identify study participants yielded, at worst, a population with persistent depressive symptomatology.[53]

Impact of Covariates and Confounders

Overall, the Su et al. study was the one exhibiting the best control of extra-interventional factors with the potential to influence, and thus confound, study results.[96] Without repeating all of the details presented in the qualitative synthesis, these investigators indicated that study groups were balanced for key population (e.g., severity of depression, age of onset, absence of other Axis I or Axis II disorders) and cointervention parameters (e.g., patients asked to maintain constant on-study medication, although they did not demonstrate between-group baseline comparability for types and doses; established a maximum weekly frequency of background fish intake). Although Peet et al. provided few population data, their undiagnosed sample did not exhibit comorbid conditions and their study groups' patterns of medication use were similar.[53] Nemets et al., on the other hand, did not evaluate whether study groups of depressed patients were similar at baseline in terms of the severity of their depressive symptomatology. They also reported that study groups varied in terms of their antidepressants. Still, their groups did not contain any individuals with unstable medical disease or substance abuse, and few comorbid conditions were observed. None of the studies reported data concerning prestudy/baseline omega-3 or omega-6/omega-3 fatty acid intake via diet or supplementation. Only Su et al. reported data regarding study groups' baseline comparability in their baseline omega-3 fatty acid content of biomarkers.[96] They did not, however, report the units of measurement for these data (e.g., absolute level; percent of total fatty acids).

Dose, omega-3 fatty acid type, and whether the exposure was purified all failed to reliably predict clinical effects. For example, significant effects were associated with the largest (6.6 g/d EPA+DHA)[96] and smallest doses (1 g/d E-EPA),[53] various types of omega-3 fatty acid (EPA+DHA[96] vs E-EPA[53,97]) and both EPA+DHA[96] and E-EPA.[53,97] Employed as a possible surrogate measure of background diet, or possibly even the background diet's omega-6/omega-3 intake ratio, the country in which a study was conducted did not predict study results. The lowest dose (1 g/d E-EPA), given to a UK population,[53] and the highest dose (6.6 g/d EPA+DHA), given to a Chinese population,[96] each yielded a significant clinical effect. The majority of study participants were female. Overall, though, there were too few studies with which to properly evaluate the impact of extra-interventional variables with the potential to influence study results.

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Depression?

As observed in Summary Tables 3 through 6 (below), derived from Evidence Tables 1 through 3 (Appendix E*), three types of evidence met eligibility criteria addressing this question. The qualitative synthesis distinguishes evidence from these types of study published between 1998 and 2004.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Overview of Relevant Studies

Three RCTs,[98-100] six observational studies[48,80,81,107,110,111] and three cross-national ecological analyses[47,108,109] were found to address this question.

Plasma DHA gradually decreases during the last trimester of pregnancy and remains low for some time during the postpartum period, and particularly in lactating women.[161] It has been postulated that brain DHA levels may be low during late pregnancy and the early postpartum period, and that these levels may contribute to the development of postpartum depression.[162] Postpartum depression is defined in DSM-IV as a major depressive, manic, or mixed episode in major depressive disorder, bipolar I or bipolar II disorder, or brief psychotic disorder. Llorente et al. thus attempted to determine the effect of DHA supplementation on the onset of postpartum depression as well as on plasma phospholipid DHA content in breastfeeding women (Summary Table 3).[98] Mothers who planned to breastfeed their children (n=138; 18-42 years) were randomly assigned, in double-blind fashion, to receive either ~200 mg/d DHA or placebo (undefined) for the first four months after delivery. Clinical outcome was determined via the BDI, and was collected at baseline, 3 weeks, 2 months, and 4 months post-delivery. Depression-related data were obtained through the Structured Clinical Interview, DSM-IV, Axis I Disorders, Clinical Version (SCID-CV). As well, scores on the Edinburgh Postnatal Depression Scale (EPDS) of postpartum depression symptoms were obtained from subgroups of the sample. Plasma phospholipid data were collected just before delivery and at 4 months.

Summary Table 3: Association between omega-3 fatty acid intake and onset, continuation or recurrence of depression (RCTs)

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Notable biomarker effects[2,3]	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)				
Llorente, 2003, US: 4 mo parallel RCT[98]	~200mg/d DHA (n=44 completers)	pb (undefined) (n=45 completers)	NS bet-group BDI difference at any time; NS bet-grp differences in EPDS & SCID-CV scores	8%↑ in plasma PL DHA in DHA grp vs 31%↓ in pb grp;$^{+}$ DHA content of DHA grp 50% higher than pb grp^{+++}	Jadad total: 5 [Grade: A]; Schulz: Adequate	II
Wardle, 2000, England: 12 wk parallel RCT[99]	Mediterranean diet (with oily fish) (n=61)	low fat diet (n=59)/ waiting list control (n=56)	↓ BDI & anger reactions in both diets;$^{+}$ ↓ stress & anxiety only in Mediterranean diet;$^{+}$ NS bet-grp differences in outcomes	n/a	Jadad total: 2 [Grade: C]; Schulz: Adequate	II
Ness, 2003, Wales: 6 mo parallel RCT (one factor in factorial RCT)[100]	advice to eat fish (n=229)	no advice to eat fish (n=223)	NS Δ in depression & anxiety for fish advice grp; NS bet-grp differences for depression & anxiety	n/a	Jadad total: 2 [Grade C]; Schulz: Unclear	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; BDI = Beck Depression Inventory; EPDS = Edinburgh Postnatal Depression Scale; SCID-CV = Structured Clinical Interview, DSM-IV, Axis I Disorders, Clinical Version; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Wardle et al.'s RCT investigated whether cholesterol-lowering diets influence mood, including depression, anxiety, anger/hostility, stress, and general psychological well-being.[99] Adult volunteers (n=176) with elevated serum cholesterol levels (>5.2 mM [198 mg/dL]) were allocated to a low-fat diet (n=59), a Mediterranean diet (n=61) or a waiting-list control (n=56). Dietary treatments were given in eight sessions over the 12-week period. Waiting-list controls were offered treatment at the end of their waiting period. Participants were exhibiting at least mild hypercholesterolemia by UK standards. Participants completed a 7-day dietary intake diary before the first assessment. Outcomes were assessed at baseline, 6 weeks and 12 weeks. These included the BDI, personal history of depression established through interview, and the following validated instruments: State-Trait Anger Inventory (STAI), the anxiety and anger subscales of the Profile of Mood States (POMS), the General Health Questionnaire (GHQ) to

assess general psychological well-being, and the Perceived Stress Scale (PSS). Dietary diaries were filled out at baseline and 12 weeks.

Reflecting one factor of a factorial RCT investigating interventions to reduce mortality in angina (including: advice [not] to eat fruits and vegetables; [no] stress management), 452 males were allocated to receive advice to eat more fatty fish (i.e., mackerel, herring, kipper, pilchard, sardine, salmon, trout) or to receive no such advice. Study participants were supplied with MaxEPA® fish oil capsules if they did not like the taste of fish.[100] Fish intake and mood (depression, anxiety) were assessed at baseline and at 6 months, the latter using the validated Derogatis Stress Profile (DSP).

In a recently published observational study, Hakkarainen et al. investigated the relationship between the dietary intake of omega-3 fatty acids and low mood, major depression, and suicide in males 50 to 69 years of age living in southwestern Finland in 1985 (Summary Table 4).[111] The study identified a cohort (n=29,133) from a primary prevention RCT (ATBC Cancer Prevention Study). Followup lasted 9 years. The intake of fatty acids and fish consumption were derived from a validated food use questionnaire focused on the "last 12 months." Self-reported depressed mood, suicides and hospital-based treatments for major depressive disorder were evaluated.

Summary Table 4: Association between omega-3 fatty acid intake and onset, continuation or recurrence of depression (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Hakkarainen, 2004, Finland: 9 y single prospective cohort from RCT[111]	males 50-69 y (n=29,133) from RCT's intervention & placebo grps		NS (adjusted) association of fish or n-3 intake (from fish, vegetables, or total) &: self-reported depressed mood or hospital treatment required due to major depressive disorder	Total quality: 5 [Grade: B]	III
Tanskanen, 2001, Finland: single population cross-sectional survey[81]	adult males & females (n=3,204)		Mild-severe symptoms more prevalent in infrequent female consumers than frequent fish eaters;$^{++}$ NS similar trend for males; infrequent consumption independently associated with symptoms (multiple regression);$^{++}$ likelihood of mild-severe symptoms 31% higher in infrequent consumers than frequent ones;$^{++}$ symptoms significantly associated with infrequent consumption for females only^{++}	Total quality: 3 [Grade: C]	III
Tanskanen, 2001, Finland: single population cross-sectional survey [80]	adult males & females (n=1,767)		Adjusted depression & suicidal ideation risks ↓ in frequent fish consumers^{+}	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Tanskanen and colleagues undertook two non-overlapping cross-sectional surveys in Finland.[80,81] Both were published in 2001. In a random sample of 3,204 Finnish adults (25-64 years), depressive symptomatology was measured using the BDI.[81] A single food-frequency question assessed fish consumption (fish type unspecified) regarding the previous 6 months. For this study, the sample was drawn from two coastal and two lakeside areas in 1992 (n=8,000). After health questionnaires were returned, and medical examinations completed, a random sample of participants was selected based on birthdays between the twelfth and the last day of each month (n=5,105). Following other clinical measurements, this group was given a questionnaire, which included psychosocial variables. The response rate was 67% (n=3,403), while another 199 individuals did not provide complete data sets. In all, 3,204 subjects became the study sample.

In Tanskanen et al.'s other study a sample was selected, in 1999, based on a random population sample (National Population Register) of both sexes (n=3,004; 25-64 years).[80] The number of respondents was 1,767 (59%), and they resided in Kuopio in the central-eastern part

of Finland (lakeside area). Data were gathered on fish consumption, depression (BDI) and suicidality. The latter was measured using a single BDI item.

Three additional studies involved more specific definitions of population in evaluating the possible relationship between omega-3 fatty acid intake and the risk of geriatric depression (Summary Table 5). In 1991-1992, Woo et al. conducted a single cohort, 3-year prospective study examining the possible relationship of physical activity, dietary habits (e.g., fish consumption), smoking and alcohol consumption with three-year mortality as well as other health outcomes.[110] Participants included 2,032 elderly Chinese subjects (mean age: 80 years) recruited by stratified (by age: e.g., 80-84 vs 85-89 vs >90 years) proportional random sampling.

Summary Table 5: Association between omega-3 fatty acid intake and onset, continuation or recurrence of depression (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Woo, 2002, China: 36 mo single prospective cohort study[110]	elderly adults (n=2,032)		NS association bet depressive symptoms & fish consumption	Total quality: 4 [Grade: B]	III
Suzuki, 2004, Japan: single population cross-sectional survey[107]	newly diagnosed primary lung cancer patients (n=902)		Adjusted difference for depression bet upper & lower quartiles of ALA & total n-3 intake, indicating inverse associations;$^{+}$ NS adjusted difference for depression bet upper & lower quartiles of EPA, DHA & EPA+DHA intake; NS adjusted association bet depression & fish/seafood intake	Total quality: 7 [Grade: A]	III
Edwards, 1998, England: multiple-group cross-sectional study[48]	depressed patients (n=10)	matched healthy controls (n=14)	NS between-grp differences for n-3 or total energy intake; for depressed pts, negative correlations bet depressive symptoms & dietary intake of total n-3^{+++} and ALA;$^{++}$ &, data from all pts revealed no dietary n-3 or n-6 variables predicted severity of depressive symptoms	Total quality: 6 [Grade: B]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

In a cross-sectional study examining the possible association of omega-3 fatty acid intake and the prevalence of depression in 902 Japanese individuals newly diagnosed with primary lung cancer, Suzuki et al. employed a food frequency questionnaire and the depression subscale from the validated Hospital Anxiety and Depression Scale (HADS).[107] Data from 771 patients were

analyzed after excluding those failing to complete the HADS (n=73) or the food frequency questionnaire (n=62), or those having incorrectly completed the latter (n=24).

Edwards et al. measured the dietary PUFA intake as well as the fatty acid content of RBCs in a cross-sectional study of ten depressed patients and fourteen matched healthy control subjects.[48] Biomarker results are described in a later section although the key study parameters are presented in relation to the current research question concerning the possible association of omega-3 fatty acid intake and depression. Analyses controlled for stress and smoking status.

Cross-national, ecological analyses can highlight evidence concerning the possible relationship between intake of omega-3 fatty acids and risk of depression in spite of certain inherent limitations of these data (see Discussion). Hibbeln [47] utilized cross-national epidemiology data from eight (of the ten) countries in Weissman et al.'s study regarding major depression (and bipolar disorder),[46] to which they added prevalence data from Japan (Summary Table 6).[47] Weissman et al.'s study had evaluated 35,000 participants using a random prospective design, repeat sampling techniques, multiple community sampling, and a structured interview process with accepted diagnostic criteria.[46] Apparent fish consumption was estimated; it is an economic measure of disappearance of seafood from the economy.[108]

Summary Table 6: Association between omega-3 fatty acid intake and onset, continuation or recurrence of depression (cross-national ecological analyses)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Hibbeln, 1998, 9 countries: cross-national ecological analysis[47]	n=9 countries		Negative correlation of apparent fish consumption & annual prevalence of major depression both with^{++} & without data from Japan^{+}	Total quality: 2 [Grade: C]	III
Hibbeln, 2002, 23 countries: cross-national ecological analysis[108]	DHA, EPA, AA content (n=16 countries; n=14,532 pts); Seafood consumption (n=22 countries)		Via simple regression & logarithmic model, ↑ national seafood consumption predicted ↓ prevalence rates of postpartum depression;$^{++++}$ ↑ DHA in mother's milk predicted ↓ prevalence rates^{++++}	Total quality: 7 [Grade: A]	III
Peet, 2004, 8 countries: cross-national ecological analysis[109]	n=8 countries		Association bet high consumption of fish/seafood & a reduced prevalence of depression^{++}	Total quality: 3 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

In a second ecological analysis, Hibbeln assessed the interrelationships among seafood consumption, the DHA content of mothers' milk, and prevalence rates of postpartum depression (n=14,532 subjects in 41 studies).[108] To maximize comparability the investigator identified only published prevalence data for postpartum depression that had used the EPDS, and correlated

these data with those indicating the EPA, DHA and AA content in mother's milk as well as published seafood consumption rates from 23 countries.

Peet's cross-national ecological analysis focused on international variations in the prevalence of depression and the outcome of schizophrenia, and their possible prediction by patterns of omega-3 fatty acid intake.[109] Data on food use were taken from the FAOSTAT database, and reflected apparent national food consumption.[163] Data on depression prevalence were again borrowed from Weissman et al.[46] and the same Japanese source used by Hibbeln.[47] Two-year outcome data relating to schizophrenia were drawn from the WHO's International Pilot Study of Schizophrenia (IPSS).[164] A second source of schizophrenia outcome data was the Determinants of Outcome of Severe Mental Disorders (DOSMED) study.[165] Schizophrenia results are presented later in this report.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. One RCT employed a parallel design with two study arms,[98] a second included three study groups,[99] and the data from the third study came from one factor of a factorial RCT design (Summary Table 3; Evidence Table 1: Appendix E[*]).[100] In one study, the focus was on the possible utility of omega-3 fatty acids to affect the likelihood or intensity of mood changes in a population at risk for postpartum depression.[98] In the other two studies, the intervention given for a medical disorder conveniently allowed the investigators to examine the possible relationship between omega-3 fatty acid intake and mood.[99,100] These two studies' inclusion and exclusion criteria therefore pertained to the primary reasons these narrowly defined populations were studied in the first place: adults with elevated serum cholesterol levels, and for whom one of their cholesterol-lowering treatments was thought to have the potential to influence mood;[99] and, males with angina, whose "fish advice" intervention was also thought to have the potential to affect mood.[100]

The populations from the latter two studies did not include individuals with formal diagnoses of depression.[99,100] Given the heterogeneous nature of the populations, it made little sense to synthesize many of the study characteristics (e.g., mean sample size). The interventions lasted an average of 18.4 (range: 12-26) weeks. Two of the studies were conducted in the UK[99,100] and a third in the US.[98] Llorente et al.'s study was supported by industry (Martek Biosciences Corporation),[98] Ness et al.'s by the UK Medical Research Council,[100] and Wardle et al.'s by government as well (Biotechnology and Biosciences Research Council).[99]

Three of the included observational studies were conducted in Finland.[80,81,111] Inclusion/exclusion criteria were published elsewhere for Hakkarainen et al.'s study,[111] while eligibility criteria were delineated in each of Tanskanen et al.'s reports.[80,81] None of the study reports made reference to a funding source.

Woo et al.'s single prospective cohort was well-defined.[110] Clearly delineated eligibility criteria regarding the cancer diagnosis were included in Suzuki et al.'s report.[107] Their survey was filled out both prior to and during hospital admission. Edwards et al. reported well-defined exclusion criteria.[48] Neither Woo et al.[110] nor Edwards et al.[48] identified their funding source(s). Funding for Suzuki et al.'s study was received as a Grant-in-Aid for Cancer Research and Second-Term Comprehensive Ten-Year Strategy for Cancer Control and Research of the Japanese Ministry of Health, Labour, and Welfare.[107]

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[*] **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Eligibility criteria were sparse in Hibbeln's first report of a cross-national ecological analysis[47] and were explicitly stated in their second one.[108] Peet's descriptions of eligibility criteria were clear.[109] Neither Hibbeln[47] nor Peet[109] reported their funding source. Hibbeln's second study was funded in part by a Young Investigators Grant from the National Association for Research on Schizophrenia and Depression (NARSAD).[108]

Population characteristics. Given the heterogeneous nature of the included studies' populations, again it made little sense to synthesize some of the population characteristics from the three RCTs (e.g., mean age, mean percent males). Racial/ethnic backgrounds included a potentially diverse UK sample,[99] a predominantly Caucasian (82%) US population,[98] and a likely Caucasian/European one.[100]

In Llorente et al.'s trial, women intending to breast-feed were excluded if they exhibited a chronic medical condition, were current smokers, or had been pregnant more than five times.[98] No significant differences were observed for baseline BDI scores for depression. As well, there were no mean differences between study groups for mother's age, education, racial/ethnic distibution, and several pregnancy/delivery/infant-related factors (i.e., parity, gravidity, delivery weight, prepregnancy weight, gestational ages of infants, infants' birth weight, sex distibutuion of births, Apgar scores at 1 or 5 minutes).

In Wardle et al.'s study, adults with elevated serum cholesterol levels (>5.2 mM [198 mg/dL]) were excluded from the RCT if they were pregnant, lactating or planning pregnancy.[99] There were no significant differences among the study groups for any of the baseline mental health (i.e., BDI; depression, anxiety or anger scores on POMS; general psychological well-being; stress; state anger and anger reactions scores on STAI), background diet (i.e., g/d or percent of energy saturated fat; g/d fiber), or other characteristics (i.e., age, marital status, sex, BMI, total, HDL, LDL cholesterol and triglyceride parameters). Seven-day diary data showed that reported energy intakes were reasonable for adults this age.

No statistical differences were observed with respect to the following baseline characteristics in Ness et al.'s RCT of adult males with angina: depression score, anxiety score, eicosapentaenoic acid (mg/d: measurment undefined), social class, past history of cardiovascular disease, smoking, fish intake, and fruit and vegetable intake.[100] Data regarding the baseline between-group comparability, or on-study change, with respect to other factors with the potential to influence mental health were not reported for the three studies (e.g., stressors, social support).[98-100] Likewise, data regarding the baseline comparability, or on-study change, with respect to key dietary characteristics (e.g., omega-3 or omega-6/omega-3 fatty acid content of the baseline or on-study diets) were not provided by study authors. For example, whether study groups' caloric/energy intake was equivalent in any of the studies could not be determined from reports.

The focus in Hakkarainen et al.'s observational study was on the mood experienced in the 4 months prior to their previous study visit.[111] Mood difficulties ranged from 5 to 8 years in duration (median=6). Alcohol consumption was also assessed via validated food-use questionnaire. Various covariates were entered into data analysis (see below). In each of Tanskanen et al.'s observational studies, the nature of the sampling meant that individuals varied in terms of their levels of depressive symptom, or even their thoughts of harming themselves.[80,81] Woo et al.'s population were elderly Chinese potentially experiencing depressive symptomatology[110] while Suzuki et al.'s population of newly diagnosed primary lung cancer patients included 436 (of 771: 56.5%) with analyzable data, and who were exhibiting depressive symptomatology.[107] Edwards et al. identified ten individuals with a major depressive episode

using DSM-IV criteria. Each was receiving antidepressant medication. Exclusion citeria included physical illness of a severity or nature suggestive of low omega-3 fatty acid levels. The 14 healthy controls showed no history of psychiatric disorder although how this was determined was not reported. Matching was based on age, sex, social class, BMI, number of children, recent life events, smoking habits, and alcohol consumption. An assessment of these data revealed the soundness of the matching strategy. All study participants were evaluated using the BDI.

Hibbeln's cross-national ecological analysis[47] identified its populations by using Weissman et al.'s cross-national prevalence study, which included a structured clinical interview employing accepted diagnostic criteria (DSM-III).[46] The core symptoms of major depression, and not merely symptom severity as reflected in rating scale scores, were identified. Hibbeln drew data on the annual prevalence of major depression in Japan from the Ministry of Welfare (n=130,000). However, one limitation of these Japanese data is that they were not produced using a structured diagnostic instrument or random population sampling techniques.

In his second analysis Hibbeln's populations were drawn from countries varying in terms of their background diet.[108] A high score indicated severe depressive symptomatology rather than a major depression. Prevalence data were derived from well-defined populations. Peet's cross-national ecological analysis[109] included data on depression prevalence once again borrowed from Weissman et al.[46] and the same Japanese source used in Hibbeln's first analysis.[47] Two-year data concerning the outcome of schizophrenia were drawn from the WHO's International Pilot Study of Schizophrenia (IPSS). A second source was the Determinants of Outcome of Severe Mental Disorders (DOSMED) study.

Intervention/exposure characteristics. Given the great divergence of interventions or exposures, it likely makes little sense to synthesize many of the intervention/exposure characteristics (e.g., mean dose or serving size; number of studies utilizing a "high" dose or serving size). Two of the RCTs encouraged specific dietary patterns[99,100] while the third provided supplementation capsules.[98] Regarding the latter investigation, Llorente et al. provided ~200mg/d DHA from algae-derived triglyceride capsules yet did not describe the number of capsules constituting a "dose" or what the placebo capsules contained.[98] Wardle et al.'s RCT allocated adults with elevated serum cholesterol levels either to a low-fat diet (i.e., reduce energy from [saturated] fats to <20%, and ingest mostly polyunsaturates), a Mediterranean diet (i.e., increase intake of fruits and vegetables, oily fish; reduce fat to 30% of calories; use monounsaturated fats instead of saturated fats) or a waiting-list control (i.e., no advice given yet not discouraged from making dietary changes). This entailed educating participants about recommended dietary changes and included a cognitive-behavioral intervention focused on implementing changes in eating behavior. Participants were also given spreadable fat and oils consistent with their assigned diet. Finally, Ness et al. observed that, at 6 months, of the men allocated to fish advice, 78% were consuming fish weekly or taking fish oil capsules (21%), as compared to 14% of those who did not receive fish advice. These details, in addition to the observation that compliance data were not always available, raise some doubt that participants in the different study groups in each RCT actually received a constant difference in their amount of omega-3 fatty acid intake, or an equivalent intake of calories/energy over the intervention period, sufficient to control for possible confounding stemming from such protocol violations.

None of the studies specifically identified the omega-6/omega-3 fatty acid content of their planned on-study[99,100] or background diets.[98] Llorente et al. did not report an attempt to maintain blinding via deodorizing their omega-3 fatty acid materials and/or by preventing oxidation and inevitable rancidity. Neither general purity data, nor data concerning possible methylmercury

contamination, were provided regarding their DHA supplementation.[98] On the other hand, Llorente et al. appeared to use appropriate methods to handle blood lipid materials.

Hakkarainen et al.'s observational study assessed habitual dietary intake over the previous year (measure undefined).[111] This included fish consumption as well as the intake of omega-3 fatty acid content from fish and vegetables, and total omega-3 fatty acid intake. Total omega-3 fatty acid intake was calculated as 2.2 g/d or 0.47 g/d from fish, a value that they asserted is considerably higher than what is observed in North American populations.[111]

Tanskanen et al's single food-frequency question assessed fish consumption over the past six months ("How often do you usually eat fish or fish meals? 1, < once a month or never; 2, once or twice a month; 3, once a week; 4, twice a week; 5, almost daily; 6, once a day or more often).[81] Responses of 2 or less constituted infrequent consumption. In their second observational study Tanskanen et al.[80] estimated fish consumption via a food-frequency questionnaire (undefined) purported to produce comparable results to a 7-day food record.[166] A frequent fish consumer was defined as someone eating fish at least twice a week.

Fish intake in Woo et al.'s study was measured via a food frequency questionnaire administered at the participants' residence.[110] Suzuki et al. utilized a validated semiquantitative food frequency questionnaire regarding 138 foods, including 18 fish and seafood items. It had in the past exhibited a significant association with dietary record data.[107] Participants were asked to report the average frequency, and usual serving size, of consumption during the year immediately preceding the onset of cancer symptoms. From this, Suzuki et al. calculated an average daily intake of food and nutrients. They then calculated the daily intake of omega-3 fatty acid content using the Fatty Acid Composition Table of Japanese Foods.[167] For the 771 participants whose data were analyzed, total omega-3 fatty acid intake was primarily ingested from vegetable oils and fats (37% of total intake), followed by 17 types of fish (35%), soybean products (11%), seasonings (5%), and cereals (4%). The daily intake consisted of 62% ALA, 20% DHA, and 11% EPA.[107] Edwards et al. completed a full analysis of the current diet using a 7-day weighted intake method.[48] Although data are reported later in this report, it should be stated here that no notable inappropriate methods to extract, prepare, store or analyze lipids were described.[48]

Hibbeln's first ecological analysis estimated apparent fish consumption as: fish catch plus imports, minus exports.[47] This method is not as reliable as direct dietary surveys but at least this analysis included comparable data across countries. In his second analysis apparent fish consumption data were drawn by Hibbeln from the National Marine Fisheries Service and the Food and Agriculture Organization of the United Nations.[108] Data on food use were taken from the FAOSTAT database,[163] and captured apparent national food consumption in Peet's analysis.[109] Food use was estimated from the total domestic production of food plus imports, minus exports, while taking into account changes in stocks (e.g., stored grain), and subtracted food lost to waste during processing. Fish and seafood data were included, and were expressed as supply in kilograms per capita per year. Annual food consumption was approximated closest to the years in which the clinical studies were conducted (i.e., IPSS=1970; DOSMED=1980; depression=1990).[109]

The manufacturer of Llorente et al.'s intervention was Martek Biosciences Corporation.[98] Purity data concerning its contents were not provided. No study report included details as to whether, or how, the presence of methylmercury was tested or eliminated from their omega-3 fatty acid exposure.

Cointervention characteristics. In Llorente et al.'s study, breast-feeding women were excluded if they used dietary supplements other than vitamins.[98] Wardle et al. excluded participants if they were currently using, or had used within the last 3 months, lipid-lowering medication.[99] In Ness et al.'s study, male adults were receiving anti-anginal medication, details of which were not provided in their report.[100] The possible use of other products with psychotropic properties was not reported for these studies.

Of the six observational studies,[48,80,81,107,110,111] only the study by Edwards et al. reported on the status of possible cointerventions. Each individual diagnosed as depressed was receiving antidepressant medication.[48] Similar data were not reported in any of the cross-national ecological analyses.[47,108,109]

Outcome characteristics. Llorente et al. employed the BDI, EPDS and the SCID-CV, with the latter supporting DSM-IV diagnostic criteria.[98] Wardle et al. used the BDI, along with the STAI, anxiety and anger subscales of the POMS, GHQ to assess general psychological well-being, and the PSS. Dietary diaries were filled out at baseline and 12 weeks. Ness et al. used the DSP to measure depression and anxiety.

Hakkarainen et al.'s study evaluated depressed mood via self-report (no measure identified).[111] Assessments were recorded three times annually. Data on hospital-based treatments for major depressive disorder were drawn from the National Hospital Discharge Register, and suicides were identified from death certificates. Cox's proportional hazards regression models estimated the relationships between baseline dietary intake of omega-3 fatty acids (from fish, vegetables, and total intake), calculated from the food-use questionnaire and categorized in tertiles (with the lowest tertile as reference category), and measures of mood level and hospital-based treatments for major depressive disorder. The following potential risk factors for major depressive disorder and suicide were entered, as covariates, into the regression models: age, BMI, energy intake, serum total cholesterol, HDL cholesterol level, alcohol consumption, education, marriage, self-reported depression, self-reported anxiety, and smoking. Dietary factors were adjusted for energy intake.

The following BDI-defined distinctions were made in Tanskanen et al.'s first study: scores below 10 indicated no or minimal depressive symptoms; scores from 10-18 indicated mild symptoms; 19-29, moderate symptoms; and 30-63, severe symptoms.[81] For bivariate analyses, the categories were normal mood, 0-9, and mild to severe symptoms, 10-63.[81] Multiple logistic regression analysis assessed the relationship between BDI-indexed depressive symptomatology and fish consumption. Adjustments were made for these potential confounders: age, marital status, unemployment, current smoker status, irregular physical activity, female, BMI, more than 120g per week of pure alcohol, at least seven cups per day of coffee, low education level, and serum cholesterol level. The other Tanskanen et al. study also employed the BDI, while analyzing separately data for the single item pertaining to suicide ideation.[80] Analyses adjusted for the following potential confounders: sex, age, marital status, education, employment status, work ability, area of residence, financial status, general health smoker status, alcohol intake, coffee intake, and physical activity.

Woo et al. utilized the GDS while adusting for age and baseline health status at the start of their 3-year study.[110] From previous validational work it was reported that a score of at least 8 on the 15-point GDS provides a sensitivity and a specificity of 96.3% and 87.5%, respectively, for a psychiatric diagnosis of depression in the local Chinese population. The HADS depression subscale was employed by Suzuki et al.[107] A cutpoint of 4 out of 5 has previously been observed to reflect good sensitivity and specificity (91.5% and 58%, respectively) for screening depression

(e.g., major depression). Analyses adjusted for age, sex, performance status, clinical stage, histology, pain, breathlessness, employment status, smoker status, alcohol consumption, and BMI. Edwards et al.'s analyses controlled for stress and smoking status.[48]

Given the limitation of the Japanese data, in that they were not produced using a structured diagnostic instrument or via random population sampling techniques, data analysis in Hibbeln's first cross-national assessment was completed both including and excluding data from Japan.[47] Since adverse personal, social and economic conditions can increase the risk of depressive symptomatology in the postpartum period, the following variables were controlled for in Hibbeln's second cross-national ecological analysis: study time postpartum, low socioeconomic status, percentage of young mothers, percentage of mothers without partners, percentage of mothers with secondary education, and the influence of Asian cultures.[108] Data on depression prevalence in Peet's cross-national ecological analysis[109] were captured from Weissman et al.[46] and the same Japanese source used by Hibbeln.[47] From the IPSS study, data on mean days out of hospital and percentage of patients with schizophrenia and severe social impairment were used as outcomes.[109] In addition, a total outcome score was derived.[145] It is a composite score taking into account all IPSS outcomes. From the DOSMED study, outcomes selected were percentage of patients never hospitalized and the percentage of patients with little social impairment. Urban data were used exclusively, where available. A "total best outcome" score was derived by adding data from various "best possible" DOSMED outcomes (e.g., remitting course with full remissions; on no antipsychotic medication during followup).

Study quality and applicability. The mean total Jadad quality score was 3,[98-100] with two of the three RCTs adequately concealing their allocation of participants to study groups.[98,99] The third RCT received an Unclear allocation concealment rating.[100] The mean quality score for the two single prospective cohort studies was 4.5, with both studies attaining a III applicability rating.[110,111] All three cross-sectional surveys received an applicability rating of III, and together they achieved a mean quality score of 4.7.[80,81,107] The single cross-sectional study received a quality score of 6 and an applicability rating of II.[48] The three cross-national ecological analyses received a mean quality score of 4, with all achieving an applicability rating of III.[47,108,109] Of all the studies, only the Edwards et al. one received an applicability rating other than III (i.e., II),[48] and only three investigations achieved a study quality grade of A.[98,107,108]

Summary Matrix 2: Study quality and applicability of evidence regarding the association between omega-3 fatty acid intake and onset, continuation or recurrence of depression (all designs)

		Study Quality								
		A			B			C		
Applicability	I	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
	II	**Author** Llorente[A]	**Year** 2003	**n** >89	**Author** Edwards	**Year** 1998	**n** 24	**Author** Ness[U] Wardle[A]	**Year** 2003 2000	**n** 452 176
	III	**Author** Suzuki Hibbeln	**Year** 2004 2002	**n** 902 16C	**Author** Hakkarainen Tanskanen Woo	**Year** 2004 2001 2002	**n** >29k >1k >2k	**Author** Tanskanen Hibbeln Peet	**Year** 2001 1998 2004	**n** >3k 9C 8C

n = number of allocated/selected participants; RCT = [A]Adequate vs [U]Unclear allocation concealment; C = Countries; k = 1,000's

Qualitative Synthesis of Individual Study Results

Llorente et al. reported data only for completers for whom they had baseline and 4-month data.[98] After 4 months of supplementation, plasma phospholipid DHA content in the DHA group had increased by 8% while the DHA content in the placebo group had decreased by 31%, the former observation indicating a reversal in the typical decline in DHA levels. The DHA content of the DHA group was 50% higher than that of the placebo group 4 months post-delivery. However, there were nonsignificant statistical differences between study groups after 4 months for the BDI, EPDS and the SCID-CV (diagnostic counts). Yet, according to BDI scores, only nine women in the placebo group and 11 women in the DHA group achieved a score of at least 10 at one of their followups, indicating minimal symptoms of depression (>9 may indicate mild symptoms). Two and four women in the placebo and DHA groups, respectively, had a BDI score of at least 20, indicating moderate symptoms. SCID-CV observations confirmed these results. Only seven women (DHA group=4; placebo group=3) met DSM-IV diagnostic criteria for a "current depressive episode" during the 4-month postpartum period.

All three of Wardle et al.'s study groups showed significant within-group improvement on many of the mental health outcomes after 12 weeks (i.e., BDI score and anger reactions in both diet groups; stress and anxiety only in Mediterranean diet group).[99] Yet, there were no significant between-group differences observed for any of the following clinical outcomes: depression, anxiety, anger/hostility, stress, and general psychological well-being. Thus, no reliable associations between intake of omega-3 fatty acids and any of the examined indices of mental health were observed.

Ness et al. observed that self-reported fish intake was higher in the fish advice group at study's end.[100] No statistical difference was observed in the fish advice group either for depression or anxiety; and, controlling for baseline mood, the between-group difference for each outcome was not statistically different. This last observation did not change following an additional adjustment made for one's status as having been randomized to the stress management arm, nor was there any statistical evidence of interaction between these factors in their effects on mood. Looking exclusively at the upper quartile of baseline depression or anxiety score did not contradict these observations.

In Llorente et al.'s study no subject withdrew due to adverse effects related to the supplement.[98] However, 37 of 138 women either withdrew or were dropped. Thirteen withdrew because of maternal illness, 14 were dropped due to lactation failure or excessive formula intake by the child (>20% of total intake), one mother moved away, five were dropped due to infant illness, and four discontinued participation. Wardle et al. reported that similar numbers of patient withdrew before 12 weeks in each study group (low-fat=7; Mediterranean=8; control=6), and typically due to attendance problems.[99] Seven men died within 7 months of randomization into Ness et al.'s trial (fish advice group=3), and for reasons other than the intervention.[100]

Hakkarainen et al.'s attempt, in their observational study, to assess the possible relationship between low dietary intake of omega-3 fatty acids and depression revealed that, accounting for the above-noted covariates, there was no significant association of fish consumption or calculated intake of omega-3 fatty acids and self-reported depressed mood, hospital treatment required due to major depressive disorder, or suicide (data not reported).[111]

Tanskanen et al. showed that, using BDI scores, 20% of their sample experienced mild depressive symptoms (n=647), 6.3% had moderate symptoms (n=201), and 1.5% reported severe symptoms (n=48).[81] Sixty-four percent reported eating fish or fish meals once or twice a week

(n=2,053), 6.3% ate fish daily (n=201), and 30% ate fish once or twice a month, or less often (n=950). From bivariate analysis, mild to severe depressive symptoms were more prevalent among women who infrequently consumed fish (less than once a week) than those who were frequent fish eaters (more than once per week). A similar trend was observed among men, yet the results were not statistically significant. Compared with frequent fish consumers (bivariate analysis), infrequent consumers were younger, less physically active, less obese, less likely to have a lower serum cholesterol level, unmarried, smoked, and drank a lot of coffee. Yet, higher age, being unmarried, unemployment, smoking, lower levels of physical activity, greater degree of obesity, low level of education, and higher serum cholesterol level were associated with depressive symptoms. Multiple logistic regression analysis, including confounders, revealed that infrequent fish consumption was independently associated with depressive symptoms. The likelihood of exhibiting mild to severe depressive symptoms was 31% higher among infrequent fish consumers than frequent consumers. Depressive symptoms were significantly associated with infrequent fish consumption for females only.

In their second cross-sectional study Tanskanen et al. observed that the risk of being depressed and the risk of suicidal ideation were significantly lower among those who frequently ate lake fish, compared with infrequent fish consumers.[80] These relationships held after adjusting for the above-noted factors.

Woo et al. found nonsignificant adjusted and unadjusted estimates of association involving fish intake and depressive symptoms in a Chinese elderly population although data were not reported per se.[110] They also observed that increasing levels of physical activity and occasional intake of alcohol were associated with a reduced risk of depressive symptoms. After 36 months, 341 participants (17%) had been lost to followup and 519 had died.

For newly diagnosed lung cancer patients Suzuki et al. reported a statistically significant adjusted odds ratio for depression between upper and lower quartiles of ALA and total omega-3 fatty acid intake, indicating a significant inverse association.[107] They also found a statistically nonsignificant adjusted difference for depression between upper and lower quartiles of intake of EPA, DHA and EPA+DHA.[107] Results of tests for trend paralleled these findings. But, no association was observed for depression and intake of fish or seafood, also following adjustments for potential confounders.

There were no significant between-group differences for current intake of omega-3 fatty acids or total energy intake assessed by 7-day dietary intake in Edwards et al.'s study.[48] Within the depressed patient group there was a significant negative correlation between the BDI-defined severity of depressive symptomatology and dietary intake of total omega-3 fatty acids as well as ALA. When data were pooled from patients and controls and entered into multiple regression, none of the dietary omega-3 or omega-6 fatty acid variables were significant predictors of depression. Data pertaining to smoker status and stress were entered only into analyses involving biomarker data.

In their first cross-national ecological analysis Hibbeln found a significant, inverse correlation between apparent fish consumption (fish pounds per person; 1 pound = 0.4536 kg) and major depression.[47] When data were excluded from Japan for the above-noted reason, a significant correlation was maintained. Data regarding potential confounders were not consistently available for each of the countries in Hibbeln's second cross-national ecological analysis.[108]. Nevertheless, simple regression and a logarithmic equation revealed that higher national seafood consumption predicted lower prevalence rates of postpartum depression, that higher DHA content in mother's milk predicted lower prevalence rates, and that the AA and EPA

content of mother's milk were unrelated to prevalence rates of postpartum depression. Only low socioeconomic status, young maternal age, the percentage of women without partners, and percentage of mothers with a secondary education predicted prevalence rates. These relationships appeared to be influenced by data from Brazil and South Africa, suggesting that these results may have confounded the findings in the primary analyses. However, first excluding Asian countries' data because of their stronger intake of omega-3 fatty acids in the background diet, and then data from Brazil or South Africa, yielded findings paralleling those from the primary analyses. This indicated the robustness of the main findings.

Peet's schizophrenia results are presented below.[109] He observed a significant association between high consumption of fish and seafood and a reduced prevalence of depression.[109]

Quantitative Synthesis

Very few of the studies that met the eligibility criteria for this question actually demonstrated the inherent capacity to afford the drawing of causal inferences regarding the possible relationship between the intake of omega-3 fatty acids and the onset of depression as disorder or symptom. Only three of 12 studies were eligible for quantitative synthesis in that they were both controlled and prospective by design.[98-100] The observation that these three RCTs employed highly different target populations, interventions, controls and outcomes made it inappropriate to consider conducting meta-analysis. Moreover, only one trial investigated the potential of specific amounts of omega-3 fatty acid content, via DHA supplementation, to protect its population (i.e., breastfeeding women) from developing (postpartum) depression.[98]

Impact of Covariates and Confounders

With such diverse designs, populations, exposures, controls and outcomes it is difficult to cull patterns of notable finding regarding the influence of extra-exposure variables on outcomes pertinent to this review. The designs with the greatest inherent potential to control for confounding influences (i.e., RCTs)[98-100] did not yield a single significant result, although the primary goal in two of them did not entail demonstrating the potential of omega-3 fatty acids as protection against depression.[99,100] At the same time, the three RCTs likely confirmed, in part, the success of their randomizations by showing that study groups were equivalent at baseline on certain important bases (e.g., mental health variables).

Likewise, the multiple-group cross-sectional study did not reveal a significant association between omega-3 fatty acid intake and depression while also reporting that study groups were equivalent in their intake of omega-3 fatty acids, for example.[48] And, while most of the uncontrolled observational studies did a reasonable job of adjusting for confounders in their analyses (e.g., age, smoker status, alcohol consumption),[80,81,107,111] their results did not consistently show a significant association between the intake of omega-3 fatty acids and the risk of depression. Even the two surveys conducted in Finland, where fish intake is considerably higher than in North America, for example, failed to produce a consistent result for both sexes.[80,81]

The ability to control for confounders in the three cross-national ecological analyses depended on the initial data collection strategies, which produced the databases from which the three studies' data were obtained. Without all of the details, many of which were not published

in the included reports, it is difficult to draw conclusions about these three analyses' successes or failures in controlling for key influences on outcomes.

Is the Onset, Continuation or Recurrence of Depression Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Tables 7 through 11 (below), derived from Evidence Tables 1 and 2 (Appendix E*), one RCT and various observational studies met eligibility criteria for this question. Studies were published between 1977 and 2003.

Overview of Relevant Studies

Seven multiple-group cross-sectional studies[48,101-106] and one RCT[98] provided data pertaining to this question. Two studies have already had their key study parameters introduced with respect to the question of the possible association of omega-3 fatty acid intake and the onset, continuation or recurrence of depression. Yet, the Llorente et al. RCT[98] and Edwards et al.'s multiple-group cross-sectional study[48] data were nevertheless placed in summary tables.

Ellis and Sanders assessed the fatty acid content of plasma choline phosphoglycerides (CPG) and RBC ethanolamine phosphoglycerides (EPG) in patients diagnosed with endogenous depression (n=6), patients on the same ward yet with non-depressive psychiatric disorders (n=4; types undefined), and age- and sex-matched controls drawn from hospital staff (n=6) (Summary Table 7).[105] Fehily et al. compared the fatty acid content of plasma CPG and RBC phospholipids in patients with: endogenous depression (n=26; mean age: 52 [21-74] years; 7 bipolar and 16 unipolar diagnoses; 54% drug-free for at least 2 weeks before study), those with reactive depression (n=23; mean age: 38 [22-65] years; 65% drug-free for at least 2 weeks), other psychiatric disorders (n=11; mean age=35 [19-59] years; 6 schizophrenia and 5 personality disorder diagnoses; 46% drug-free for at least 2 weeks) and age- and sex-matched healthy controls (n=undefined; age undefined).[106]

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 7: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Ellis, 1977, England: multiple-group cross-sectional study[105]	endogenous depression (n=6)	non-depressive psychiatric disorders (n=4)/ age- & sex-matched healthy controls (n=6)	Proportions of plasma CPG EPA^{++} & DHA^{++} ↑ in endogenous depression grp vs matched controls; NS bet-grp difference for AA; results less pronounced for RBC EPG data; NS bet non-depressed pts & healthy controls	Total quality: 2 [Grade: C]	II
Fehily, 1981, England: multiple-group cross-sectional study[106]	endogenous depression (n=26)/ age- & sex-matched controls (n=NR)	reactive depression (n=23)/ other psychiatric disorders (n=11)	Concentrations of DHA^{+++} & EPA^{+} in plasma CPG ↑, but LA ↓,$^{+++}$ in endogenous depression grp than controls; NS bet-grp difference for AA; NS plasma CPG in reactive depression or other disorders vs controls; DHA concentrations correlated with BDI severity in endogenously depressed,$^{++}$ but not with reactive depression; smaller bet-grp differences for RBCs in endogenous depression vs controls (i.e., ↑ DHA in EPGs;$^{+}$ ↑ EPA in serine phosphoglycerides^{+})	Total quality: 3 [Grade: C]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; BDI = Beck Depression Inventory; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Maes et al. examined the fatty acid composition of serum cholesterol esters and phospholipids in 36 patients with major depressive disorder (with [n=11] or without melancholia [n=25]), 14 with minor depression (i.e., adjustment disorder with depressed mood and dysthymia) and 24 healthy volunteer subjects (staff or their family members) (Summary Table 8).[103]

Summary Table 8: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Maes, 1996, Belgium: multiple-group cross-sectional study[103]	inpatients with major depression (with [n=11] or without melancholia [n=25]) (n=36)	minor depression (i.e., adjustment disorder with depressed mood & dysthymia) (n=14)/ healthy volunteers (staff or their family members) (n=24)	Age & sex as covariates, major depressed pts ↑ AA/EPA in serum cholesteryl esters^{+} & PLs^{++} & ↑ total n-6/n-3 in cholesteryl ester fractions;$^{++}$ NS in total n-3, total n-6, or n-6/n-3, in PLs; correlations of HDRS & AA/EPA^{+} or total n-6/n-3^{+} in PLs; major depressed pts ↓ ALA in cholesteryl esters^{++} than controls; major depressed pts had ↓ total n-3 in cholesteryl esters^{++} & ↓ EPA in serum cholesteryl esters^{++++} & PLs; ALA, EPA & DHA cholesteryl ester fractions discriminated 3 grps.$^{++++}$ ALA, EPA & DHA cholesteryl ester fractions as dependent variables showed differences for 3 grps;$^{++++}$ negative relationship bet EPA in cholesteryl esters & HDRS^{+}	Total quality: 6 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; HDRS = Hamilton Depression Rating Scale; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Peet et al. investigated fatty acid composition in the RBC membranes of 15 drug-free patients with major depressive disorder, unipolar variety, and 15 age- and sex-matched healthy controls (Summary Table 9).[102] All medication was stopped for 8 to 91 days prior to blood sampling.

Summary Table 9: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Peet, 1998, England: multiple-group cross-sectional study[102]	major depressive disorder (n=15)	healthy controls (n=15)	↓ RBC total n-3^{+} & DHA^{+++} in depressive pts; ↓ LA,$^{+++}$ DGLA^{+} & total n-6;$^{+}$ NS for AA/EPA, AA/DHA or total n-6/n-3	Total quality: 4 [Grade: B]	II
Edwards, 1998, England: multiple-group cross-sectional study[48]	depressed patients (n=10)	matched healthy controls (n=14)	RBC EPA,$^{+}$ DHA^{+} & total n-3^{+} ↓ in depressed pts; NS for n-6; negative correlations for n-3 & BDI severity for ALA,$^{+++}$ DHA^{++} & total n-3;$^{+}$ only RBC ALA predicted BDI severity;$^{++}$ when dietary & RBC data entered, only DHA^{++++} & LA^{+} predicted BDI severity	Total quality: 6 [Grade: B]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; HDRS = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; RBC = red blood cells; PL = phospholipid; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Edwards et al. measured the dietary PUFA intake as well as the fatty acid content of RBCs in a cross-sectional study of ten depressed patients diagnosed with major depression using DSM-IV criteria, and 14 matched healthy control subjects.[48] Each depressed patient was receiving antidepressant medication. Analyses controlled for stress and smoking status. Additional details regarding exclusion criteria or matching requirements were presented in relation to the question concerning the possible association between omega-3 fatty acid intake and the onset, continuation or recurrence of depression.

Maes et al.'s second study investigated 34 major depressed inpatients and 14 healthy volunteers in an attempt to establish whether major depression was associated with a decrease in omega-3 fatty acids or an increase in omega-6 fatty acids in serum phospholipids and cholesteryl esters (Summary Table 10).[101] They also assessed the relationship between these PUFAs and levels of serum zinc (with a low level being a marker of the inflammatory response system's activation), as well as the effects of 5 weeks of subchronic treatment with antidepressants (i.e., fluoxetine 20 mg/d alone or with trazodone 100 mg/d or pindolol 7.5 mg/d) on fatty acid levels in 20 patients. Patients underwent a 10-day drug-free period upon hospital admission.

Summary Table 10: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Maes, 1999, Belgium: multiple-group cross-sectional study[101]	major depressed inpatients (n=34)	healthy volunteers (n=14)	Serum PLs= major depression ↓ EPA,$^{+}$ ↑ AA/EPA ratio fractions; ↓ LA,$^{++}$ ↓ AA,$^{+++}$ ↓ total n-6,$^{+++}$ ↓ ALA,$^{+}$ ↓ EPA,$^{+}$ ↓ DHA,$^{+}$ & ↓ total n-3^{++} concentrations; Serum cholesteryl esters= major depression ↓ ALA,$^{+++}$ EPA,$^{++}$ total n-3,$^{++}$ ↑ total n-6/n-3,$^{++}$ & ↑ AA/EPA^{++} fractions; ↓ LA,$^{++}$ ↓ total n-6,$^{++}$ ↓ ALA,$^{+++}$ ↓ EPA,$^{++}$ & ↓ total n-3^{++} concentrations; NS correlations bet HDRS & FAs	Total quality: 6 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; PL = phospholipid; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Tiemeier and colleagues investigated whether community-dwelling elderly with depression have a fatty acid composition different from those who are not depressed (Summary Table 11).[104] As part of the Rotterdam population-based cohort study (n=7,983), 3,884 adults of at least 60 years of age were screened for depressive symptoms. Those that screened positive had a psychiatric interview to diagnose depressive disorders. After excluding individuals with other disorders (n=29), and following the loss of 14 subjects, study groups became: those with depressive disorder (n=106; 61-97 years), those with subclinical depressive symptoms (n=115; 61-93 years) and randomly selected controls who had screened negative for depression in the Rotterdam study (n=461; 61-101 years). The analysis included an assessment of the possible roles played by atherosclerosis and the inflammatory response, the latter measured by C-reactive protein. Given that certain factors such as chronic diseases, smoking and cholesterol concentrations have been related in community-dwelling populations to depression and fatty acid composition,[168] they were investigated for their possible roles as confounders. Other confounders included: age, sex, level of education, history of stroke, cognitive function (Mini Mental State examination), functional status, and blood pressure.

Summary Table 11: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Tiemeier, 2003, Holland: multiple-group cross-sectional study[104]	depressive disorders in elderly (n=106)	subclinical depressive symptoms (n=115)/ screened negative for depression (n=461)	AA^{+} & DHA^{+} ↑ & ↓ in depressed pts; ↑ in depressed vs controls: total n-6/n-3^{+} & AA/DHA.$^{+}$ difference in n-6/n-3 for depressed vs controls ↑ with ↓ concentrations of C-reactive protein;$^{+}$ only for those below median, depressed pts had ↓ %'s of certain n-3's than controls; depressives had ↓ EPA,$^{+}$ DHA^{+} & total n-3;$^{++}$ depressives had ↑ n-6/n-3,$^{++}$ AA/EPA^{++} & AA/DHA.$^{+}$	Total quality: 5 [Grade: B]	III
Llorente, 2003, US: 4 mo parallel RCT[98]	~200mg/d DHA (n=44 completers)	pb (undefined) (n= 45 completers)	NS correlations bet plasma PL DHA content, either at baseline or 4 mo, &: BDI, EPDS or SCID-CV	Jadad total: 5 [Grade: A]; Schulz: Adequate	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; BDI = Beck Depression Inventory; EPDS = Edinburgh Postnatal Depression Scale; SCID-CV = Structured Clinical Interview, DSM-IV, Axis I Disorders, Clinical Version; RBC = red blood cells; PL = phospholipid; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Llorente et al. assessed the effect of DHA supplementation on the onset of postpartum depression as well as on plasma phospholipid DHA content in women who breast-feed.[98] Mothers who planned to breast-feed their children (n=138; 18-42 years) were randomly assigned, in double-blind fashion, to receive either ~200 mg/d DHA or placebo (undefined) for the first 4 months after delivery. Plasma phospholipid data were collected just before delivery and at 4 months. Additional data regarding study, population and intervention parameters are presented with reference to evidence concerning the possible association of omega-3 fatty acid intake and the onset, continuation or recurrence of depression.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. With the exception of Llorente et al.'s RCT,[98] studies were cross-sectional studies involving at least two groups.[48,101-106] Some study reports provided very detailed inclusion/exclusion criteria establishing strong experimental controls,[101,103] whereas others provided very little information.[105] Other reports provided sufficient detail to allow for an appreciation of the rigor associated with these studies.[48,98,102,104,106] Study sizes varied between 16[105] and 682 participants.[104] Countries where the studies were conducted included England,[48,102,105,106] Belgium,[101,103] Holland[104] and the US.[98] Fehily et al's study was supported

by a grant from the South Thames Regional Health Authority.[106] The first Maes et al. study was funded by numerous sources, including the National Funds for Scientific Research (Belgium), the IUAP program (Belgium), as well as grants from the US Preventive Health Services (USPHS) and the Elisabeth Severance Prentiss and John Pascal Sawyer Foundations.[103] One author was the receipient of a USPHS Research Center Career Scientist Award. The second Maes and colleagues study was funded in part by the National Funds for Scientific Research (Belgium), the Clinical Research Center for Mental Health (Belgium), in addition to an Staglin Investigator Award given to the lead investigator.[101] Tiemeier et al.'s work was supported by the Research Institute for Diseases in the Elderly, which is funded by the Ministry of Education and Science, and the Ministry of Health, Welfare, and Sports through the Netherlands Organization for Scientific Research, and a grant from Numico Research.[104] Llorente et al.'s study was supported by industry (Martek Biosciences Corporation).[98] Three groups did not report a funding source.[48,102,105]

Population characteristics. Complete population age data were not reported for both the full sample and/or the different study groups in some studies, this despite the avowal of the authors that study groups were matched by age and sex.[48,102,105] In the study by Fehily et al., the group of subjects with endogenous depression was older than the control group.[106] The pregnant women examined in Llorente et al.'s study were between 18 and 42 years of age; there was no significant difference in ages of the participants between study groups.[98] In each of Maes et al.'s studies, neither the between-group age of participants nor the between-group female/male ratio were significantly different.[101,103] Neither age nor sex significantly predicted any omega-3 fatty acid fractions or any omega-6/omega-3 ratios in these two studies.[101,103] Yet, both variables were entered as covariates in subsequent analyses due to their possible relationship with fatty acid levels.[101,103] Peet et al.'s study population was between 18 and 65 years of age, and the authors confirmed successful matching for this possible confounder.[102] Tiemeier et al.'s study groups were age-matched, with ages ranging from 61 to 101 years of age; subjects with depressive disorder were more likely to be female.[104] Six of the study populations were not described in terms of ethnic/racial background, while Maes et al.'s participants were explicitly identified as Caucasian of Flemish origin.[101,103]

The studies conducted by Ellis and Sanders[105] and Fehily et al.[106] each included heterogeneous subtypes of endogenous depression, with subtypes undefined in the former[105] and with neither report presenting outcome data broken down by any of these subtypes. The remaining studies identified reasonably well-defined groups for which to compare biomarkers data. The Maes et al. studies likely serve as the best examples of a well-conceived and operationalized separation of study groups.[101,103] In this regard, their depressed patients were identified using DSM-III-R diagnostic criteria applied via the SCID, patient version.[101,103] Peet et al. employed DSM-IV criteria to identify depressed patients.[102] Neither Ellis and Sanders nor Fehily et al. described their diagnostic criteria.[105,106] Depressive disorders were identified by Tiemeier et al. via a score of at least 16 (i.e., clinically significant depressive symptoms) on the validated Dutch version of the Center for Epidemiologic Studies Depression scale (CES-D) during a home interview, followed by a psychiatric workup using the Dutch version of the Present State Examination (i.e., a semistructured interview from the validated Schedules for Clinical Assessment in Neuropsychiatry). DSM-IV criteria were used to guide the diagnosis, with categories including major depression and dsythymia in addition to minor depression.[104]

Few studies adequately ruled out the presence of possible psychopathology, or risks thereto, in subjects typically identified as "healthy volunteers" or "healthy controls."[102,105] Maes et al.'s

investigations carefully provided the basis for separating their study groups to achieve control of this confounder. Healthy volunteers were excluded for present, past and family (first degree) history of Axis I or Axis II disorders using the SCID, Lifetime version.[101,103] All participants had low scores on the Zung Depression and Anxiety Scales (<32) and the BDI (<9).[103] Controls were medication-free for at least 1 month prior to blood sampling.[101,103] None had ever taken psychotropic drugs[103] or was a regular drinker.[101,103]

A few studies established the baseline severity of symptomatology. For example, Fehily et al. used the BDI,[106] Maes et al. employed the HDRS, and Peet et al. used the MADRS (no data reported).[102,103] In their first study Maes et al. observed that those with major depression had significantly higher baseline HDRS severity scores than did those with minor depression.[103] Ellis and Sanders, for example, did not measure severity.[105] Baseline data concerning the duration of the current episode, age of onset, number of previous episodes, and time since diagnosis were rare.

In attempts to control for possible confounding from variability due to comorbid conditions, some studies applied strict exclusion criteria. For example, in both of the studies by Maes et al., patients were excluded if they had Axis I diagnoses other than unipolar depression, including psychotic disorders, organic mental disorders, impulse control disorders, substance use disorder or substance abuse (within the last 6 months), or borderline and antisocial personality (Axis II) disorders.[101,103] Also excluded were individuals with abnormal X-rays of heart and lungs, electrocardiogram or electroencephalogram.[101,103] All study participants had normal chemical and hematologic tests relating to, for example, liver function and renal function,[101,103] as well as electrolyte, thyroid hormone and thyroid stimulating hormone levels.[101] All were free of medical illness (e.g., immune and endocrine disorders such as diabetes, inflammatory bowel syndrome, autoimmune disorders, essential hypertension and arteriosclerosis).[101,103] None exhibited evidence of allergic, inflammatory or immune responses for at least 2 weeks prior to blood sampling.[101,103] BMI was within normal limits.[101,103] Heavy smokers (>15 cigarettes per day) were excluded.[101]

Peet et al. excluded those individuals with a physical illness of a severity or nature associating it with abnormal levels of omega-3 fatty acid levels.[102] Controls were medication-free, and without a history of psychiatric illness, personality disorder, substance abuse or medical illness (method undefined). Yet, Tiemeier et al. noted differences in their study groups, with elderly individuals with depressive disorders more likely to have had a stroke and to exhibit significantly lower activities of daily living scores and cognitive scores compared with those without depressive symptoms.[104] Some studies did not identify possible psychiatric comorbidity or control for it via the application of clearly stated exclusion criteria.[105,106] Yet, Peet et al. did note the absence of significant between-group differences regarding smoker status or in the relationship between smoker status and PUFA content.[102]

Six of eight studies did not involve an intervention or exposure. Only Llorente et al. employed supplementation,[98] as possible prophylaxis, and Edwards et al. assessed dietary intake of omega-3 fatty acids.[48] In both Maes et al. studies all participants were consuming a normal Belgian diet (PS ratio=0.54$\pm$0.43); and, those on a low fat diet were excluded.[101,103] No other studies controlled statistically for background diet in their analyses. No study reported inappropriate methods by which lipids were extracted, prepared, stored or analyzed.

Ellis and Sanders did not describe the medication status of their participants (i.e., medication-naïve, medication-free or medicated, with type and dose).[105] Fehily et al. reported that different percentages of individual within study groups were drug-free, indicating heterogeneity within

diagnostic groups.[106] This situation could confound the results. Those receiving medication were receiving a hypnotic and/or a tranquillizer. Two schizophrenic patients that had been admitted to the study, yet whose data were not analyzed separately, were taking a neuroleptic. The investigators reported that the fatty acid content of those taking these drugs and those who were medication-free was not different (no data or p-value reported).[106] Peet et al.'s patients were drug-free at first assessment.[102] Seven patients then received dothiepin, three took paroxetine, and one each received trazodone and lofepramine.[102]

Maes et al. excluded those individuals receiving treatment with MAOIs, antipsychotic doses of neuroleptic, anticonvulsants, lithium or ECT in the previous year.[101,103] Maes et al. also specified fluoxetine and trazadone in their second study.[101] No cholesterol-lowering drugs were permitted.[101] Use of any medication known to influence fatty acid metabolism or endocrine and immune function was prohibited as well.[101] No significant between-group differences were observed for the prestudy use of antidepressants, benzodiazepines or antipsychotics in Maes et al.'s first study.[103] Prestudy use of the different drug classes did not significantly predict any of the omega-3 fatty acid fractions or any omega-6/omega-3 ratios.[103] All antidepressant, benzodiazepine or low dose antipyschotics were discontinued the month prior to an 8-10 day washout period.[103] The second Maes et al. study mandated the discontinuation of antidepressants upon hospital admission.[101] Twenty-six depressed patients had been treated with antidepressants during the depressive episode.[101]

Twenty-seven patients with depression in Maes et al.'s first study,[103] and 18 patients in their second study,[101] used a low dose of benzodiazepines for severe agitation, anxiety sleep disorders or suicidal ideation during the study period. There was no significant between-group difference in the use of these on-study medications.[101,103] As well, there were no significant differences in EFA status data for those depressed patients who did or did not use on-study benzodiazepines.[101]

Outcome characteristics. Outcomes included all types of fatty acid, from various sources, and were expressed either as percentages, or fractions (i.e., composition), or concentrations.

Study quality and applicability. The seven cross-sectional studies received a mean quality score of 4.6, with four achieving an applicability rating of II,[48,102,105,106] and three attaining an applicability rating of III.[101,103,104] The single RCT was assigned an Jadad total quality score of 5, an Adequate allocation concealment rating, and an applicability score of I.[98]

Summary Matrix 3: Study quality and applicability of evidence regarding the association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of depression (all designs)

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author	Year	n	Author	Year	n	Author	Year	n
		Llorente[A]	2003	>89	Peet	1998	30	Ellis	1977	16
					Edwards	1998	24	Fehily	1981	>60
	III	Author	Year	n	Author	Year	n	Author	Year	n
					Maes	1996	74			
					Maes	1999	48			
					Tiemeier	2003	682			

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

Qualitative Synthesis of Individual Study Results

The proportions of plasma CPG EPA and DHA were each significantly greater in the endogenous depression group as compared to healthy controls in the Ellis and Sanders study.[105] On the other hand, AA did not differ between these two groups. These differences were less pronounced for RBC EPG data (no data or p-values reported). There were no significant differences in fatty acid status between non-depressed patients and healthy controls.

Concentrations of DHA and EPA in plasma CPG were each significantly higher, but LA was significantly lower, in Fehily et al.'s endogenous depression group compared with matched controls.[106] There was no significant difference between these two groups in terms of AA levels. The plasma CPG status of patients with reactive depression or other psychiatric disorders did not differ from the controls. Eighty percent of those with endogenous depression had DHA levels of more than 54 mg/g total fatty acid esters detected, as compared to 19% of matched controls. DHA concentrations were correlated with BDI severity score for those identified as endogenously depressed, but not for those with reactive depression. Similar, but smaller, between-group differences were observed for the fatty acid content of RBCs of patients with endogenous depression compared with matched controls (i.e., higher DHA in EPGs; higher EPA in serine phosphoglycerides).

By ANCOVA, with age and sex as covariates, major depressed patients exhibited a significantly higher AA/EPA ratio in both serum cholesteryl esters and phospholipids in addition to a significantly increased total omega-6/omega-3 ratio in cholesteryl ester fractions than did healthy volunteers or minor depressed subjects in Maes et al.'s first study.[103] Significant between-group differences were not observed for total omega-3 or total omega-6 fatty acid content, or their ratio, in phospholipids. The only significant correlations involved the HDRS score with the AA/EPA or total omega-6/omega-3 fatty acid ratios in phospholipids. Major depressed patients had significantly lower ALA in cholesteryl esters compared with healthy controls. Major depressed patients showed significantly lower total omega-3 fatty acids in cholesteryl esters and significantly lower EPA in serum cholesteryl esters and phospholipids compared with minor depressed subjects or healthy controls. ALA, EPA and DHA cholesteryl ester fractions successfully discriminated the three study groups. MANOVA using ALA, EPA and DHA cholesteryl ester fractions as dependent variables showed highly significant differences among the three study groups. There was a significant negative relationship between EPA in cholesteryl esters and HDRS scores.

Peet et al. observed a significant reduction in RBC membrane total omega-3 fatty acids and DHA content in drug-free depressive patients.[102] They also observed a significant reduction in LA, DGLA and total omega-6 fatty acids. No significant between-group differences were found for AA/EPA, AA/DHA or total omega-6/omega-3 fatty acid ratios. Subsequent intervention with anti-depressants failed to have a significant effect on the RBC omega-3 fatty acid status. Yet, this study failed to fully control for possible confounding influences such as stress, smoking or diet.

Edwards et al. reported that RBC membrane EPA, DHA and total omega-3 fatty acid levels were significantly lower in the depressed patient group.[48] There were no significant differences for any omega-6 fatty acid levels. There were no significant between-group differences for current dietary intake of omega-3 fatty acids or total energy intake (via 7-day weighted intake). The only significant, and negative, correlations involved omega-3 fatty acids and BDI-defined severity score: for ALA, DHA and total omega-3 fatty acid content. Multiple regression revealed

that only RBC membrane ALA significantly predicted BDI score. When dietary and RBC membrane data were entered in stepwise fashion, DHA and LA emerged as the only predictors of BDI severity score. Neither current smoker status nor recent stress had an effect on RBC membrane values.

Maes et al. found in serum phospholipids that major depression was associated with (all significant): higher MUFA fractions, lower adrenic acid (omega-6) yet higher (omega-6-)DPA, lower EPA, lower (omega-3-)DPA, higher AA/EPA ratio, higher (omega-6-)DPA/DHA fractions (i.e., composition: weight as percent of total).[101] In addition, lower concentrations (mg/dL) of SFAs, MUFAs, LA, AA, adrenic acid (omega-6), total omega-6 fatty acids, ALA, EPA, (omega-3-)DPA, DHA, and total omega-3 fatty acids (all significant) were found in the serum phospholipids of patients with major depression.[101] For serum cholesteryl esters, major depression was associated with (all significant): lower ALA, EPA, and total omega-3 fatty acids; and, higher total omega-6/omega-3 fatty acids and AA/EPA fractions. Additionally, major depression was associated with lower total saturated fatty acids, MUFAs, LA, DGLA, total omega-6 fatty acids, ALA, EPA, and total omega-3 fatty acid concentrations (all significant), in serum cholesteryl esters.[101] All analyses included age and sex as covariates. There were no significant correlations between HDRS score for depressive patients and any of the fatty acid variables.

In the phospholipids of major depressed patients, serum zinc was significantly and positively correlated with the percentages and concentrations of EPA, DHA and total omega-3 fatty acids.[101] Significant negative correlations were observed for percentage of total omega-6 fatty acids, AA/EPA, (omega-6-)DPA/DHA, and total omega-6/omega-3 fatty acids. In their cholesteryl esters, only the total omega-3 fatty acid percentage, and EPA, were significantly and positively correlated with major depression. There was no significant effect of antidepressant treatment on fatty acid levels. With a decrease of at least 50% in HDRS score defining a good clinical response to antidepressants after 5 weeks, depressed patients were divided into responders and non-responders.[101] There were no significant differences in fatty acid percentages between responders and non-responders.

Tiemeier et al. found no significant differences in the percentages or ratios of plasma phospholipid fatty acids between controls and those exhibiting subclinical depressive symptoms.[104] When the comparisons involved depressed subjects and controls, only a few, marginal differences were observed. By ANCOVA, with the above-noted covariates, percentages of AA and DHA were higher and lower, respectively, in the depressed subjects compared with controls. The ratios of total omega-6/omega-3 fatty acids and AA/DHA were higher in the depressed subject group when compared to reference subjects. Neither the inflammation marker C-reactive protein nor atherosclerosis affected these results. A test of interaction showed that the relation between the omega-6/omega-3 ratios and depressive disorders depended on the C-reactive concentration. That is, the difference in the omega-6/omega-3 ratio between depressed and reference subjects increased with lower concentrations of C-reactive protein. Stratification of the analysis at the median of C-reactive protein concentrations (1.5 mg/L), and involving subjects above this cutpoint, revealed no significant difference in fatty acid composition between the depressed and reference groups. Yet, when data were analyzed from those falling below the cutpoint, it was observed that depressed persons had significantly lower percentages of certain omega-3 fatty acids than did reference subjects. By ANCOVA, subjects with depressive disorder showed lower levels of EPA, DHA and total

omega-3 fatty acids. As well, depressed subjects showed higher values for total omega-6/omega-3 fatty acids, AA/EPA and AA/DHA.

In their RCT, Llorente et al. observed no statistically significant correlations between plasma phospholipid DHA content, either at baseline or at 4 months, and self-rating (BDI, EPDS) or syndromal measures of depression (SCID-CV).[98]

Quantitative Synthesis

Although all of the included studies were controlled, only one was prospective by design. Thus, meta-analysis was considered inappropriate. The exact nature of the inappropriateness of cross-sectional study data to address the question of onset is described in the Discussion.

Impact of Covariates and Confounders

Numerous factors have the capacity to influence EFA levels, including dietary intake, smoking and alcohol consumption.[101-103] Most of the studies did not control for smoking, for example, which alone could produce a picture of omega-3 fatty acid deficiency.[60] Only a minority of studies adequately controlled for the possible influence of this or any other variable.

The study by Peet et al.,[102] and especially the two studies by Maes et al.,[101,103] employed strict controls, and results suggested an omega-3 fatty acid deficiency in depressed patients. Edwards et al. controlled for stress and smoker status.[48] However, less well-controlled studies—for example, failing to formally rule out psychopathology in the controls—also produced a similar picture of an omega-3 fatty acid deficiency in depressed patients. It is possible that the between-group differences might have been more pronounced in the latter studies had the possible influence of this and other potential confounding factors been minimized.

Failure to include even minimally homogeneous groups of depressed individual may have produced the only two study results suggesting that, compared with depressed patients, healthy controls exhibited an omega-3 fatty acid deficiency.[105,106] As well, in studies where patients were either already receiving antidepressant medication,[48] or received medication sometime after the initial blood sampling and were subsequently retested,[101,102] analyses revealed that antidepressant medication did not substantially modify the between-group difference in omega-3 fatty acid levels in biomarkers. The country in which the study was conducted could not readily be used as a surrogate for background diet in assessing the impact of the latter on study results since there was insufficient variability in study results.

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Suicidal Ideation or Behavior?

As observed in Summary Table 12 (below), derived from Evidence Table 2 (Appendix E*), two observational studies met eligibility criteria. The studies were published in 2001 and 2004.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Overview of Relevant Studies' Characteristics and Results

Each observational study has already had its key characteristics described with reference to the question of the possible association of omega-3 fatty acid intake and the onset, continuation or recurrence of depression. Hakkarainen et al. investigated the relationship between dietary intake of omega-3 fatty acids and low mood, major depression, and suicide in males 50 to 69 years of age living in southwestern Finland in 1985.[111] The study utilized a cohort (n=29,133) from a primary prevention RCT (ATBC Cancer Prevention Study). Followup lasted nine years. The intake of fatty acids and fish consumption were derived from a validated food use questionnaire focused on the "last 12 months." Suicides were determined from Central Population Register data.

Summary Table 12: Association between omega-3 fatty acid intake and onset, continuation or recurrence of suicidal ideation or behavior

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Hakkarainen, 2004, Finland: 9 y single prospective cohort from RCT[111]	males 50-69 y from RCT's intervention & placebo grps (n=29,133)		NS association (no data reported)	Total quality: 5 [Grade: B]	III
Tanskanen, 2001, Finland: single population cross-sectional survey[80]	adult males & females (n=1,767)		Adjusted depression & suicidal ideation risks ↓ in frequent fish consumers[+]	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; [+]p<.05 or significant with 95% confidence interval; [++]p<.01; [+++]p<.001; [++++]p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Tanskanen et al.'s sample was selected based on a random population sample (National Population Register) of both sexes (n=3,004; 25-64 years).[80] Data were gathered on fish consumption, depression (BDI) and suicidality. Suicidality was measured using a single BDI item. Given that the studies varied on the basis of their focus, that is, one on "successful" suicidal behavior and the other on suicidal ideation, and that the key study and population parameters have already been contrasted in an earlier part of the report, only the results are now presented. Quantitative analysis was considered inappropriate.

Adjusting for numerous factors (i.e., age, sex, marital status, education, employement status, work ability, area of residence, financial status, general health, smoking, alcohol intake, coffee drinking, and physical activity), Tanskanen et al. found that the risk of suicidal ideation was significantly lower among frequent consumers of lakefish.[80] Adjusting for many factors as well

(i.e., age, BMI, energy intake, serum cholesterol level, HDL level, alcohol use, education, marriage, self-reported depression and anxiety, and smoking), Hakkarainen et al. observed no significant association between fish consumption or intake of omega-3 fatty acids and suicide.[111] Both Hakkarainen et al. and Tanskanen et al.'s results, while indicating good statistical control for important key confounders, are insufficient to allow us to infer the role of any covariates or confounders. Meta-analysis was not considered since outcomes were not comparable.

Study quality and applicability. Although they employed different research designs, both studies were assigned a level III for applicability, and together they received a mean quality score of 4.5.[80,111]

Summary Matrix 4: Study quality and applicability of evidence regarding the association between omega-3 fatty acid intake and onset, continuation or recurrence of suicidal ideation or behavior (all designs)

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author Hakkarainen Tanskanen	Year 2004 2001	n >29k >1k	Author	Year	n
n = number of allocated/selected participants; k = 1,000's										

Are Omega-3 Fatty Acids Efficacious as Supplemental Treatment for Bipolar Disorder?

As observed in Summary Table 13 (below), derived from Evidence Table 1 (Appendix E*), two controlled studies met eligibility criteria. While both were published, only Stoll et al. (1999) provided sufficient study-related data to permit its full review.[112] Akkerhuis and Nolen (2003) reported some peripherally-related data in a letter to the editor in which they referred to the placebo-controlled study from which their anecdotal data were derived.[93] A search via Pubmed did not locate a report of the full study. Thus, a comprehensive qualitative synthesis (or meta-analysis) could not be achieved (e.g., impact of covariates and confounders). A summary matrix could not be derived.

Overview of Relevant Studies' Characteristics and Results

Stoll et al. randomized 44 patients with bipolar disorder (18-65 years) to receive either 9.6 g/d of omega-3 fatty acids (6.2 g/d EPA, 3.4 g/d DHA) from menhaden fish body oil, via seven capsules twice daily, or identical gelatin placebo capsules containing olive oil ethyl ester (Summary Table 13).[112] Capsules were vacuum deodorized, and both tertiary butylhydroquinone

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

(0.2 mg/g) and tocopherols (2 mg/g) were added as antioxidants. Randomization was stratified by sex (n=9/14 completers in omega-3 fatty acid group; n=11/16 completers in placebo group), concurrent lithium use (n=6/14 completers in omega-3 fatty acid group; n=6/16 completers in placebo group), and rapid cycling status (n=7/14 completers in omega-3 fatty acid group; n=5/16 completers in placebo group). Diagnosis was established using the SCID and DSM-IV criteria for Types I or II bipolar disorder (n=2/14 completers with Type II in omega-3 fatty acid group; n=3/16 completers with Type II in placebo group). Eight patients entered the study without receiving psychotropic medication, and a post hoc analysis of their data constituted an evaluation of omega-3 fatty acids as primary treatment (n=4 per study group). Mood states varied at study entry both across study groups and within each study group.

Summary Table 13: Omega-3 fatty acids as supplemental treatment for bipolar disorder

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)			
Stoll, 1999, US: 4 mo parallel RCT[112]	9.6g/d EPA+DHA (6.2g/d EPA, 3.4g/d DHA) (n=~22)	olive oil ethyl ester pb (n=~22)	n-3 grp had longer remission;$^{++}$ same result for pts without medication;$^{+}$ bet-grp differences on CGI,$^{++}$ GAS,$^{+}$ & HDRS;$^{++}$ sex, rapid cycling status or disorder type did not predict response	Jadad total: 4 [Grade: A]; Schulz: Adequate	I
Akkerhuis, 2003, NR: 4 wk "controlled study"[93]	maximum 6g/d EPA ethyl ester (n=NR)	pb (source undefined) (n=NR)	NR	Could not evaluate	X

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; HDRS = Hamilton Depression Rating Scale; CGI = Clinical Global Impression scale; GAS = Global Assessment Scale; YMRS = Young Mania Rating Scale; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Patients were free of notable medical and psychiatric comorbidity. They were required to have experienced at least one manic or hypomanic episode within the past year.[112] The investigators argued that this inclusion criterion would enhance the study's power to detect a difference since such episodes were likely to recur. Forty percent of participants had exhibited rapid-cycling symptoms (i.e., at least four mood episodes in the past year). While participants were permitted to continue with existing psychotherapies (data unreported), no new regimens were permitted. Those receiving psychotropic medication continued to do so on-study, at constant dosages, and irrespective of whether they were in the therapeutic range (n=4/14 and n=3/16 patients in the active and placebo arms, respectively, received no medication). However, there was considerable heterogeneity both between- and within-study groups in terms of which types of on-study medication (doses unreported) were taken. Clinical assessments took place

every second week for four months. The investigators defined the followup required to observe an effect as 30 days, thereby establishing the criterion for data that could be entered into analysis.

While planned as a 9-month trial with 60 patients required based on a sample size calculation, a stoppage in the production of the fish oil material and a significant between-group difference observed via a preplanned interim analysis, conducted when 20 patients had either failed treatment or completed 4 months, together led to ending accrual and reanalyzing data from 30 patients. P-values were adjusted accordingly. While it was reported that the exposure was produced by the National Marine Fisheries Fish Oil Program (US), no data were provided regarding its purity or whether the presence of methylmercury was tested or eliminated.

There were no significant differences in the baseline characteristics of the study groups (i.e., age, sex, rapid cycling in past year, Clinical Global Impression [CGI] scale, Global Assessment Scale [GAS], Young Mania Rating Scale [YMRS], HDRS).[112] Results of analyses involving 30 evaluable patients were reported (n=14 in active treatment group).[112] Kaplan-Meier survival analysis revealed that the active treatment group exhibited a significantly longer period of remission (i.e., duration of time remaining in the study) than did the placebo group. When data were analyzed exclusively from those subjects who entered the study without receiving psychotropic medication, the same difference was observed. For the full sample, the time to a 50% rate of ending the trial prematurely ("nonresponse") was 65 days for the placebo group. The investigators interpreted this result as being consistent with the study population. Significant differences in improvement on the CGI, GAS, and the HDRS were observed in favor of the active treatment group. The latter result suggests that depression was also positively affected by supplementation. Post hoc analyses showed that sex, rapid cycling status and bipolar disorder type did not predict response (no data reported).

There was some evidence that the blind had been broken. A "fishy" aftertaste was more often reported in the active treatment group, such that 86% of participants guessed that they had received fish oil capsules. Only 63% in the placebo group guessed correctly. However, debriefing revealed that clinical response, or lack thereof, also played a role in tipping-off subjects to which study group they had been allocated.

Akkerhuis and Nolen reported the spontaneous reduction of psoriasis in a double blind trial wherein patients with bipolar disorder were allocated either to a maximum of 6g/d EPA ethyl ester or placebo (undefined).[93] Neither results relating to clinical outcomes nor other study details were provided.

Study quality and applicability. The Stoll et al. trial received an internal validity grade of A (Jadad total score=4), exhibited Adequate concealment of allocation to study groups, and was rated as being applicable to a North American population.[112] The Akkerhuis and Nolen report did not provide sufficient data to permit an evaluation of its study's internal validity or applicability.[93]

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Bipolar Disorder?

As observed in Summary Table 14 (below), derived from Evidence Table 3 (Appendix E*), one study published in 2003 met eligibility criteria. A comprehensive qualitative synthesis (e.g., impact of covariates and confounders), summary matrix and meta-analysis were not possible.

Overview of Relevant Study's Characteristics and Results

Noaghiul and Hibbeln conducted a cross-national ecological analysis assessing the possible association of seafood consumption and published lifetime prevalence rates (ages 18-64 years) of bipolar disorder and schizophrenia.[90] Bipolar I disorder prevalence data from six countries (US, Canada, Puerto Rico, Taiwan, Korea and New Zealand) were obtained from the Cross-National Collaborative Group epidemiological study of 10 countries. To these were added data from Germany, Italy, Israel, Iceland and Switzerland. All studies used structured diagnostic instruments and appropriate sampling methods to obtain clearly defined community samples. For example, with the exception of Switzerland and Israel, all studies used the NIMH Diagnostic Interview Schedule (DIS). The former used the SPIKE and Schedule for Affective Disorders and Schizophrenia, respectively. A Hungarian study of bipolar II disorder met eligibility criteria, as did a study from Norway. The latter used the DIS yet did not provide data subdivided by diagnostic subcategory. Data from Norway were compared with those from other countries after data from different diagnostic subcategories were first combined. All rates were reported as cases per 100,000 persons. Prevalence rates drawn from the Cross-National Collaborative Group epidemiological study were standardized at each site, with a weight calculated per subject, and stratified for age and sex. Data from other sources could not be weighted in this manner since primary data were unavailable. Socioeconomic status and educational level were not taken into consideration. The female-to-male ratio was roughly equal at all sites, with slightly higher rates seen for Canada, Puerto Rico, Korea and New Zealand. Sources of lifetime prevalence data for schizophrenia are described later in our report.

National seafood consumption data were obtained from the National Marine Fisheries Service and the Food and Agriculture Organization of the WHO. The rates of consumption appeared to be stable across the period in which the data were collected. As a measure of the disappearance of seafood from the economy per year, apparent seafood consumption (lb/person/year) was calculated as total catch plus imports minus exports.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 14: Association between omega-3 fatty acid intake and onset, continuation or recurrence of bipolar disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Noaghiul, 2003, 11 countries: cross-national ecological analysis[90]	**11 countries**		Logarithmic regression = greater seafood consumption predicted lower prevalence rates of bipolar I disorder,$^{+}$ bipolar II disorder^{+++} & bipolar spectrum disorder;$^{+++}$ when subcategories combined, linear regression^{+++} & exponential decay regression^{+++}	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Results indicated variability in the rates of bipolar disorder across the countries.[90] By simple linear regression, greater national seafood consumption predicted lower prevalence rates of bipolar spectrum disorder and bipolar II disorder, but not bipolar I disorder, for which a nonsignificant association was observed. An investigation of the residual plots of these findings suggested that nonlinear models would better express the association. By logarithmic regression, greater seafood consumption predicted lower prevalence rates of bipolar I disorder, bipolar II disorder and bipolar spectrum disorder. The best curve fitting entailed a simple exponential decay regression whereby greater seafood consumption again predicted lower rates of bipolar I disorder, bipolar II disorder and bipolar spectrum disorder. When all subcategories were combined, both linear regression and exponential decay regression remained significant. When outlier data from Iceland (by far the highest seafood consumption, very low rates of bipolar I and bipolar spectrum disorder) were excluded, the association strengthened involving bipolar II disorder but did not change the results for bipolar I or bipolar spectrum disorder.

Study quality and applicability. Given its multiple national entries of data, Noaghiul and Hibbeln's study received an applicability rating of III.[90] Its total quality score was 4.

Is the Onset, Continuation or Recurrence of Bipolar Disorder Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 15 (below), derived from Evidence Table 2 (Appendix E*), two studies met eligibility criteria. One was published in 1996 and the other in 2003. Since

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Mahadik et al.'s investigation was focused primarily on schizophrenia, with bipolar patients used as a comparator group along with normal controls, most of the details regarding this study are described with respect to the topic of schizophrenia.[114] As a result, a full qualitative synthesis is not produced here. Nevertheless, it is clear from both study reports that the study of Chiu et al. more extensively controlled for possible confounding factors.[113]

Overview of Relevant Studies' Characteristics and Results

Both studies employed a cross-sectional design.[113,114] Only Chiu et al. reported their funding source: three National Science Council grants, and the China Chemical and Pharmaceutical Company.

Mahadik et al. investigated AA and DHA compositions of cultured skin fibroblasts of schizophrenic patients (n=12; eight drug-naïve and in a first episode of nonaffective psychosis, four drug-free although presently admitted for recurrence), bipolar patients (n=6; two in first manic episode) and normal controls (n=8).[114] Bipolar patients were selected because they do not tend to manifest prominent negative symptoms. Mahadik et al. reported no significant differences between bipolar patients and normal controls for AA or DHA although schizophrenic patients exhibited significantly lower DHA compositions compared with either bipolar patients or normal controls.[114]

Summary Table 15: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of bipolar disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Mahadik, 1996, US: multiple-group cross-sectional study[114]	bipolar pts (n=6)	drug-free schizophrenic pts (n=12)/ normal controls (n=8)	NS differences for AA & DHA bet bipolar pts & normal controls	Total quality: 5 [Grade: B]	I
Chiu 2003, Taiwan: multiple-group cross-sectional study[113]	bipolar patients, acute manic episode (n=20)	healthy volunteers (n=20)	↓ AA^{+} & DHA^{+} RBC in bipolar manic pts vs controls; NS total n-3 or total n-6; NS AA/EPA or total n-6/n-3; NS impacts of medication, age, age of onset, smoker status, number of episodes or illness duration on FAs	Total quality: 5 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Chiu et al. examined whether there was a depletion of PUFAs in RBC membranes of patients admitted to hospital with DSM-IV diagnosed bipolar I disorder and whose most recent episode manic (n=20; 18-65 years), compared with healthy volunteer controls (n=20; 18-65 years).[113]

Excluded were bipolar patients with mixed symptom episodes or comorbid Axis I psychiatric disorders (i.e., due to a medical condition or induced by substance use). The mean age of onset of the bipolar patients was 26.5 (SD=9.9) years with an average duration of 11.1 (SD=9.6) years. The mean number of mood (i.e., manic or depressive) episodes was 5.2 (SD=4.5) and the mean number of hospitalizations was 3.8 (SD-3.2). The mean YMRS score was 32.1 (range: 14-42). During index hospitalization, all bipolar patients continued to receive their mood stabilizers, benzodiazepine or antipsychotic drugs. Fifteen patients were receiving mood stabilizers, including lithium (n=9), valproate (n=5), and valproate with carbamazepine (n=1). Of these, ten were taking antipsychotics. At the time of blood sampling, five patients had been free of psychotropic medication for at least one week. Healthy controls did not have a positive family history of psychiatric disorder or take psychotropic medication although no method to rule out psychiatric disturbance was described.[113] All study participants were of Han background, were free of medical illness (e.g., immune or endocrine disorders) and were exluded if they were on a low fat or vegetarian diet. There were no significant between-group baseline differences for age, sex or BMI.

Chiu et al. found significantly reduced AA and DHA compositions in RBC membranes in bipolar manic patients relative to healthy volunteers.[113] There were no significant differences in either total omega-3 or total omega-6 fatty acid compositions. No significant differences were observed for either the AA/EPA or total omega-6/omega-3 fatty acid ratio. An assessment of the impact of medication on PUFAs in bipolar patients revealed no significant differences for AA and DHA levels. AA and DHA levels were not significantly correlated with age, age of onset, number of episodes or length of illness. There were no significant differences in AA or DHA levels for bipolar patients varying on the basis of their smoker status. No inappropriate methods to extract, prepare, store or analyze lipids were described in either report.[113,114]

Although both included studies were controlled, neither was prospective by design. Thus, meta-analysis was not considered. That said, the studies collected fatty acid status data using two very different methodologies, and from different sources. The small numbers of study precluded any meaningful evaluation of the possible impact of covariates or confounders.

Study quality and applicability. Mahadik et al. and Chiu et al.'s studies received applicability ratings of I and III, respectively. Each study received a quality score of 5.

Summary Matrix 5: Study quality and applicability of evidence regarding the association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of bipolar disorder

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author Mahadik	Year 1996	n 26	Author	Year	n
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author Chiu	Year 2003	n 40	Author	Year	n
n = number of allocated/selected participants										

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Anxiety?

As observed in Summary Table 16 (below), derived from Evidence Table 1 (Appendix E*), two studies met eligibility criteria. One was published in 2000 and the other in 2003. The key parameters describing these studies have already been presented with regards to the evidence for the possible association of intake of omega-3 fatty acids and the onset, continuation or recurrence of depression. Neither study included patients with diagnoses of anxiety disorder.

Overview of Relevant Studies' Characteristics and Results

Wardle et al.'s RCT investigated whether cholesterol-lowering diets influence mood, including depression, anxiety, anger/hostility, stress, and general psychological well-being.[99] Adult volunteers (n=176) with elevated serum cholesterol levels (>5.2 mM [198 mg/dL]) were allocated to a low-fat diet (n=59), a Mediterranean diet (n=61), or a waiting-list control (n=56). Dietary treatments were given in eight sessions over the 12-week period. Participants completed a seven-day dietary intake diary before the first assessment. The outcome measure was the anxiety subscale of the POMS. Dietary diaries were filled out at baseline and 12 weeks. There were no significant between-group differences observed for anxiety. There was no reliable association between intake of omega-3 fatty acids and anxiety.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 16: Association between omega-3 fatty acid intake and onset, continuation or recurrence of anxiety

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Wardle, 2000, England: 12 wk parallel RCT[99]	Mediterranean diet (with oily fish) (n=61)	low fat diet (n=59)/ waiting list control (n=56)	↓ anxiety only in Mediterranean diet;[+] NS bet-grp difference in anxiety	Jadad total: 2 [Grade: C]; Schulz: Adequate	II
Ness, 2003, Wales: 6 mo RCT (one factor in factorial RCT)[100]	advice to eat fish (n=229)	no advice to eat fish (n=223)	NS Δ in anxiety for fish advice group; NS bet-grp differences for anxiety	Jadad total: 2 (Grade: C]; Schulz: Unclear	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; BDI = Beck Depression Inventory; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Reflecting one factor within a factorial RCT investigating interventions to reduce mortality in angina (including: advice [not] to eat fruits and vegetables; [no] stress management), 452 males were allocated to receive advice to eat more fatty fish (i.e., mackerel, herring, kipper, pilchard, sardine, salmon, trout) or to receive no such advice. Ness et al. supplied MaxEPA® fish oil capsules to study participants if they did not like the taste of fish.[100] Fish intake and mood (depression, anxiety) were assessed at baseline and at six months, the latter using the validated Derogatis Stress Profile (DSP). Ness et al. observed that self-reported fish intake was higher in the fish advice group at study's end.[100] No statistical difference was observed in the fish advice group for anxiety; controlling for baseline mood, the between-group difference was not statistically different. This last observation did not change following an additional adjustment made for randomization to the stress management arm, nor was there any statistical evidence of interaction between these factors in their effects on mood. These observations were not contradicted when they looked exclusively at the upper quartile of baseline anxiety scores.

The very different interventions and outcomes precluded quantitative synthesis. The dearth of data concerning covariates and confounders did not permit a meaningful assessment of their possible influence. That said, neither study demonstrated a significant clinical effect.

Study quality and applicability. Both RCTs received a Jadad total quality score of 2, indicating low quality, and level II applicability ratings.[99,100] Wardle et al.'s trial[99] described adequate allocation concealment while Ness et al.'s report was unclear.[100]

Summary Matrix 6: Study quality and applicability of evidence regarding the association between omega-3 fatty acid intake and onset, continuation or recurrence of anxiety

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author	Year	n	Author	Year	n	Author Ness[U] Wardle[A]	Year 2003 2000	n 452 176
	III	Author	Year	n	Author	Year	n	Author	Year	n

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

Are Omega-3 Fatty Acids Efficacious as Supplemental Treatment for Obsessive-Compulsive Disorder?

As observed in Summary Table 17 (below), derived from Evidence Table 1 (Appendix E[*]), one placebo-controlled crossover RCT published in 2004 met eligibility criteria.

Overview of Relevant Study's Characteristics and Results

At one Israeli site, Fux et al. selected eleven patients from an anxiety disorders clinic (18-75 years; racial/ethnic background unreported) meeting DSM-IV criteria for obsessive-compulsive disorder (duration: 14.1±8 years).[115] Participants began either with 2 g/d E-EPA (96% pure semi-synthetic E-EPA; plus stabilized with 0.2% vitamin E) or matched 2 g/d placebo (liquid paraffin) gelatin capsules in a six-week, two-phase crossover RCT. Selection criteria included having been on a stable dose of SSRIs (paroxetine: n=8; fluvoxamine: n=1; fluoxetine: n=1) for at least 2 months, and having demonstrated some response to treatment yet without further improvement over the last 2 months. Exclusion criteria included no unstable medical disease, alcohol or drug abuse, or comorbid Axis II psychiatric diagnosis. Patients maintained their SSRI dose over the study. None received psychotherapy aside from basic clinical management or support. The primary outcome measures were scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS), HDRS, and the Hamilton Anxiety Rating Scale (HAM-A). The intervention was prepared by Laxdale, Ltd. No data described its purity or whether methylmercury was tested for and eliminated.

[*] **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 17: Omega-3 fatty acids as supplemental treatment for obsessive-compulsive disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Fux, 2004, Israel: 6 wk crossover RCT[115]	2g/d E-EPA phase (n=11)	2g/d liquid paraffin pb phase (n=11)	NS effects of treatment order on HDRS or HAM-A; main effect for time on YBOCS, with significant ↓ by wk 6 for pb & E-EPA;$^{++}$ NS treatment effect for clinical outcomes; NS drug-by-time interaction	Jadad total: 3 [Grade: B]; Schulz: Unclear	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; HDRS = Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scake; YBOCS = Yale-Brown Obsessive-Compulsive Scale; HAM-A = Hamilton Anxiety Rating Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Overall, 91% of the sample completed the full 12 weeks (n=10/11); however, data were analyzed based on an ITT basis, with the last value carried forward for the participant who dropped out at week 10 of the study (i.e., moved out of city). Results indicated that there were no effects of order of treatment on HDRS or HAM-A. Time had a main effect on YBOCS scores, with significant decreases by week 6 for both placebo and E-EPA phases. There was neither a treatment effect for any clinical outcome, or a significant drug-by-time interaction. No assessment of the impact of covariates or confounders was possible. This RCT received a Jadad total quality score of 3 and an applicability rating of III.

Is the Onset, Continuation or Recurrence of Anorexia Nervosa Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 18 (below), derived from Evidence Table 3 (Appendix E*), two cross-sectional studies published in 1985 and 1995 met eligibility criteria.

Overview of Relevant Studies' Characteristics and Results

Both studies had a cross-sectional design and were conducted in the US.[116,117] Langan and Farrell's study was funded by the NIH[117] while Holman et al.'s work was supported by the Carle Foundation, NIH, Harmel Foundation and by Scotia Pharmaceuticals.[116]

Langan and Farrell investigated the plasma fatty acid composition in a group of females with anorexia nervosa admitted to a hospital (n=17; mean age: 16.8 years; duration of anorexia: 17.2

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

months) compared to healthy females serving as controls (n=11; mean age: 20.7 years).[117] The anorexic patients were admitted because of an electrolyte imbalance, a greater than 25 percent loss of ideal body weight (mean: 28.5 pounds) and severe psychosocial problems. Patients varied in their degree of malnutrition. The control group was slightly older than the patient group. Compared with the control group, the weight-to-height ratio (lb/in) was significantly reduced in the patient group.

Summary Table 18: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of anorexia nervosa

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Langan, 1985, US: multiple-group cross-sectional study[117]	anorexic females (n=17)	healthy female controls (n=11)	NS bet-grp difference in FA in total plasma lipids; ↓ plasma PL LA^{++} & ALA^{+} in anorexics; ↑ plasma PL DHA in anorexics;$^{+}$ ↓ total n-6 in anorexics;$^{+}$ ↑ AA/LA in anorexics^{++}	Total quality: 2 [Grade: C]	I
Holman, 1995, US: multiple-group cross-sectional study[116]	young anorexic females (n=8)	young healthy controls (n=19)	↓ PL total n-6, EPA, DHA, ALA & total n-3 in anorexics;$^{+++}$ NS bet-grp difference in plasma cholesterol esters n-3; ↓ DGLA in anorexics; $^{+}$ ↓ total n-3 in plasma triglycerides in anorexics;$^{+}$ ↓ (n-6-)DPA & GLA in plasma triglycerides in anorexics^{+}	Total quality: 1 [Grade: C]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; N/A = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Holman et al. compared the plama phospholipid fatty acid composition in young females with anorexia nervosa (n=8; mean age: 18.4 [15-24] years) admitted to a treatment program in an urban clinic, with that of healthy female adults (n=19; mean age: 23.5 years).[116] All patients had lost at least 15% of their usual body weight. No inappropriate methods to handle lipids were described in either study.

Langan and Farrell showed that there were no significant between-group differences in the fatty acid composition of total plasma lipids.[117] Only plasma phospholipid LA and ALA were significantly reduced in the group with anorexia compared with controls, while DHA was significantly higher in the females with anorexia. The total amount of omega-6 fatty acids was significantly lower in those with anorexia compared with normal controls, yet the AA/LA ratio was significantly higher among patients with anorexia compared with controls.

Holman et al. observed that the phospholipid content of total omega-6 fatty acids was significantly reduced in the patients with anorexia compared with controls.[116] The same observation was made with respect to EPA, DHA, ALA and total omega-3 fatty acids. When the analysis was performed on plasma cholesteryl esters, there were no significant between-group differences for the omega-3 fatty acids, while DGLA was significantly lower in patients than in controls. For the plasma triglycerides fraction, total omega-3 fatty acid content was significantly

reduced in patients compared to healthy subjects. The only two omega-6 fatty acids exhibiting a significant reduction in the patient group were DPA and GLA.

Study quality and applicability. Both studies received an applicability rating of I. Their mean quality score was 1.5.

Summary Matrix 7: Study quality and applicability of evidence regarding the association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of anorexia nervosa

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author Holman Langan	Year 1995 1985	n 27 28
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author	Year	n	Author	Year	n
n = number of allocated/selected participants										

Although all of the included studies were controlled, none were prospective by design. Thus, meta-analysis was not considered. Insufficient data precluded an assessment of the possible impact of covariates and confounders.

Are Omega-3 Fatty Acids Efficacious as Primary Treatment for Attention Deficit/Hyperactivity Disorder?

As observed in Summary Table 19 (see below), derived from Evidence Table 1 (Appendix E*), three RCTs and one comparative before-after study met eligibility criteria. Studies were published between 2001 and 2004.

One RCT conducted by Brue et al. included children allocated, in part, on the basis of whether or not they were receiving methylphenidate (Ritalin®).[118] As a result, data for those not receiving this medication reflect the primary treatment of AD/HD and are reviewed here. Other data from this RCT are presented below as evidence concerning the supplemental treatment of AD/HD. To minimize the presentation of redundant information, Brue et al.'s study is described once in detail.

Overview of Relevant Studies

Richardson and Puri's RCT evaluated the effects of supplementation with highly unsaturated (HUFA) fatty acids in children (n=41; 8-12 years) with both AD/HD-related symptoms and specific learning difficulties (mainly dyslexia).[119] Children were not formally assigned a

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

diagnosis of AD/HD. Teacher-identified children were allocated to receive for 12 weeks either olive oil placebo or a "cocktail" including 186mg/d EPA, 480mg/d DHA, 96mg/d GLA, 60 IU/d vitamin E (as antioxidant), 864mg/d *cis*-linolenic acid, 42mg/d AA and 8mg/d thyme. Behavioral and learning problems associated with AD/HD were assessed using Conners Parent Rating Scale (CPRS). Analyses of teacher ratings were not conducted given that the children were new to their school.

Summary Table 19: Omega-3 fatty acids as primary treatment forattention deficit/hyperactivity disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Richardson, 2002, UK: 12 wk parallel RCT[119]	186mg/d EPA, 480mg/d DHA, 96mg/d GLA, 864mg/d *cis*-linolenic acid, 42mg/d AA & 8mg/d thyme (n=22)	olive oil pb (n=19)	All PP analyses: ↓ DSM Inattention,$^{+}$ Conners ADHD Index^{+} & psychosomatic symptoms^{+} in treatment grp	Jadad total: 5 [Grade: A]; Schulz: Adequate	II
Hirayama, 2004, Japan: 2 mo parallel RCT[120]	3.6g/wk DHA & 700mg/wk EPA (n=20)	olive oil pb (n=20)	No improvement of AD/HD symptoms; ↓ errors of commission^{++} & ↑ shortterm memory in controls^{+}	Jadad total: 3 [Grade: B]; Schulz: Unclear	III
Brue, 2001, US: 12 wk parallel RCT[118]	No Ritalin: 2g/d flaxseed + dietary supplements (n=15)/ No Ritalin: dietary supplements + slippery elm pb (n=15)	Ritalin: 2g/d flaxseed + dietary supplements (n =15)/ Ritalin: dietary supplements + slippery elm pb (n = 15)	No Ritalin pts: NS effect for parent & teacher rated inattentiveness; ↓ teacher-rated hyperactivity/impulsivity^{+} in flaxseed+supplement grp whereas opposite observed for parent ratings^{+}	Jadad total: 2 [Grade: C]; Schulz: Unclear	I
Harding, 2003, US: 4 wk comparative before-after study[121]	180 mg/d EPA + 120 mg/d DHA (n=10)	Ritalin (n=10)	for both grps: ↑ FSRCQ^{++} & ↑ FSACQ;$^{+++}$ NS bet-grp differences on FSRCQ & FSACQ; NS bet-grp differences yet both groups' ↑ for ARCQ,$^{++}$ VRCQ,$^{+}$ AAQ^{++} & VAQ^{++}	Total quality: 4 [Grade: C]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; FSRCQ = Full Scale Response Control Quotient; FSACQ = Full Scale Attention Control Quotient; ARCQ = Auditory Response Control Quotient; VRCQ = Visual Response Control Quotient; AAQ = Auditory Attention Quotient; VAQ = Visual Attention Quotient; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Hirayama et al. investigated primarily the effects of DHA on symptoms of AD/HD.[120] They conducted an RCT of children (6-12 years) recruited by psychiatrists. Children were assigned to

receive, for 2 months, either 3.6 g/wk DHA plus 700mg/wk EPA from fish oil contained in active foods (fermented soybean milk, bread rolls and steamed bread) or these same foods without fish oil. Most of the children were not receiving medication (n=34/40). AD/HD related symptoms, aggression, visual perception, visual and auditory short-term memory, development of visual-motor integration, continuous performance and impatience were assessed in this study.

Brue et al. conducted two 12-week trials to evaluate the efficacy of a dietary supplement combination and flaxseed for the treatment of inattentiveness and hyperactivity in children with AD/HD (mean age: 8.4 years; 4-12 years).[118] Each child was supposed to participate in both studies. However, 51 of 60 children enrolled in the first study completed the second RCT as well. To initiate the first RCT, 30 children were chosen randomly from a group not taking any stimulant medication and 30 were randomly chosen from those taking methylphenidate. Each RCT included two experimental and two control groups. Here, we are interested only in the second trial because the first one did not include an omega-3 fatty acid exposure.

The second trial consisted of unmedicated patients randomly allocated to receive either 2 g/d flaxseed plus a dietary supplement combination (40 mg/d Ginkgo biloba [proposed effect: mental clarity/alertness], 800 mg Melissa officinalis [proposed effect: relaxing effect], 120 mg Grapine [proposed effect: attention, memory], 140 mg dimethyaminoethanol [proposed effect: memory, learning], 400 mg L-glutamine [proposed effect: mental clarity/alertness]) or the dietary supplement combination paired with a slippery elm supplement as placebo (amount not reported).[118] As will be described below, children taking methylphenidate were likewise randomized to these study groups. Participants were instructed to take their intervention twice daily, once with breakfast and then with an afternoon snack or dinner. Only the results with respect to unmedicated children are presented here. Data from children receiving the intervention supplemental to methylphenidate are described below. The CPRS and CTRS were used to measure study outcomes.

Harding et al. conducted a study in children (7-12 years) with AD/HD. They were recruited by a clinical child psychologist. They were then divided, by parental choice, into two groups. They received, for 4 weeks, either Ritalin at a dose of 5-15 mg two to three times daily (n=10), or dietary supplementation containing a mix of essential fatty acids (e.g., 180 mg/d EPA and 120 mg/d DHA from 1g salmon oil), a multiple vitamin (e.g., thiamine, niacin), multiple minerals (e.g., magnesium, calcium), phytonutrients, phospholipids (soy lecithin), probiotics (n=10) and amino acids (e.g., glutamine).

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Three parallel RCTs[118-120] and one comparative before-after study,[121] each involving children, were conducted to evaluate the efficacy of omega-3 fatty acids as a primary treatment for AD/HD. Inclusion and exclusion conditions were well-defined in three studies.[118,119,121] Hirayama et al. did not specify any exclusion criteria.[120] Only Brue et al.[118] employed a design having more than two groups (i.e., 4). However, only one of their study arms addressed the present question. A total of 161 children were randomized. The mean sample size for the four studies was 40.25 (range: 20-60) participants, with the Brue et al. trial being the largest (n=60) and the Harding et al. study being the smallest (n=20). Study participants received the intervention for an average of 9 weeks, with the Harding et al. intervention being the shortest (i.e., 4 weeks).[121] The RCTs were conducted in the US,[118] the UK [119] and Japan.[120] The UK RCT was funded by the Dyslexia Research Trust Funding,[119] and the study from Japan by

Japan Fisheries Association and the Foundation for Total Health Promotion.[120] The funding sources for the two US trials were not reported.[118,121]

Population characteristics. The mean age of study participants across the four trials was impossible to determine given that full sample means were not provided in two trials.[120,121] The age of the participants ranged from 4 to 12 years when all studies were combined. The sex ratio was provided in three studies.[118-120] Males were consistently more strongly represented in these studies (80%-86%). With respect to racial/ethnic backgrounds, Hirayama et al.'s study likely included an Asian population[120] while similar data were not reported for the UK, or for the US, sample populations.[118,121,121]

All studies used DSM-IV criteria to identify AD/HD.[118-121] Hirayama et al. reported that eight of 40 children might not have been identifiable as AD/HD according to DSM-IV criteria but this diagnosis was nevertheless "strongly suspected" by two psychiatrists.[120] Even though there were no significant differences between the two study groups on a number of bases, it should be noted that, in the control group there were more patients taking medication/polymedication (4 vs 2) than in the DHA group. As well, there were more patients in the control group with a comorbid condition (15 vs 12), including Asperger's syndrome (7 vs 2), conduct disorder (3 vs 0) or mood disorder (5 vs 1). Conversely there were more patients with learning disorders in the DHA group than in the controls (10 vs 5).[120] Overall, almost three-quarters (n=27/40) of the children exhibited comorbidity. At baseline, no significant between-group differences were observed on outcome measures.

In the study conducted by Richardson et al. the participants had, in addition to AD/HD-related symptoms, specific learning difficulties assessed by the Similarities and Matrices subtests from the British Ability Scales (BAS).[119] Patients with a history of any other neurological or major psychiatric disorder or significant medical problems were excluded. No patients were receiving any medication. At baseline, the two groups did not differ significantly for age, sex, ethnicity or on any of the Conners scales.

The Brue et al. report indicated that participants taking a stimulant medication other than methylphenidate were excluded, as were those with serious and preexisting medical or psychological conditions such as asthma or depression.[118] These authors did not report any baseline data. Harding et al. excluded patients with co-existing conduct disorder or oppositional defiant disorder, medication use, street drugs, or use of other nutritional or botanical supplements.[121]

Intervention/exposure characteristics. In the study conducted by Richardson and Puri, children in the treatment group received a supplement containing both omega-3 and omega-6 fatty acids. The sources of these agents were not identified. Vitamin E was added as an antioxidant. The placebo group received an unspecified dose of olive oil in identical capsules.[119] In the study by Hirayama et al., the treatment group received active foods containing fish oil (fermented soybean milk; bread rolls and steamed bread) that provided 3.6 g/wk DHA and 700 mg/wk EPA.[120] Fermented soybean milk was given three times per week and provided 600 mg DHA per 125 mL. Bread rolls and steamed milk were given twice a week, providing 300 mg DHA per 45g and 600 mg DHA per 60g, respectively. The placebo group received the same foods but containing olive oil.[120] The authors masked the fishy taste in the milk product using special flavors (no method reported). For the other active foods, the fish oil was emulsified with fruit juices. No mention was made as to whether these same procedures were applied to placebo-containing foods. Parents were asked to maintain their child's habitual diet other than reducing bread consumption to accommodate the inclusion of breads containing the exposure.[120] Brue et

al.'s dietary supplement "cocktail" is well described above. Harding et al.'s active ingredients are too numerous to mention them all here.[121]

Not one of the trial reports described the manufacturers of the sources of their interventions, the purity of their exposures, or whether, or how, the presence of methylmercury was tested for, or eliminated from, the sources.[118-121]

Cointervention characteristics. Omega-3 fatty acids were often given concurrently with other agents, including omega-6 fatty acids, vitamins, minerals, polynutrients, probiotics and amino acids.[119,121] Hirayama et al. stated that DHA, from fish oil, was added to foods (fermented soybean milk, bread rolls and steamed bread).[120] However, the nutritional content of these foods was not reported. In these investigators' control group, four patients were receiving medication, including methylphenidate (n=1), methylphenidate plus risperidone (n=1), carbamazepine plus fluvoxamine (n=1) or carbamazepine plus sulpiride (n=1).[120] Two patients in the DHA group were exclusively taking methylphenidate.

Outcome characteristics. Richardson and Puri defined changes in CPRS scores (AD/HD subscales, AD/HD global scales) as the primary outcome.[119] Hirayama et al. powered their study to assess changes in aggression using a questionnaire developed by the authors.[120] Other assessments included AD/HD-related symptom criteria based on DSM-IV, visual perception, visual and auditory shortterm memory, visual-motor integration, a continuous performance test and an impatience test. Brue et al. employed the DSM-IV Inattentive and Hyperactive-Impulsive subscales.[118] The primary outcome in the Harding et al. study was the Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT) although CPRS data were obtained as well.[121] Two major quotients are derived from the six primary IVA/CPT scales: the Full Scale Response Control Quotient (FSRCQ: prudence, consistency, stamina) and the Full Scale Attention Control Quotient (FASCQ: vigilance, focus, speed).

Study quality and applicability. The three RCTs received a mean Jadad total quality score of 3.3, indicating sound internal validity.[118-120] Their three applicability ratings ranged from I to III. The applicability rating for the comparative before-after study was I, and it received a total quality score of 4.

Summary Matrix 8: Study quality and applicability of evidence regarding the primary treatment of attention deficit/hyperactivity disorder (all designs)

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
								Brue[U]	2001	60
								Harding	2003	20
	II	Author	Year	n	Author	Year	n	Author	Year	n
		Richardson[A]	2001	41						
	III	Author	Year	n	Author	Year	n	Author	Year	n
					Hirayama[U]	2003	40			

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

Qualitative Synthesis of Individual Study Results

Richardson and Puri compared the changes in CPRS subscale scores after 12 weeks.[119] From the 41 patients enrolled, 15 in the active group and 14 in the placebo group completed the study. Analyses at endpoint revealed that the active treatment group had significantly lower scores on DSM Inattention, Conners ADHD Index and psychosomatic symptoms.

Hirayama et al. reported that all subjects completed the study. Data analyses did not show any improvement in AD/HD symptoms (e.g., problems of inattention, hyperactivity/impulsivity) in the DHA group compared to the placebo group. The number of errors of commission on the continuous performance test decreased significantly in the control group. Visual short-term memory was significantly improved in the control group. Excluding data from those receiving medication (i.e., supplemental treatment patients) or from those only suspected of being AD/HD did not change these results (no data reported). Food consumption was estimated to be close to 100% (no data reported).

Brue et al.'s results indicated no significant between-group differences on parent and teacher ratings of inattentiveness. Teacher-reported hyperactivity/impulsivity was significantly lower in the flaxseed plus supplement combination group, compared with the supplement combination plus placebo group. However, the opposite was observed for parent ratings.

Significant improvements were observed on both the FSRCQ and FSACQ in each of the study groups of Harding et al.[121] There were no significant between-group differences on either the FSRCQ or the FSACQ. No significant between-group differences were observed for the following four subquotients although both study groups' improvements were statistically significant: Auditory Response Control Quotient, Visual Response Control Quotient, Auditory Attention Quotient and the Visual Attention Quotient.

Quantitative Synthesis

Meta-analysis was not attempted for several reasons. The two studies employing DHA and EPA as active treatment employed different research designs (i.e., Harding et al.'s noncomparative before-after study[121] vs Hirayama et al.'s RCT[120]). More importantly, though, in the only two studies using a common comparator (i.e., olive oil pacebo), their active treatments were completely different (i.e., Richardson and Puri's "cocktail"[119] vs Hirayama et al.'s DHA+EPA exposure[120]).

Impact of Covariates and Confounders

A few studies attempted to control for possible confounding, including the study of Harding et al.,[121] which excluded children with externalizing disorders commonly associated with AD/HD (i.e., conduct disorder, oppositional defiant disorder), as well as the study of Hirayama et al., where the children maintained their background diets.[120] On the other hand, the latter study also included subjects with a wide range of comorbid conditions;[120] and, Richardson and Puri included children with a variety of learning difficulties.[119] Yet, the inconsistent findings, including a small number of significant clinical effects, and the variability in both the types of intervention and comparator made it impossible to begin to reliably identify key covariables affecting clinical outcomes.

Are Omega-3 Fatty Acids Efficacious as Supplemental Treatment for Attention Deficit/Hyperactivity Disorder?

As observed in Summary Table 20 (see below), derived from Evidence Table 1 (Appendix E*), three RCTs met eligibility criteria. Studies were published in 2001 or 2003. Results for children on methylphenidate from the Brue et al. trial are described here.

Overview of Relevant Studies

Voigt et al. conducted an RCT investigating DHA supplementation in children (n=63; 6-12 years) diagnosed with AD/HD.[122] Children being treated successfully with stimulant medication were recruited by a pediatrician. They were randomly assigned to receive either 345mg/d DHA or placebo (undefined) for 4 months. Children with comorbid conduct disorder or oppositional defiant disorder were eligible. Measures of attention and impulsivity were assessed by changes in scores on the Test of Variables of Attention (TOVA) and the Children's Color Trails Test. Other outcomes included scores on the Child Behavior Checklist (CBCL), and the Conners Rating Scale, in addition to plasma phospholipid fatty acid concentrations.

*__Note:__ Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 20: Omega-3 fatty acids as supplemental treatment for attention deficit/hyperactivity disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Notable biomarker effects[2,3]	Notable clinical-biomarker correlations	Internal validity	Applicability
Brue, 2001, US: 12 wk parallel RCT[118]	No Ritalin: 2g/d flaxseed + dietary supplements (n=15)/ No Ritalin: dietary supplements + slippery elm pb (n=15)	Ritalin: 2g/d flaxseed + dietary supplements (n =15)/ Ritalin: dietary supplements + slippery elm pb (n = 15)	Flaxseed + supplement: fewer attention problems (teacher only);$^{+}$ NS difference: hyperactivity/ impulsivity	n/a	n/a	Jadad total: 2 [Grade: C]; Schulz: Unclear	I
Voigt, 2001, US: 4 mo parallel RCT[122]	345mg/d DHA (n=32)	pb (undefined) (n=31)	NS bet-grp differences on TOVA, Color Trails tests, CBCL or Conners	NS Δ DHA in pb; ↑ DHA^{++} & ↓ (n-3-) DPA^{++} in DHA grp	NS correlations for plasma PL DHA & TOVA or Color Trails	Jadad total: 4 [Grade: A]; Schulz: Adequate	I
Stevens, 2003, US: 4 mo parallel RCT[123]	480mg/d DHA, 80mg/d EPA, 40mg/d AA, 96mg/d GLA & 24mg/d vitamin E (n=25)	6.4g/d olive oil pb (n= 25)	2/16 improved outcomes: conduct problems^{+} & attention symptom;$^{+}$ more oppositional/ defiant disorders improved in PUFA grp^{+}	NS bet-grp differences for Δ in plasma FAs; size of ↓ RBC AA greater in PUFA group^{+}	% Δ in parent ASQ negatively correlated with % Δ in RBC EPA^{+} & positively with RBC AA;$^{+}$ % Δ in teacher attention negatively correlated with RBC DHA^{+}	Jadad total: 3 [Grade: B]; Schulz: Adequate	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; ASQ = Abbreviated Symptom Questionnaire; CBCL = Child Behavior Checklist; DBD = Disruptive Behavior Disorders; RBC = red blood cells; PL = phospholipid; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Stevens et al. conducted an RCT to evaluate the effects of supplementation with PUFA on the behavior and blood fatty acid composition of children (n= 50; 6-13 years) with AD/HD-like symptoms, who were also reporting thirst and skin problems potentially indicative of omega-3 fatty acid deficiency.[123] Fifty children were randomized to receive daily either the PUFA supplement Efalex® (480 mg/d DHA, 80 mg/d EPA, 40 mg/d AA, 96 mg/d GLA and 24 mg/d vitamin E as anti-oxidant preservative) or 6.4 g/d olive oil as placebo for 4 months. Only five participants in each group were not receiving medication. The primary outcome measures were the parent- and teacher-endorsed Conners Abbreviated Symptom Questionnaires (ASQ) and the

Disruptive Behavior Disorders (DBD) Rating Scale. Other outcomes measures were the Conners CPT and the Woodcock-Johnson Psycho-Educational Battery-Revised (WJ-R). Brue et al. conducted the third RCT, described with respect to the primary treatment of AD/HD.[118]

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Three RCTs examined the use of omega-3 fatty acids as supplemental treatment for AD/HD.[118,122,123] A total of 131 children were randomized. The mean sample size for the three studies was 43.3 (range: 30-51) children. Participants received the intervention for an average of 14.6 weeks (range: 12-16 weeks). All three studies were conducted in the US. The study conducted by Voigt was funded in part by the US Department of Agriculture.[122] The Stevens et al. study was funded by grants from the NIMH, National Fisheries Institute and Scotia Pharmaceuticals, Ltd.[123] Brue et al.'s funding source was not reported.[118]

Population characteristics. The mean age of children enrolled in these 3 trials was approximately 9.16 years (range: 4-13 years).[118,122,123] Those in the Brue et al. study tended be younger (mean: 8.4 years). Males were consistently better represented in the three studies (~80%). The percentage of white participants in Voigt et al.'s study was 100% in the DHA group and 85% in the placebo group.[122] These data were not provided for the other two RCTs.[118,123]

Two studies employed DSM-IV diagnostic criteria[118,122] while a third one did not report how AD/HD was identified.[123] Brue et al. excluded children with serious and preexisting medical or psychological conditions such asthma or depression.[118] Voigt et al. excluded patients who had experienced ineffective treatment with stimulant medication, treatment with other psychotropic medications, previous diagnoses of other childhood psychiatric disorders, use of dietary supplements other than vitamins, occurrence of a significant life event in the past six months, a history of head injury, receipt of special education services for mental retardation or a pervasive developmental disorder, premature birth, exposure to tobacco, drugs or alchol, or the diagnosis of a disorder of lipid metabolism or any other chronic medical condition.[122] There were no significant between-group baseline differences for sex, methyphenidate dose, TOVA scores or Color Trails scores. All participants in the DHA group were white compared to 85% in the placebo group. While 22 of those allocated to the DHA group received a DSM-IV subtype diagnosis of combined (inattentive plus hyperactive) AD/HD and five were identified as predominantly inattentive, all children in the placebo group met criteria for combined subtype. Thirteen children in the DHA group and 15 children in the placebo group met DSM-IV criteria for oppositional defiant disorder. Six children in the DHA group and two children in the placebo group met criteria for conduct disorder. Minor between-group differences for age (i.e., slightly older in placebo group) and AD/HD subtype were controlled for in analyses.

Stevens et al. included children under the care of a clinician for AD/HD who were receiving standard therapy and were required to have a high frequency of skin/thirst symptoms evaluated by a questionnaire administered to parents.[123] They excluded children with chronic health problems such as diabetes and kidney disease. Study groups were balanced for sex and medication status. No significant between-group differences were observed for age, height, sex, medication status, frequency of thirst/skin symptoms or nutrient intake. At baseline, few between-group differences in clinical outcomes were noted. The inattention score on the Disruptive Behavior Disorders (DBD) Rating Scale scores was higher in the placebo group.

Parent-rated, Conners-related Abbreviated Symptom Questionnaire (ASQ) scores were also higher in the placebo group. Inconsistent between-group differences were seen for measures of reaction time. No significant between-group differences were seen for either plasma or RBC fatty acid levels.

Intervention/exposure characteristics. Voigt et al. identified the source of their intervention as an algae-derived triglyceride capsule providing 345mg of DHA per day. Although, it was stated that the placebo was identical in appearance and was supplied by the same company, the content was not defined.[122] Patients in the Steven et al. study received either eight capsules a day of Efalex® or placebo.[123] The intervention characteristics of the study conducted by Brue et al. have been described previously (see above).[118] Voight et al. reported their exposure's manufacturer (Martek Biosciences Corporation, Columbia, MD)[122] as did Stevens et al. (Efamol Ltd).[123] None of the reports provided either purity data regarding their treatments or descriptions about whether, and how, the presence of methylmercury was tested or eliminated from the omega-3 fatty acid exposure. In the two studies that evaluated the fatty acid content of biomarkers, no notable inappropriate methods to extract, prepare, store or analyze lipids were described.[122,123]

Cointervention characteristics. In each study, omega-3 fatty acids were supplied as supplemental treatment. The patients enrolled in Voigt et al.'s trial received either methyphenidate at a dose of 29.2±30.1 mg/d in the DHA group (n=25) or 29.3±17.6 mg/d in the placebo group (n=22), dextroamphetamine at a dose of 15.0 mg/d (n=1) in the DHA group or 16.3±8.8 mg/d in the placebo group (n=2) or amphetamine/dextroamphetamine at a dose of 10 mg/d (n=1) in the DHA group or 15.0+/-8.7 in the placebo group (n=3).[122] The treatment duration was 26.3 months in the DHA group compared to 29.5 months in the placebo group. In the Stevens et al. trial, children received methylphenidate, methylphenidate plus an antidepressant, or other medication such as pemoline or dextroamphetamine salts. Both study groups in the Brue et al. RCT were receiving methylphenidate.[118]

Outcome characteristics. Voigt et al. employed as primary outcome the changes in scores on the TOVA.[122] They also evaluated the impact of supplementation on the omega-3 fatty acid content of plasma phospholipid fractions. In Stevens et al.'s trial, the parent- and teacher-rated ASQ and the DBD were the primary outcomes.[123] Brue et al. employed the DSM-IV's Inattentive and Hyperactive-Impulsive subscales as outcomes.[118]

Study quality and applicability. The mean Jadad total quality score was 3, with each RCT receiving an applicability rating of I.[118,122,123]

Summary Matrix 9: Study quality and applicability of evidence regarding the supplemental treatment of attention deficit/hyperactivity disorder

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
		Voigt[A]	2001	63	Stevens[A]	2003	50	Brue[U]	2001	60
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author	Year	n	Author	Year	n

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

Qualitative Synthesis of Individual Study Results

Voigt et al. only conducted statistical analyses on complete TOVA and Color Trails test data available at baseline and at the end of the 4-month study.[122] This amounted to data from only 49 (DHA=25, placebo=24) of the 63 randomized children. Capsule counts indicated high levels of compliance. After 4 months, there were no statistically significant between-group differences in scores on any component of the TOVA, for scores from either of the Color Trails tests, on the parent-endorsed CBCL or Conners Rating Scales. The plasma phospholipid DHA content in the placebo group remained unchanged, whereas that of the DHA group increased significantly. This increase was accompanied by a nonsignificant decline in AA, and a significant decrease in (omega-3-)DPA. No significant correlations were seen between initial plasma phospholipid DHA content and initial TOVA scores, final plasma phospholipid DHA content and final TOVA scores, or between changes in these two variables. The same patterns held for Color Trails data.

In the Stevens et al. study, the analyses of primary endpoints ASQ and DBD were conducted on those subjects who completed the 4-month intervention and had a minimum compliance of 75%.[123] The total number of subjects evaluated for clinical outcomes at the end of the study were 18 in the PUFA group and 15 in the placebo group. Secondary analyses were performed on an ITT basis, with the last observation carried forward for all subjects who were randomized and who had received the first dose of the supplement.

A clear benefit of PUFA supplementation on behavioral characteristics of AD/HD was not observed. A significant improvement in the PUFA compared to placebo was observed in only two of sixteen outcome measures: conduct problems rated by parents and attention symptoms rated by the teacher. Only one of eight DBD rating scales showed a treatment effect, with a significantly greater proportion of children's oppositional defiant disorder improving clinically in the PUFA group. Supplementation did not produce a significant benefit in decreasing the frequency of thirst/skin symptoms. No significant between-group differences were found related to changes in plasma fatty acid levels. The magnitude of the decrease in RBC AA was significantly greater in the PUFA group. The percentage change in parent-rated ASQ scores was significantly and negatively correlated with the percentage change in RBC EPA and positively correlated with RBC AA. Percentage change in teacher-endorsed Attention scores on the DBD was significantly and negatively correlated with RBC DHA.

Brue et al.'s teacher-endorsed data revealed that children taking the dietary supplement combination, with flaxseed in addition to methylphenidate, manifested significantly less inattentiveness. Parent data did not confirm this finding. No significant between-group differences for either parent or teacher ratings of hyperactivity/impulsivity were found.

Quantitative Synthesis

Given the lack of comparability in the interventions, comparators, and their combinations, in addition to the variability in the three studies' populations especially related to the presence of varying types of comorbid condition, meta-analysis was not performed. Only one report explicitly identified the AD/HD subtypes included in their RCT.[122] This is a key population source of clinical heterogeneity.

Impact of Covariates and Confounders

Voigt et al.'s trial was the best controlled of the three studies.[122] They identified the subtypes of DSM-IV AD/HD allocated to each study group although their baseline assessments revealed that the DHA group contained a less homogeneous distribution of subtypes than did their control group. They also controlled for other confounders (e.g., other psychiatric diagnoses, use of dietary supplements), while at the same time allowing entry into the study various types of comorbid condition with the potential to influence outcomes (e.g., oppositional defiant disorder, conduct disorder). Voigt et al. provided the simplest of the three active treatments, focusing exclusively on DHA supplementation. Yet, they found no benefits relating to their very small dose, which in and of itself may have contributed to the failure to find a significant clinical effect.

The other two trials exercised considerably less experimental control, and when viewed together, the three studies provided at best an inconsistent picture of the benefits of providing omega-3 fatty acids. Thus, as with the topic pertaining to the primary treatment of AD/HD, the inconsistent findings, including a small number of significant clinical effects, and the variability in both the types of intervention and comparator made it impossible to begin to reliably identify key covariables affecting clinical outcomes.

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Attention Deficit/Hyperactivity Disorder?

As observed in Summary Table 21 (below), derived from Evidence Table 3 (Appendix E*), one cross-sectional study published in 1999 met eligibility criteria.

Overview of Relevant Study's Characteristics and Results

Yang et al. employed a cross-sectional design to investigate whether there were any differences in dietary intake between children diagnosed with AD/HD and normal healthy children.[94] The AD/HD group (n=20; 4-8 years) consisted of outpatients (90% male) with a mean age of 5.7 (SD=0.9) years, who met DSM-IV criteria for AD/HD (duration not reported). Inclusion criteria for this group included a score of greater than 80% on the Standard Child Activity Level Form filled out by parents and teachers. The normal control group (n=32) consisted of children (91% male) with a mean age of 5.2 (SD=1.1) years recruited from junior and senior kindergarten, as well as grades one and two from schools in Taipei, Taiwan. Inclusion criteria for controls included being ages 4 to 8 years, and verification of good health. Excluded were children with AD/HD. The male–to-female ratio in the control group approximated that of the AD/HD group.

Anthropometric measurements were taken and participants filled out a dietary survey containing four categories: dietary intake from the previous 24 hours, 3-day dietary records,

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

frequency of food intake, and dietary history. During the initial visit participants completed all categories of the dietary survey except for the 3-day dietary record. The latter was filled out following the initial visit and returned by mail. Given the extremely shortterm followup, and the data collected regarding past and present dietary intake, the study was considered a cross-sectional design. Funding was provided by the Chun Qing Infant and Child Nutritional Research Foundation.

Summary Table 21: Association between omega-3 fatty acid intake and onset, continuation or recurrence of attention deficit/hyperactivity disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Yang, 1999, Taiwan: multiple-group cross-sectional study[94]	AD/HD children (n=20)	healthy controls (n=32)	via 24-hour dietary recall, the hyperactive grp had lower intake of LA^{+} & ALA;$^{+}$ only ALA^{+} ↓ in AD/HD via 3-day dietary record	Total quality: 5 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Response rates for the 3-day dietary record for the AD/HD and control subjects were 60% (n=12) and 87.5% (n=28), respectively. The two groups did not differ significantly in age, height, body weight, weight-for-length index, chest circumference or tricep skin thickness. There were no significant between-group differences in intake of tryptophan, cholesterol or saturated fatty acids. According to the 24-hour dietary recall, the hyperactive group had significantly lower intake of LA and ALA. Only ALA was reduced in AD/HD children, relative to controls, measured by the 3-day dietary record.

Meta-analysis was not considered, and the existence of a single study, reporting few details, made it impossible to assess the possible impact of covariates and confounders. Yang et al.'s study received an applicability rating of III and a total quality score of 5.

Is the Onset, Continuation or Recurrence of Attention Deficit/Hyperactivity Disorder Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 22, derived from Evidence Table 2 (Appendix E*), three cross-sectional studies met eligibility criteria. Studies were published between 1983 and 1995.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Overview of Relevant Studies' Characteristics and Results

Mitchell et al.'s study was supported by Efamol Research Ltd. and the Medical Research Council of New Zealand,[125] Stevens et al.'s funding source was the State of Indiana,[124] and the second Mitchell et al. study did not report this information.[126]

Mitchell et al. investigated the RBC fatty acid content in hyperactive children compared to normal control children.[126] Inclusion and exclusion criteria were not described, and a formal diagnosis was not assigned. Enrolled were children (n=23; 91% male; 7.5-13 years) identified with "maladjusted disorder" (nomenclature not reported) from a residential school for maladjusted children. The central clinical feature was hyperactivity. The controls were children (n=20; 50% male; 10-13 years) from a regular intermediate school. No inappropriate methods to extract, prepare, store or analyze lipids were described.

Summary Table 22: Association between omega-3 or omega-6/omega-3 content of biomarkers and onset, continuation or recurrence of AD/HD

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Mitchell, 1983, New Zealand: multiple-group cross-sectional study[126]	maladjusted (hyperactive) children (n=23)	normal children (n=20)	NS bet-grp differences in RBC FA content	Total quality: 1 [Grade: C]	III
Mitchell, 1987, New Zealand: multiple-group cross-sectional study[125]	hyperactive children (n=48)	age- & sex-matched normal children (n=49)	↓ DHA,$^{+}$ DGLA^{++} & AA^{+} in hyperactive children	Total quality: 4 [Grade: B]	III
Stevens, 1995, US: multiple-group cross-sectional study[124]	hyperactive boys (n=53)	normal boys (n=43)	↑ PUFA intake in AD/HD;$^{+}$ ↓ plasma AA,$^{+}$ EPA,$^{+}$ DHA^{+} & total n-3^{+++} in AD/HD; ↑ n-6/n-3 in AD/HD;$^{++}$ ↓ RBC AA & DPA in AD/HD^{+}	Total quality: 3 [Grade: C]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; N/A = not applicable; pb = placebo; grp = group; wk = week(s); mo = month; RBC = red blood cells; PL = phospholipid; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase; ↓ = decrease/reduction

Mitchell et al.'s 1987 study examined the clinical characteristics and serum phospholipid EFA levels in DSM-III diagnosed hyperactive children (n=48; mean age: 9.1 years) compared with age- and sex-matched controls (n=49; mean age: 8.7 years).[125] Subjects were recruited from the general population of Auckland using the Revised Behaviour Problem Checklist (RBPC) and the Conners Teacher Rating Scale (CTRS). The control group was drawn from two primary schools. The study groups exhibited no statistically significant differences for age, sex, ethnicity (92% European) and socioeconomic status. Some children in the hyperactive group (n=12) were on special diets, with ten on the Feingold diet and seven on sugar reduction diets. Between-

group baseline differences were statistically significant for the RBPC Inattention subscale and CTRS scores, with higher scores in the hyperactive children. There was no significant between-group difference in medication use (no data reported).

Stevens et al. evaluated the RBC and plasma fatty acid content in boys with AD/HD and sex-matched children without this disorder.[124] The sample was drawn from the general population. The diagnosis was made using the CPRS and CTRS. Questionnaires measured food intake and health information. The AD/HD children (n=53, mean age: 9.1 years) and normal controls (n=43, mean age: 9.1 years) were well matched for age, height, weight BMI and socioeconomic status. AD/HD children were less likely to have been breastfed but more likely to have temper tantrums, problems getting to sleep and waking up, to be taking medications (e.g., Ritalin), to have stomachaches, ear infections and asthma. Baseline Conners scores were significantly higher in the AD/HD group.

By univariate analysis, Mitchell et al. showed that there were no significant between-group differences for any RBC fatty acid content.[126] Multivariate analysis revealed that a model involving ALA and AA, among other fatty acids, distinguished maladjusted and control children. There was no significant difference for RBC PUFA content between the sexes.

In Mitchell et al.'s second study the absolute levels of DHA, DGLA and AA in serum phospholipids were significantly lower in hyperactive children compared to controls.[125] No other omega-3 or omega-6 fatty acid compositions distinguished the two study groups. When hyperactive children were subdivided on the basis of their concentrations of DHA, DGLA and AA, high and low DHA subgroups did not differ significantly on any clinical outcomes. Higher probabilities of speech difficulties, slower development and learning difficulties were each associated with low AA levels.

Stevens et al. demonstrated that the hyperactive group had a significantly higher PUFA intake in their diet compared to controls.[124] The plasma levels of AA, EPA, DHA and total omega-3 fatty acids were significantly lower in hyperactive children. The plasma omega-6/omega-3 fatty acid ratio was significantly higher in the hyperactive group. Patients with hyperactivity had significantly lower RBC AA and (omega-6-)DPA levels. There was a significant and negative correlation between DHA concentration and CPRS scores.

Each of the Mitchell et al. studies received an applicability rating of III while the Stevens et al. study was assigned a I. Mean study quality for these studies was 2.7.

Summary Matrix 10: Study quality and applicability of evidence regarding the association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of attention deficit/hyperactivity disorder

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author Stevens	Year 1995	n 96
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author Mitchell	Year 1987	n 97	Author Mitchell	Year 1983	n 43
n = number of allocated/selected participants										

Although all of the included studies were controlled, none were prospective by design. Thus, meta-analysis was not considered. As well, the three studies did not investigate the same biomarker sources. Given the small number of studies, and the variability in the definition of the study populations and their controls, it was impossible to meaningfully explore the possible impact of predefined covariates or confounders.

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Mental Health Status Difficulties?

As observed in Summary Table 23 (below), derived from Evidence Table 2 (Appendix E*), one cross-sectional study published in 2002 met eligibility criteria.

Overview of Relevant Study's Characteristics and Results

Silvers and Scott conducted a cross-sectional survey investigating the possible association between dietary intake of fish and self-reported mental health status in adults (15-65+ years) living in New Zealand.[127] The data collected were from a combined 1996/1997 health survey and a 1997 nutrition survey. Participants were sampled using a stratified design based on contingent geographic areas. The sample consisted of 11,921 households. The final response rate was 73.8% (n=7,862) for the health survey and 50% (n=4,644) for the nutrition survey. Analysis was conducted on data from 4,644 participants. Participants completed the SF-36 questionnaire regarding their self-reported mental health status. Adjustments were made for the following potential confounders: age (four groups: 15-24 years; 25-44 years; 45-64 years; 65+ years), annual household income (four groups: < $20,000; $20,001-30,000; $30,001-50,000; $50,000+), smoking status (smokers, ex-smokers and non-smokers), alcohol use (non-drinkers, moderate drinkers scoring 1-7 on Alcohol Use Disorders Identification Test [AUDIT], problem drinkers scoring 8+ on AUDIT), and eating patterns (meat eaters, vegetarians, vegans). Funding was provided by the New Zealand Ministry of Health.

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 23: Association between omega-3 fatty acid intake and onset, continuation or recurrence of mental health difficulties

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Silvers, 2002, New Zealand: single population cross-sectional survey[127]	householders (n=4,644)		Univariate analysis: NS correlation between fish consumption & mental health status; hierarchical regression, with age & income adjustments, association observed;$^{+++}$ adjusting for age & household income, mental health status ↓ in fish consumers;$^{+++}$ adjusting for age, household income, smoking, alcohol consumption, & eating patterns an association^{++}	Total quality: 5 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Respondents were divided on the basis of those who did (<once a month, to at least twice a day), or did not, consume fish.[127] Univariate analysis revealed no significant correlation between fish consumption and mental health scores. By hierarchical regression, with age and income adjusted for, there was a significant association between fish consumption and mental health status. The mental health score was significantly lower in the group which consumed no fish, compared with the fish eaters. After adjusting for age, household income, smoking, alcohol consumption, and eating patterns this difference remained significant. This study received an applicability rating of III and a total quality score of 5.

Given that only one study was identified, meta-analysis and a formal assessment of the potential influence of covariates and confounders were not undertaken. Although this study conducted their analysis by controlling for several confounders, results need to be replicated before any meaningful conclusions can be drawn.

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Tendencies or Behaviors With the Potential to Harm Others?

As observed in Summary Tables 24 through 28 (below), derived from Evidence Tables 1 through 3 (Appendix E*), seven studies met eligibility criteria. These studies were published

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

between 1996 and 2004. Five studies employed an RCT design while one cross-sectional study and a cross-national ecological analysis were also included. Although each question addressed the possible association of omega-3 fatty acid intake with the onset of tendencies or behaviors with the potential to harm others, the types of population fit into three categories. This is the order in which the studies are presented.

The first three RCTs investigated the possible protective effects of omega-3 fatty acids against aggression in healthy volunteers.[128-130] One RCT and a cross-sectional survey examined the possible protective potential of the exposure against anger and/or hostility in populations identified at risk for heart disease[132] or identified as having cholesterol problems.[99] The latter study, by Wardle et al., has been reviewed elsewhere with respect to depression and anxiety.[99] One RCT assessed the possible protective effect on the antisocial behavior in young adult prisoners, making this the only study designed specifically to investigate the exposure's possible influence on the continuation of this behavior (i.e., secondary prevention).[131] The final study assessed the possible association of seafood consumption and homicide mortality.[133]

Overview of Relevant Studies

Hamazaki and colleagues conducted all three of the RCTs investigating the effect of omega-3 fatty acid supplementation on aggression.[128-130] The first two studies assessed the possible benefits of the exposure on healthy college volunteers[129,130] while the final RCT enrolled elderly volunteers.[128]

Hamazaki et al.'s first trial randomly assigned nonsmoking university students to receive 3 months of either 1.5-1.8 g/d DHA (from fish oil; n=26) or control oil capsules (n=27) containing some omega-3 fatty acid content (97% soybean oil plus 3% fish oil; exact omega-3 fatty acid content not reported). The active intervention also contained some EPA and some omega-6 fatty acid content (see intervention/exposure characteristics below). Doses varied because they were adusted according to participants' weight. The study began at the end of the students' summer vacation and was completed in the middle of final exams (i.e., the stressor). The rationale was to see if stress could be prevented from becoming frustration and aggression.

Summary Table 24: Association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies or behavior with the potential to harm others (RCTs)

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Notable biomarker effects[2,3]	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)				
Hamazaki, 1996, Japan: 3 mo parallel RCT[130]	1.5-1.8g/d DHA & some EPA (n=27)	oil capsules (97% soybean oil + 3% fish oil) (n=26)	extraggression ↑ in controls;$^{++}$ NS Δ for DHA grp; bet-grp difference^{+}	NS bet-grp differences in Δ for AA, EPA or DHA	Jadad total: 3 [Grade: B]; Schulz: Unclear	III
Hamazaki, 1998, Japan: 3 mo parallel RCT[129]	1.5 g/d DHA capsules (n=29)	control capsules with some ALA & DHA (n=30)	extraggression ↓ in controls;$^{+}$ NS Δ for DHA grp; bet-grp difference;$^{+}$ NS Δ hostility in either study group	↑ RBC DHA^{+++} & EPA^{+++} in DHA grp; ↑ LA^{++} in controls	Jadad total: 3 [Grade: B]; Schulz: Unclear	III
Hamazaki, 2002, Thailand: 2 mo parallel RCT[128]	1.5g/d DHA + 0.2g/d EPA from 3g/d fish oil capsules (n=20)	3g/d mixed plant oil control (n=21)	NS Δ for extraggression for university controls; ↓for DHA grp;$^{+}$ bet-grp difference in extraggression;$^{+}$ NS bet-grp difference for villagers; university= NS Δ for controls; ↓ for DHA grp;$^{+}$ villagers= NS bet-grp difference for extraggression	NS changes in FA in controls; In DHA group EPA & DHA ↑;$^{+++}$ AA ↑$^{++}$	Jadad total: 3 [Grade: B]; Schulz: Unclear	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; PL = phospholipid;; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↑ = decrease(d)/reduction/lower

Hamazaki et al.'s second trial examined possible protective effects against aggression in normal volunteers under nonstressful conditions.[129] Fifty-nine nonsmoking university students, with 15 males per study group, were randomized to receive 3 months of either DHA-rich fish oil capsules containing 1.5 g/d DHA (n=29) or the same control oil capsules (97% soybean oil plus 3% fish oil; n=30) used in their first study. None of the participants had been enrolled in the first RCT. The timing of the trials' initiation and completion determined that volunteers would not likely be subjected to the same stressful conditions as arranged in the first study (i.e., final exams).

The third study focused on elderly Thai subjects.[128] Forty-one subjects (50-60 years) were randomly assigned to receive either 1.5 g/d DHA (n=20) via 3g/d fish oil capsules or 3g/d of mixed plant oil via capsules (n=21) for 2 months. Extraggression was assessed at the beginning and end of the study. Immediately prior to its assessment at study end subjects were shown a 20-minute, stress-inducing videotape of real crimes and accidents as the study's stressor. Participants were recruited from two sources: university employees and villagers.

Wardle et al.'s RCT investigated whether cholesterol-lowering diets influence mood, including depression, anxiety, anger/hostility, stress, and general psychological well-being.[99]

Adult volunteers (n=176) with elevated serum cholesterol levels (>5.2mM [198mg/dL]) were allocated to a low-fat diet (n=59), a Mediterranean diet (n=61), or a waiting-list control (n=56). Dietary treatments were given in eight sessions over the 12-week period. Participants completed a seven-day dietary intake diary before the first assessment. Outcomes included the STAI, the anger subscale of the POMS, GHQ to assess general psychological well-being, and the PSS. Dietary diaries were filled out at baseline and 12 weeks.

Summary Table 25: Association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies or behavior with the potential to harm others (RCT)

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Notable biomarker effects[2,3]	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)				
Wardle, 2000, England: 12 wk parallel RCT[99]	Mediterranean diet (with oily fish) (n=61)	low fat diet (n=59)/ waiting list control (n=56)	All grps had within-grp improvement for STAI's anger reactions;$^{+}$ NS bet-grp differences for anger/hostility, stress, or general psychological well-being	n/a	Jadad total: 2 [Grade: C]; Schulz: Adequate	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; STAI = State-Trait Anger Inventory; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Iribarren et al. assessed the possible association between dietary omega-3 fatty acids, omega-6 fatty acids and fish intake with the level of hostility in a sample of 3,581 urban white and black young adults.[132] Their cross-sectional survey was conducted as part of the ongoing CARDIA cohort study investigating heart disease risk factors and subclinical coronary disease. The dietary assessment took place in 1992-1993, while data pertaining to hostility and other covariates were collected in 1990-1991. At baseline (1985-1986; n=5,115) participants had been 18 to 30 years of age. Sampling ensured a balanced racial distribution, and included random-digit dialing (Birmingham, Alabama), door-to-door recruitment (Minneapolis, Minnesota) and random selections from files at a medical care program (Oakland, California). Reassessments took place 2, 5, 7, 10 and 15 years from baseline. Retention was high even after 15 years (73%).

Summary Table 26: Association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies or behavior with the potential to harm others (cross-sectional study)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Iribarren, 2004, US: single population cross-sectional survey[132]	urban white & black young adults (n=3,581): black females (n=967) & males (n=672), white females (n=1,017) & males (n=925)		Adjusted multivariate odds ratios of scoring in the upper quartile of hostility scores associated with one standard deviation increase in DHA intake;$^{+}$ consumption of fish rich in omega-3 fatty acids, when compared to no consumption, was associated with lower odds of high hostility.$^{+}$	Total quality: 5 [Grade: B]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Gesch et al. empirically tested whether a "cocktail" of vitamins, minerals and essential fatty acids (0.08 g/d EPA, 0.044 g/d DHA, 1.26 g/d LA and 0.16 g/d GLA) would produce a reduction of antisocial behavior in adult prisoners at least eighteen years of age when compared to placebo.[131] It had been hypothesized that offenders suffer from a lack of essential nutrients. The main focus was on whether or not antisocial behavior leading to disciplinary incidents would decrease from baseline. Given the requirements of life in an institution (e.g., parole), the analysis allowed participation ranging from 2 weeks to 9 months. Although 231 volunteers were identified, the number randomized to each group was not reported. The average time spent on supplementation was 142.6 days for the active treatment group (n=57 completers) and 142 days for the placebo group (n=55 completers). Randomization was stratified based on the four wings of the institution in which participants resided.

Summary Table 27: Association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies or behavior with the potential to harm others (RCT)

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)			
Gesch, 2002, UK: ~142-day (mean) RCT[131]	0.08g/d EPA, 0.044g/d DHA, 1.26g/d LA & 0.16g/d GLA) capsules & vitamin/ mineral capsules (n=57 completers)	identical vegetable oil placebo capsules for fatty acids & identical vegetable oil placebo capsules for vitamins/ minerals (n=55 completers)	Bet-grp difference in favor of fewer offences for those receiving active treatment;$^{+}$ using data from those who received at least two weeks of supplementation, only for those receiving supplementation did the number of incidents ↓;$^{+}$ greatest ↓ was observed for most serious incidents;$^{++}$ minor reports exhibited the same bet-grp difference	Jadad total: 5 [Grade: A]; Schulz: Adequate	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ITT = intention-to-treat analysis; PP = per-protocol analysis (e.g., completers); ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Hibbeln undertook a cross-national ecological analysis investigating the possible association between seafood consumption and homicide mortality.[133] They posited that, since rates of death due to homicide demonstrate a 20-fold variation across countries paralleling cross-national differences in mortality from cardiovascular disease, then similar dietary factors might underlie both patterns. They argued that this relationship might be important since factors like hostility, depression and anger can increase the risk of cardiovascular morbidity. They considered violent behavior to sit at the extreme of a continuum that includes hostility. Homicide rates were taken from the 1995 Annual Health Statistics report of the WHO. Data concerning apparent seafood consumption were taken from the FAOSTAT database as was achieved in numerous other cross-national ecological analyses. Planned analysis included data from 26 countries.

Summary Table 28: Association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies or behavior with the potential to harm others (cross-national ecological analysis)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Hibbeln, 2001, 26 countries: cross-national ecological analysis [133]	n=26 countries		Simple[++] & logarithmic regressions:[+++] countries with ↓ apparent seafood consumption had ↑ rates of homicide mortality; excluding Asian data maintained the association[++]	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; RBC = red blood cells; PL = phospholipid; [+]p<.05 or significant with 95% confidence interval; [++]p<.01; [+++]p<.001; [++++]p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Five RCTs,[99,128-131] one cross-sectional survey[132] and one cross-national ecological analysis[133] were deemed relevant for the review. Two of the RCTs were conducted in Japan,[129,130] two in the UK[99,131] and one in Thailand.[128] The cross-sectional survey was undertaken in the US[132] while the cross-national ecological analysis obtained data from many countries.[133] Except the cross-sectional ecological analysis, eligibility criteria for each of the studies were adequately described. Hamazaki et al.'s first trial was funded by the Nissin Seifun Foundation and a grant from the Japan-US Cooperative Medical Science Program.[130] Their second study was supported by the Shorai Foundation for Science and Technology and by the Special Coordination Funds for Promoting Science and Technology of the Science and Technology Agency of the Japanese government.[129] Their study of elderly volunteers received funds from the Special Coordination Funds for Promoting Science and Technology of the Science and Technology Agency of the Japanese government in addition to the Goho Life Sciences International Fund and a grant from the Japan-US Cooperative Medical Science Program.[128] Wardle et al.'s trial was supported by a grant from the Biotechnology and Biological Sciences Research Council.[99] Iribarren and colleagues received two NIH grants from the National Heart, Lung and Blood Institute, with the lead author also awarded a Scientist Development Grant from the American Heart Association.[132] Gesch et al.'s study was supported by a grant from the research charity Natural Justice and its various contributors.[131] Funding support for Hibbeln's ecological analysis was not reported.[133]

Population characteristics. The "healthy" status of student volunteers in the first two Hamazaki et al. RCTs was determined by physical examination and interview,[129,130] although one also included blood tests completed three to four months prior to study entry.[130] In their second and third studies, Hamazaki et al.'s volunteers had to be free of chronic illness, including alcoholism and any regular medication use.[128-130] Additional reasons for exclusion in the trial with elderly subjects were health problems such as myocardial or cerebral infarction, cancer, severe hypertension and other serious diseases.[128] Both samples of student were asked to keep their body weight and physical activity constant during the study[129,130] In their study involving a

stressor component, Hamazaki et al. described their students as ranging in age from 19 to 30 years, with more than half being female (n=34/53).[130] In the RCT conducted without a stressor, subjects ranged from 20 to 30 years and slightly more than half were male (n=30/59).[129] Elderly Thai subjects were between the ages of 50 and 60 years, with more male participants (n=22/41).[128]

There were no significant differences among the study groups for any of the baseline mental health (i.e., anger scores on POMS; general psychological well-being; stress; state anger and anger reactions scores on STAI), background diet (i.e., g/d or percent of energy saturated fat; g/d fiber), or other characteristics (i.e., age, marital status, sex, BMI, total, HDL and LDL cholesterol and trigyceride parameters) in Wardle et al.'s trial.[99] Iribarren et al.'s observational study evaluated young adult white and black males and females.[132] Significant heterogeneity was observed when the different subgroups were compared. For example, the mean hostility score was highest in black males, followed by white males, black females and white females. White participants were older than black subjects. Total energy intake was highest in black males, followed by white males, black females and white females. Intake of LA and ALA were each highest in black females, lowest in white females, and intermediate in males. Intake of AA was highest in black males and lowest in white females. Intake of EPA and DHA were each higher in black than white subjects. Omega-6/omega-3 fatty acid intake was significantly lower in white females than any of the other subgroups. Black participants consumed more total omega-6 fatty acid and total omega-3 fatty acid content than did white subjects. Alcohol intake was higher among males than females, and higher in white females than black females. While total fish intake did not vary by sex and/or race, black subjects consumed more fish rich in omega-3 fatty acids than did white participants. In black subjects, the proportion of current smokers and the prevalence of unemployment were higher while the level of education and the likelihood of being married were lower.

There were no statistically significant between-group differences at baseline on any of the measures of intelligence, verbal ability, anger, anxiety, malaise or depression in Gesch et al.'s trial.[131] Countries included those from Asia (e.g., Japan, Hong Kong), continental Europe (e.g., Germany, Holland), the UK, Scandinavia (e.g., Norway, Sweden), South America (e.g., Chile), the Middle East (e.g., Israel), Australia, New Zealand, Canada and the United States in Hibbeln's cross-national ecological analysis.[133] This suggests considerable variability in the background diet in general and not merely related to fish consumption.

Intervention/exposure characteristics. The exposure was weight-adjusted only in Hamazaki et al.'s first trial.[130] In both studies involving students, each capsule contained 300mg of oil with the antioxidant α-tocopherol (0.3%) added to stabilize the exposure.[129,130] The fish oil received by those in the DHA group contained 49.3% (wt/wt) DHA, 6.7% EPA, 9% palmitic acid, 7.3% oleic acid, 3.2% AA, 3.2% palmitoleic acid, 2.3% stearic acid and other contents (no data reported).[129,130] The control oil was not inactive in that it contained 3% concentrated sardine oil that had been partially deodorized, and included 54.1% LA, 22.3% oleic acid, 10.8% palmitic acid, 6.8% ALA, 3.7% stearic acid, 0.5% DHA and other contents (no data reported).[129,130] In the study of elderly Thai subjects, the DHA group took 1.5g/d DHA in addition to 0.2g/d EPA.[128] Controls received 3g/d of mixed plant oil (47% olive oil, 25% rapeseed oil; 25% soybean oil, 3% fish oil), indicating that these subjects received some omega-3 fatty acid content as well.[128] Capsules were typically taken around meal time.[128-130] In none of the Hamazaki et al. trials were descriptions provided indicating the inappropriate handling of lipids.[128-130]

On three occasions, participants in Hamazaki et al.'s first RCT were asked to complete a food frequency questionnaire, to provide data concerning their dietary intake of various lipids, and to maintain their background diet.[130] Participants in Hamazaki et al.'s last two trials completed the food frequency questionnaire at study's start and end.[128,129] Compliance was monitored by capsule counts in their first RCT.[130] Only 45% of subjects in each study group in the second trial reliably guessed which exposure they had been receiving.[129] Likely due to having placed some fish oil in the control exposure, and perhaps also because of a briefing at study initiation which outlined this plan for study participants, elderly subjects could not reliably guess which exposure they had received (although villagers did significantly better).[128]

Portion sizes were established in Iribarren et al.'s observational study using cups and spoons, and reference was made to intake during the month preceding each clinical visit.[132] Daily nutrient intake was estimated using the validated CARDIA diet history questionnaire. The intake of omega-3 and omega-6 fatty acid content was expressed as nutrient density (kcal/1000kcal/d). Intake of total fish or fish rich in omega-3 fatty acids (i.e., salmon, mackerel, trout, herring, eel, cod) were expressed as occasions per week.

The vitamin/mineral supplement combination (Vitamins A, D, B1, B2, B6, B12, C, E, K; biotin, nicotinamide, pantothenic acid, folic acid, calcium, iron, copper, magnesium, zinc, iodine, manganese, potassium, phosphorus, selenium, chromium, molybdenum) in Gesch et al.'s trial of young adult prisoners was matched with a vegetable oil placebo given in an identical, opaque bicolored gelatin shell.[131] To this was added an Efamol Marine® product containing both omega-3 and omega-6 fatty acids. The daily dose was 80 mg EPA, 44 mg DHA, 1260 mg LA and 160 mg GLA. A vegetable oil placebo of identical color was delivered via a clear gelatin shell. Diet was assessed via a 7-day food diary. Meal portion weights were determined as well. Compliance was 89.3% and a significant between-group difference was not observed. Participants could not reliably guess which exposure they had been receiving.[131] Hibbeln's apparent seafood consumption was defined as catch plus imports minus exports. Wardle et al.'s dietary changes have been described twice already and these details are not repeated here.[99]

Only Gesch et al. identified the manufacturer of their omega-3 fatty acid exposure (Efamol Ltd.),[131] with no reports of interventional studies describing purity data or details as to whether, and how, the presence of methylmercury was tested or eliminated from the omega-3 fatty acid exposure.

Cointervention characteristics. No cointervention data were described in any of the study reports.

Outcome characteristics. All three of Hamazaki et al.s' trials used the Japanese version of Rosenzweig's validated adult Picture-Frustration test at pre- and poststudy.[128-130] First responses to cards depicting frustrating scenarios were categorized as aggression varying in terms of its direction (extraggression: toward others; intraggression: toward self; imaggression: against nobody). In the second study, the Cook and Medley hostility scale (0/low to 50/high)was also employed.[129] Blinded ratings were highly reliable (no data reported).[130] The fatty acid composition of serum phospholipids was assessd in their first study,[130] with phospholipid fractions of RBCs measured in their other two trials.[128,129]

Hostility was measured using the Cook-Medley Scale in Iribarren et al.'s observational study.[132] Two types of incident report were defined by Gesch et al.: serious (e.g., violence) and minor (i.e., failure to comply with requirements).[131] Homicide mortality rates were collected by Hibbeln.[133] Wardle et al.'s outcomes are described above.[99]

Study quality and applicability. The five RCTs received a mean Jadad total quality score of 3.2, indicating sound internal validity.[99,128-131] Two studies achieved a rating indicating Adequate allocation concealment,[99,131] and three received an Unclear rating regarding allocation concealment.[128-130] Three RCTs attained an applicability rating of III,[128-130] whereas two trials achieved an applicability score of II.[99,131] The cross-sectional survey was assigned a quality score of 5 and an applicability rating of II.[132] The cross-sectional ecological analysis achieved a quality score of 4 and an applicability rating of III.[133]

Summary Matrix 11: Study quality and applicability of evidence regarding the association between omega-3 fatty acid intake and onset, continuation or recurrence of tendencies of behavior with the potential to harm others

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author Gesch[A]	Year 2002	n 112	Author Iribarren	Year 2004	n >3k	Author Wardle[A]	Year 2000	n 176
	III	Author	Year	n	Author Hamazaki[U] Hamazaki[U] Hamazaki[U] Hibbeln	Year 1996 1998 2002 2001	n 53 59 41 26C	Author	Year	n

n = number of allocated/selected participants; RCT = [A]Adequate vs [U]Unclear allocation concealment; C = Countries; k = 1,000's

Qualitative Synthesis of Individual Study Results

In Hamazaki et al.'s first study, dropouts and withdrawals did not present a notable barrier to the integrity of their study or in turn the meaningful interpretation of their results. Aggression directed toward others (extraggression) at times of stress was significantly increased in the control group by study's end, while no significant change was observed in the DHA group.[130] The between-group difference was significant. Yet, under nonstresssful conditions (second study) it was found that extraggression decreased significantly in the control group whereas no significant change was observed for the DHA group.[129] The between-group difference was barely significant. Hostility scores did not change significantly within either study group.[129]

There were no significant differences in changes in extraggression over Hamazaki et al.'s study of elderly Thai subjects for either males and females or for those varying in terms of their smoker status.[128] Given that villagers in the control group had their extraggression scores decrease significantly more than did university employees, their data were analyzed separately. Extraggression did not change for those university employees receiving the control exposure while it did decrease significantly for those taking the DHA capsules. There was also a significant difference in extraggression between the two study groups. There was no significant between-group difference for the villager subjects. Results relating to the university employees showed that extraggression did not change over time for the control group yet decreased significantly for participants receiving DHA. For those subjects receiving the control exposure, the fact that they had been consuming approximately 150-160 mg/d of DHA from their regular food sources was insufficient to have a positive effect on responses to the test procedure.[128]

No significant between-group differences in changes from baseline were observed for AA, EPA or DHA in Hamazaki et al.'s first study.[130] But, in their second trial they found significant increases in RBC membrane DHA and EPA in the DHA group while LA increased in the control group.[129] AA decreased significantly in the DHA group as well.[129] The two studies evaluated different biomarker sources. Hamazaki et al.'s trial enrolling elderly Thai subjects found no significant differences in fatty acid compositions between those varying on the basis of their sex, smoker status or urban status.[128] As a result, these data were combined in subsequent analyses. No significant changes in fatty acid composition were observed in the control group. In the DHA group both EPA and DHA levels increased significantly over the trial. At the same time AA decreased significantly.

Each of Wardle et al.'s three study groups showed a significant within-group improvement only for the STAI's anger reactions after 12 weeks.[99] Yet, there were no significant between-group differences observed for any of the following clinical outcomes: anger/hostility, stress, or general psychological well-being.

Iribarren et al. reported that total energy was positively correlated with hostility for the full sample and for all sex-by-race groups.[132]. ALA was exclusively and negatively associated with hostility for black males. EPA intake for all subjects was negatively correlated with hostility. Among black males, intakes of DHA, LA, total omega-6 fatty acid content, total omega-3 fatty acid content and of fish rich in omega-3 fatty acids were each correlated negatively with hostility. Omega-6/omega-3 fatty acid intake was uncorrelated with hostility for each of the sex-by-race groups. Alcohol intake was positively associated with hostility only in black subjects. Total energy and alcohol consumption were significantly and positively correlated with high hostility (>75th percentile). Adjusting for age, sex, race, center, educational level, marital status, BMI, smoking, alcohol consumption and physical activity, the multivariate odds ratios of scoring in the upper quartile of hostility scores associated with one standard deviation increase in DHA intake was statistically significant. Consumption of fish rich in omega-3 fatty acids, when compared to no consumption, was significantly associated with lower odds of high hostility. When consumption of fish rich in omega-3 fatty acids was entered into a multivariate model along with intake of DHA, the association of the former variable with hostility was no longer significant. The investigators suggested that the original significant association was accounted for by DHA content.

Gesch et al.'s ITT analysis (n=231) revealed a statistically significant between-group difference in favor of fewer offences for those receiving active treatment. Those receiving active capsules showed a reduction of 26% compared to those taking placebo. Using data exclusively from those who received at least two weeks of supplementation (n=172; study group sizes not reported), only for those receiving supplementation did the number of incidents decrease significantly. The greatest reduction was observed for the most serious incidents. Minor reports exhibited the same pattern of difference between active and placebo groups.

US data were excluded from Hibbeln's cross-national ecological analysis since their rate of mortality due to homicide was 20 per 100,000 persons, making it more than double the rate from any other country, or 10-fold greater than the mean.[133] Simple regression and logarithmic regression respectively revealed that countries with lower apparent seafood consumption had higher rates of death due to homicide. Excluding data from logarithmic regression for Asian countries (n=21 countries), which exhibited both high rates of seafood consumption and low rates of homicide mortality, maintained the significant relationship.

Quantitative Synthesis

Meta-analysis was not conducted because of noncomparable outcomes (i.e., aggression vs anger/hostility vs antisocial behavior vs homicide), populations (i.e., healthy vs at risk for heart disease vs cholesterol problems vs young adult prisoners vs multiple national populations) and designs (RCTs vs observational studies vs cross-national ecological analyses). As well, of the three studies investigating the possible protective influence of exposures containing omega-3 fatty acids on aggression, one included a narrowly defined population (i.e., elderly volunteers).[128] The remaining two Hamazaki et al. studies[129,130] varied in terms of whether they weight-adjusted their doses, and only one of them employed a stressor against whose effects the exposure was targeted. More importantly, since the latter two studies used "cocktails" from which the exact contributions of omega-3 fatty acids could not readily be teased out, any attempt to combine their results would fail to elucidate the possible protective influence of omega-3 fatty acids per se.

Impact of Covariates and Confounders

Given the noncomparability of the studies, it is difficult to identify threads of consistency across all of them. Even looking at the most homogeneous collection of studies, what cannot be ascertained are the individual or collective impacts on study outcomes of Hamazaki et al.'s attempts to control for body weight, physical activity and background diet in all three RCTs,[128-130] smoking in their two RCTs with university students,[129,130] for alcohol consumption in their second and third studies,[128,129] their stratification for age and sex in their second study[129] or for sex and smoker status in their study of the elderly.[128] In their first trial report, Hamazaki et al. noted that there were no significant differences in the intake of DHA, EPA, LA, total omega-6/omega3 fatty acids or total lipid intake per day.[130] This likely eliminated several possible sources of confounding. Other sources were seen to have been similarly controlled by virtue of specific observations. For example, the on-study intake of total energy did not change significantly for either study group in Hamazaki and colleagues' second trial;[129] and, in their third study, daily on-study intake of DHA from food sources was similar for both study groups although the result of a statistical test was not reported.[128]

In other studies, many variables with confounder potential were likewise controlled. Wardle et al. found no between-group differences for age, sex, marital status or baseline clinical outcome scores for any disorder/condition, and not just anger.[99] Iribarren adjusted analyses for age, sex, race, center, educational level, marital status, BMI, smoking, alcohol consumption and physical activity.[132] Gech et al. noted no clinically significant between-group differences with respect to dietary intake.[131] On the other hand, Hibbeln failed to control for important confounding factors such as alcohol consumption and smoking.[133] Yet, regardless of these observations it is not possible to abstract clear and consistent patterns of influence by covariates and confounders.

Is the Onset, Continuation or Recurrence of Tendencies or Behaviors With the Potential to Harm Others Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 29 (below), derived from Evidence Table 2 (Appendix E*), three cross-sectional studies published between 1987 and 2003 met eligibility criteria.

Overview of Relevant Studies' Characteristics and Results

Hibbeln et al.'s research was supported by the National Association for Research on Schizophrenia and Depression (NARSAD)[134] while Buydens-Branchey et al.'s study was funded by the Veterans Administration, the National Institute of Drug Abuse (NIDA) and the National Institute of Alcohol Abuse and Alcoholism (NIAAA).[136] Virkkunen et al. did not report their funding source.[135]

Virkkunen et al. evaluated EFA levels in plasma phospolipids in two groups of habitually violent and impulsive male offenders (n=34, mean age: 33.2 years) compared to a healthy control group (n=16; mean age: 33 years).[135] Each participant in the former had commited at least one violent crime and had had at least two discrete episodes of loss of control of aggressive impulses. The first subgroup included males meeting DSM-III criteria for antisocial personality (n=15) and had exhibited evidence of conduct disorder since childhood. The second subgroup of patients were habitually violent and had had problems with impulsivity only in adulthood. Their behavior satisfied DSM-III criteria for intermittent explosive disorder. Exclusion criteria were patients with mental retardation, chromosome abnormalities, antisocial personality without any habitually violent tendencies or schizophrenia. All fulfilled DSM-III criteria for alcohol abuse, yet without liver disease. They had been in prison an average of 5 months, with no access to alcohol. Patients and controls were well matched by age and weight. Controls were healthy men drawn from the personnel of a Psychiatric Clinic. None exhibited problems with aggression or alcohol. The diet of controls and patients was maintained in the hospital for 3 days prior to blood sampling, and none took any medication over that period.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 29: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of tendencies or behaviors with the potential to harm others

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Virkkunen, 1987, Finland: multiple-group cross-sectional study[135]	violent antisocial personality (n=15)	intermittent explosive disorder (n=19)/ healthy controls (n=16)	↓ LA in intermittent explosive disorder vs controls;$^{+++}$ ↑ DGLA in both patient grps vs controls;$^{++}$ ↓ DHA in violent antisocial personality disorder vs controls^{++}	Total quality: 4 [Grade: B]	III
Hibbeln, 1998, US: multiple-group cross-sectional study[134]	violent group (n=27)	nonviolent control group (n=31)	NS bet grps for n-3 & n-6 FA; ↓ CSF 5-HIAA in violent pts^{+}	Total quality: 2 [Grade: C]	I
Buydens-Branchey, 2003, US: multiple-group cross-sectional study[136]	aggressive cocaine addict males (n=6)	non-aggressive cocaine addict males (n=18)	NS total FA, PUFA & total n-6 FA bet grps; ↓ DPA,$^{+}$ total n-3 FA^{+} & DHA^{++} in aggressive pts	Total quality: 4 [Grade: B]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; N/A = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; RBC = red blood cells; PL = phospholipid; $^{+}$p<.05 or significant with 95% confidence interval; ++p<.01; +++p<.001; ++++p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower; 5-HIAA = 5-hydroxindolacetic acid; HVA = homovanillic acid

Hibbeln et al. assessed plasma EFA contents and their correlation with serotonin and dopamine metabolites in cerebrospinal fluids in violent and nonviolent subjects (n=31; 71% male; mean age: 39.9 years).[134] The group of violent subjects (n=27; 78% male; mean age: 38.5 years) were included if they had a history, within the last 3 months, of more than five episodes of violent, physical aggression that could cause bodily harm. Violent and control subjects were excluded if they had a history of a major psychotic or major affective disorder, panic disorder, illicit drug dependence, seizure or other neurological disorders. The controls were also excluded if they had a history of one episode of violent physical aggression. Thirteen violent participants met DSM-III-R diagnostic criteria for current alcohol dependence. No participants were taking any medication. The diagnostic tests used to perform the multidimentional clinical assessment were the Brown-Goodwin Lifetime Aggression Rating scales and the Buss-Durkee Hostility Inventory scales. Baseline scores on both scales were significantly higher in the violent subject group. All subjects were maintained on a low-monoamine diet for at least 3 days prior to blood and cerebrospinal fluid sampling. Confounders controlled for were age, alcohol consumption and alcohol-related liver damage.

Buydens-Branchey et al. examined the plasma levels of fatty acids in cocaine addicted males with or without aggressive behavior.[136] The enrolled subjects were hospitalized for treatment of their DSM-IV diagnosed cocaine dependence. They were physically healthy and were not receiving any medication. The diagnostic test employed to assess aggression was the Brown-Goodwin Assessment for Life History of Aggression, and subjects with a score of 8 or more

were considered to have a history of aggression (n=6; mean age: 38 years). The control group (n=18; mean age: 39.6 years) included non-aggressive cocaine addicts. No significant between-group baseline differences were observed for age, weight, number of years of cocaine use and amounts of cocaine used during the preceeding month. None of the three studies provided descriptions indicating inappropriate handling of lipids.

Virkkunen et al. found that the patients with intermittent explosive disorder had a significantly lower content of LA in plasma phospholipids compared to controls.[135] DGLA was significantly higher in both violent groups compared with controls. The content of DHA was significantly reduced in the group of patients with violent antisocial personality disorder compared to controls.

Hibbeln et al. observed no significant between-group differences for omega-3 or omega-6 fatty acid content in plasma.[134] The violent subjects group had a significantly lower concentration of cerebrospinal 5-hydroxindolacetic acid (CSF 5-HIAA) than did controls. Age, height, weight, plasma total cholesterol, frequency and quantity of alcohol consumed, lifetime alcohol consumption, Hollingshead socioeconomic scale, Michigan Alcohol Screening Test (MAST) and CAGE scores (derived from MAST) were not significantly associated with CSF 5-HIAA, CSF homovanillic acid (HVA), cholesterol, or plasma fatty acid contents (e.g., DHA).

Buydens-Branchey et al. did not find a significant full-sample correlation between EFA levels and patients' age, weight, number of years of cocaine use or amount of cocaine used during the preceeding month.[136] No significant between-group differences were observed for plasma total fatty acids, PUFA content or total omega-6 fatty acid composition. (Omega-6)DPA, total omega-3 fatty acids and DHA were significantly lower in the aggressive patients compared to nonaggressive addicts. The omega-6/omega-3 fatty acid ratio was higher in the aggressive patient group, and the difference was only marginally nonsignificant ($p = 0.055$).

Study quality and applicability. Two of the studies received an applicability rating of I[134,136] and a third was assigned a III.[135] Mean study quality for the studies was 3.3.

Summary Matrix 12: Study quality and applicability of evidence regarding the association between the omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of tendencies or behavior with the potential to harm others

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author Buydens-Branchey	Year 2003	n 24	Author Hibbeln	Year 1998	n 58
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author Virkkunen	Year 1987	n 50	Author	Year	n
n = number of allocated/selected participants										

Quantitative Synthesis

Although all of the included studies were controlled, none were prospective by design. Thus, meta-analysis was not considered.

Impact of Covariates and Confounders

Too few studies, reporting too few details, and involving different combinations of target and control populations, precluded even an informal assessment of the possible influence of covariates and confounders.

Is the Onset, Continuation or Recurrence of Alcoholism Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 30 (below), derived from Evidence Table 2 (Appendix E*), two cross-sectional studies published in 1984 and 1998 met eligibility criteria.

Overview of Relevant Studies' Characteristics and Results

Alling et al.'s study was supported by the Swedish Medical Research Council and the pharmaceutical company Merck Darmastadt.[138] Hibbeln et al.'s investigation was funded by the National Alliance for Research on Schizophrenia and Depression (NARSAD).[137]

Alling et al. measured the RBC and plasma fatty acid compositions in males with chronic alcoholism hospitalized for detoxication after a heavy drinking period (n=13; mean age: 54 [41-68] years) compared to healthy male controls drawn from hospital ward staff (n=21; mean age: 39 [22-58] years).[138] Data included in this review focus exclusively on the baseline period, before detoxification began. No attempts to control for confounders were reported.

Hibbeln et al. investigated the relationship between concentrations of plasma EFAs and CSF 5-HIAA in abstinent alcoholics and healthy volunteers.[137] Patients were admitted to the National Institute on Alcohol Abuse and Alcoholism (early-onset: n=88; late-onset: n=39). The diagnosis was made using different tools, including the Research Diagnostic Critera for alcoholism, the Schedule of Affective Disorders and Schizophrenia-Lifetime (SADS), MAST scores, Hollingshead ratings of socioeconomic class, the SCID (DSM-III-R) and the HDRS. The healthy volunteers (n=49, mean age: 37 years, 77.5% male) had to have a negative alcohol breath test and urine drug test in addition to a clinical history indicating no current or lifetime psychiatric or substance abuse disorders. Subjects with a history of major psychotic illness or bipolar affective disorder were excluded. All patients were medication-free. Both patients and controls were maintained on a low-monoamine diet for at least three days prior to blood sampling. Late-onset alcoholics were significantly older than early-onset ones, but there was no difference in age between either group and healthy controls. There were no significant differences between the three groups in terms of height, weight or BMI. The alcoholic patients did have a significantly higher number of cigarettes smoked per year as well as met more criteria indicating antisocial tendencies than did controls. Controls had a significantly higher Hollinghead score than did the early-onset alcoholics.

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*__Note:__ Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 30: Association between omega-3 and omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of alcoholism

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Alling, 1984, Sweden: multiple-group cross-sectional study[138]	chronic alcoholic males (n=13)	healthy control males (n=21)	↓ EPG RBC LA,$^{+++}$ DGLA, AA & DHA^{++} in pts vs controls; ↓ LA^{++} & AA^{+++} in CPG RBCs & plasma in patients vs controls	Total quality: 2 [Grade: C]	III
Hibbeln, 1998, US: multiple-group cross-sectional study[137]	abstinent early-onset (<25 y age) alcoholics (n=88)	abstinent late-onset alcoholics (n=39)/ healthy controls (n=49)	↑ plasma DHA, LA, DGLA & AA in pts vs. controls;$^{++++}$ NS bet early & late-onset alcoholics	Total quality: 3 [Grade: C]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; N/A = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Alling et al. found significantly reduced phosphatidylcholine RBC membrane concentrations of LA, DGLA, AA and DHA in chronic alcoholic patients compared to healthy controls.[138] There was a significantly reduced LA and AA content in phosphatidylethanolamine RBC membrane concentrations and in plasma in patients compared with controls.

Each of Hibbeln et al.'s alcoholic patient groups had significantly higher plasma cholesterol concentrations of total PUFAs, LA, AA, (omega-6-)DPA and DHA compared with healthy controls.[137] No significant between-group differences characterized the remaining omega-3 and omega-6 fatty acid contents. Only the plasma concentration of DHA predicted CSF neurotransmitter metabolite concentrations in all three study groups.

Study quality and applicability. The mean study quality score was 2.5. Alling et al.'s study[138] received an applicability rating of III whereas Hibbeln et al.'s rating was I.[137]

Summary Matrix 13: Study quality and applicability of evidence regarding the association between the omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of alcoholism

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author Hibbeln	Year 1998	n 176
	II	Author	Year	n	Author	Year	n	Author	Year	n
	III	Author	Year	n	Author	Year	n	Author Alling	Year 1984	n 34

n = number of allocated/selected participants

Quantitative Synthesis

Although all of the included studies were controlled, none were prospective by design. Thus, meta-analysis was not considered.

Impact of Covariates and Confounders

Too few studies, focusing on different biomarker sources, and involving different combinations of target and control populations, precluded even an informal assessment of the possible influence of covariates and confounders.

Are Omega-3 Fatty Acids Efficacious as Primary Treatment for Borderline Personality Disorder?

As observed in Summary Table 31 (below), derived from Evidence Table 1 (Appendix E*), one RCT published in 2003 met eligibility criteria. Meta-analysis was not considered.

Overview of Relevant Study's Characteristics and Results

Zanarini et al. randomized 30 female outpatients (76.7% Caucasian; mean age: 26.3 [SD=6.2] identified with borderline personality disorder (duration unreported).[139] Participants received either 1 g/d (97% pure; Laxdale Ltd.) E-EPA (n=20) or placebo (mineral oil; n=10) in a parallel design for 8 weeks (followups at 2, 3, 4, 6, and 8 weeks). The 2:1 randomization ratio was selected to permit the investigators to gain experience working with E-EPA as an exposure. Participants had to meet both the Revised Diagnostic Interview for Borderlines (DIB-R) and DSM-IV criteria for borderline personality disorder. By these criteria, patients were considered moderately ill. Exclusion criteria were those patients who were currently on psychotropic medication, medically ill, taking E-EPA supplements, eating more than one to two servings of fatty fish per week, alcohol or drug abusers, acutely suicidal, meeting current or lifetime criteria for schizophrenia, schizoaffective disorder, bipolar I, bipolar II or in the midst of a major depressive episode. Scores over the course of the study on the Modified Overt Aggression Scale (MOAS) and MADRS served as the primary outcome measures. Funding was provided by NARSAD.

*__Note:__ Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 31: Omega-3 fatty acids as primary treatment for borderline personality disorder

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Zanarini, 2003, US: 8 wk parallel RCT[139]	1g/d E-EPA (n=20)	mineral oil pb (n=10)	E-EPA grp had ↓ MADRS^{++++} & MOAS^{++++} at study end	Jadad total: 3 [Grade: B]; Schulz: Unclear	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; MADRS = Montgomery-Asberg Depression Rating Scale; MOAS = Modified Overt Aggression Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Ninety percent of both E-EPA (n=20 with at least two followups) and placebo participants (n=10 with at least three followups) completed the 8-week trial. The three participants who dropped out of the study did so because of life events unrelated to the study or intervention. Statistical analyses were conducted on those participants who completed the full 8-week intervention. At baseline, results showed that there were no significant between-group differences on demographic characteristics or history of treatment (i.e., n=7/30 [23.3%] had taken psychotropic medication; 25/30 [83.3%] had received psychotherapy; n=3/20 [10%] had been hospitalized for psychiatric reasons). There were also no significant differences between the groups at baseline on either the MADRS or MOAS. This study report did not provide details as to whether, or how, the presence of methylmercury was tested or eliminated from the omega-3 fatty acid exposure. It received an applicability rating of I and an Jadad total quality score of 3, indicating good internal validity. There were significant clinical effects over the course of the study, as the E-EPA group had, at study end, significantly lower mean scores on both the MADRS and MOAS compared to the placebo group.

Are Omega-3 Fatty Acids Efficacious as Primary Treatment for Schizophrenia?

A publication by Peet et al. in 2001 reported one study examining the use of omega-3 fatty acids as a primary treatment for schizophrenia, as well as a second study describing its use as a supplemental treatment for schizophrenia.[58] The former is described here (Summary Table 32; Evidence Table 1: Appendix E*). Meta-analysis was not considered, and a meaningful assessment of the impact of covariates and confounders was not possible.

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Overview of Relevant Study's Characteristics and Results

Peet et al.'s pilot RCT allocated 30 DSM-IV diagnosed, drug-free schizophrenic patients to receive either 3 months of 2g/d EPA of enriched oil (Kirunal®; n=15) or corn oil placebo (n=15) via identical capsules (Summary Table 32).[58] Patients were either newly diagnosed or had relapsed. For ethical reasons, medication was permitted, as required. Clinical judgement, and not predetermined criteria, guided these decisions. No significant between-group differences were observed for age, sex, duration of the illness, baseline total Positive and Negative Syndrome Scale (PANSS) or PANSS positive symptoms scores. Nine patients were drug-naïve and the others had had no medication for at least 2 weeks. Outcomes included the need for, and duration of, conventional medication in addition to the PANSS assessed at baseline and at study's end. Some financial assistance for this project was provided by a colleague of the investigators and by Laxdale Limited, the manufacturer of the EPA product. Purity data were not reported. No attempts to test for and eliminate methylmercury from the exposure were described.

Summary Table 32: Omega-3 fatty acids as primary treatment for schizophrenia

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Peet, 2001, India: 3 mo parallel RCT[58]	2g/d EPA (n=15)	corn oil placebo (n=15)	12/12 pb & 6/14 EPA required antipsychotic medication by study's end;$^{+}$ EPA pts spent fewer days on medication;$^{+}$ EPA pts had ↓ total PANSS^{+} & PANSS positive;$^{+}$ responder analysis 2/12 placebo & 8/14 EPA pts were responders^{+}	Jadad total: 3 [Grade: B]; Schulz: Adequate	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; PANSS = Positive and Negative Syndrome Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Analyses were based on sixteen completers with final PANSS scores (n=12/15 in placebo group). Three patients were lost to followup, and one died of accidental burns unrelated to the illness or study protocol. All 12 patients in the placebo group and six of fourteen in the treatment group required antipsychotic medication by study's end. Of the latter six patients, four required no medication over the 3 month period, one needed antipsychotic medication during the first week, and one received a dose of depot antipsychotic medication (25 mg flupenthixol deconoate) at study initiation. Patients receiving EPA spent significantly fewer days on medication. In spite of the positive effect on symptoms that may have accrued to placebo patients, those receiving EPA had significantly lower total PANSS and PANSS positive scores when compared with placebo patients. The small sample size did not permit a statistical

comparison of scores based on patients who were and were not drug-naïve. Responder analysis (50% improvement on PANSS positive) revealed that two of 12 placebo patients and eight of 14 EPA patients achieved responder status. This trial received a Jadad total score of 3, indicating good quality, an allocation concealment rating of Adequate, and an applicability rating of III.

Are Omega-3 Fatty Acids Efficacious as Supplemental Treatment for Schizophrenia?

Four RCTs published either in 2001 or 2002 were identified as addressing this question (Summary Tables 33 through 36; Evidence Table 1: Appendix E*). The second study in Peet et al.'s report is reviewed here.[58]

Overview of Relevant Studies

Peet et al. have pointed out that EPA and DHA exhibit different metabolic functions. DHA is primarily a membrane structural component and EPA is implicated in eicosanoid synthesis.[58] These metabolites have also been observed to have varying physiological effects.[169] Together, these patterns suggest the need to differentiate between the possible effects of EPA and DHA in the treatment of schizophrenia.

As a result, Peet et al. conducted an RCT (n=55 allocated) designed to examine the impact, over 3 months, of 2 g/d EPA enriched fish oil (Kirunal®; 15 completers), 2 g/d DHA enriched oil (source undefined; 16 completers) or a corn oil placebo (14 completers) on symptomatic (PANSS score of at least 40), DSM-IV diagnosed schizophrenic individuals (Summary Table 33).[58] Delivery of the exposure involved pourable bottles of oil. Participants were to continue on-study with stable doses of antipsychotic medication, and the study protocol anticipated that no changes in dose would be required. A psychiatrist monitored on-study medication. Outcomes included the PANSS score and RBC PUFA levels.

* **Note:** Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 33: Omega-3 fatty acids as supplemental treatment for schizophrenia

Author, Year, Location: Length & Design	Study groups[1]		Notable clinical effects	Notable biomarker effects[2,3]	Notable clinical-biomarker correlations	Internal validity	Applicability
	Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)					
Peet, 2001, England: 3 mo parallel RCT[58]	2g/d EPA enriched fish oil (n=15 completers)	2g/d DHA enriched oil (source undefined) (n=16 completers)/ corn oil pb (n=14 completers)	EPA's total PANSS ↓ than pb;$^{+}$ treatment effect for EPA over DHA ((+) PANSS^{+}); ↑ ↓ in EPA than DHA;$^{+}$ NS for (-) symptoms; EPA pts had ↑ ↓ for EPA than DHA^{+} or pb^{+} grps	Largest ↑ in EPA & DHA in EPA^{+++} & DHA grps;$^{+++}$ Smaller ↑ in EPA & DHA in DHA^{+} & EPA grps;$^{+}$ NS Δ for AA	EPA grp = greatest ↓ in total PANSS had highest baseline EPA^{+} & AA;$^{+}$ baseline EPA predicts clinical ↓;$^{+}$ NS correlations in all other grps	Jadad total: 4 [Grade: A]; Schulz: Adequate	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; PANSS = Positive and Negative Syndrome Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower; (+) = positive; (-) = negative

Fenton et al. conducted an RCT evaluating the efficacy of 16 weeks of 3 g/d E-EPA (n=45) compared to placebo (n=45) in 90 outpatients diagnosed with DSM-IV schizophrenia (n=61/87) or schizoaffective disorder (n=26/87) and clinically significant residual symptoms (Summary Table 34).[89] Residual symptoms were defined as one or more positive and/or negative symptom scores greater than 4, or total scores greater than 45 with a score of 3 or more on at least three positive or negative items on the PANSS. Blind assessments took place at baseline and then every second week. The EFA content of RBCs was assessed at baseline and at study's end. Three patients withdrew consent in the first week of the trial (n=2 in placebo group).

Summary Table 34: Omega-3 fatty acids as supplemental treatment for schizophrenia

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Notable biomarker effects[2,3]	Notable clinical-biomarker correlations	Internal validity	Applicability
Fenton, 2001, US: 16 wk parallel RCT[89]	3g/d E-EPA (n=45)	mineral oil pb (n=45)	Time effect on total PANSS,$^{+++}$ MADRS^{+++} & CGI;$^{+++}$ NS time-by-grp interaction; NS effects for time or time-by-grp for cognitive impairment, EXP or TD; NS effects on (+) or (-) PANSS; improvement in pb in 1st 2 wk	EPA grp had higher % EPA^{+++} & ↓ % AA;$^{+++}$ EPA ↑in pb grp;$^{+}$ AA/EPA ↓ greater for EPA;$^{+++}$ DHA % ↓ in smokers^{++} vs nonsmokers, & males had ↓ DHA^{+} & EPA %'s^{+} vs females	Δ in AA/EPA not linked to efficacy; DHA Δ negatively correlated with Δ in (+) symptoms;$^{++}$ sex & current smoking status related to FA compositions $^{+ - ++}$	Jadad total: 4 [Grade: A]; Schulz: Unclear	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Improvement Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower; TD = tardive dyskinesia; EXP = extrapyramidal symptoms; (+) = positive; (-) = negative

Emsley et al. undertook a trial including 40 (18-55 years) DSM-IV diagnosed schizophrenic patients with persistent symptoms, randomized to receive, via 500 mg capsules twice daily, either 3 g/d E-EPA or placebo (liquid paraffin) as 12 weeks of supplemental treatment (Summary Table 35).[140] All had received stable doses of antipsychotic for 6 months and had a total PANSS score of greater than 50. Patients were assessed at baseline and every 3 weeks thereafter using the PANSS and Extrapyramidal Symptom Rating Scale.

Summary Table 35: Omega-3 fatty acids as supplemental treatment for schizophrenia

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable clinical effects	Internal validity	Applicability
Emsley, 2002, South Africa: 12 wk parallel RCT[140]	3g/d E-EPA (n=20)	liquid paraffin pb (n=20)	With^{+} or without^{+} controls, total PANSS ↓'s greater in E-EPA grp; difference favored E-EPA patients in % Δ of general psychopathology (PANSS);$^{+}$ dyskinesia ↓ greater for E-EPA pts at 12 wk^{++}	Jadad total: 3 [Grade: B]; Schulz: Unclear	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; PANSS = Positive and Negative Syndrome Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Peet and colleagues conducted a dose-ranging study of the effects of E-EPA on outpatients (n=122; 18-70 years) with persistent schizophrenic symptoms despite treatment with adequate doses of antipsychotic drug (typical [n=36 in ITT population], new atypical [n=48 in ITT population] or clozapine [n=31 in ITT population]) (Summary Table 36).[87] Participants across nine sites were diagnosed as schizophrenic via DSM-IV criteria and were randomized to receive twelve weeks of either 1 g/d, 2 g/d or 4 g/d E-EPA, or placebo (liquid paraffin in identical gelatin capsule). These investigators selected EPA since it can inhibit the enzyme phospholipase A_2. This enzyme's cycle entails the release of AA, and its overactivity and the concomitant loss of AA from cell membranes have been observed in association with schizophrenia.[87] Change from baseline on the PANSS was the primary outcome. Assessments were conducted at baseline and then every 4 weeks.

Summary Table 36: Omega-3 fatty acids as supplemental treatment for schizophrenia

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable clinical effects	Notable biomarker effects[2,3]	Notable clinical-biomarker correlations	Internal validity	Applicability
Peet, 2002, England: 12 wk parallel RCT[87]	4g/d E-EPA (n=27)/ liquid paraffin pb (n=31)	2g/d E-EPA (n=32)/ 1g/d E-EPA (n=32)	typical neuroleptics: all doses improved total PANSS (size of Δ covaries with dose);$^{+ - ++}$ large pb effects;$^{+ - ++}$ NS differences vs pb; atypical neuroleptics: improvement for 1g/d$^{+ - +++}$ & 2g/d$^{+ - +++}$ (total & subscale); NS effect for 4g/d; pb effects;$^{+++}$ NS differences vs pb; clozapine: all doses had effects;$^{+ - +++}$ 2g/d had greatest % Δ; 2g/d E-EPA effect on total PANSS^{+} & general psychopathology^{+}	Δ in pb grp: ↑ in AA in pts on atypical antipsychotics;$^{+}$ clozapine: ↑ in AA^{+} in 2g/d grp; ↓ for DHA^{+} & AA^{+} in 4g/d grp on atypical antipsychotics	Δ in AA positively related to Δ in all clinical outcomes;$^{+ - +++}$ Δ in DHA or EPA unrelated to Δ in clinical outcomes	Jadad total: 4 [Grade: A]; Schulz: Adequate	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; PANSS = Positive and Negative Syndrome Scale; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Two of the trials were conducted in England,[58,87] one in the US,[89] and one in South Africa.[140] Peet et al.'s RCT provided, by far, the most comprehensive information concerning inclusion and exclusion criteria. All trials employed a parallel design, with the number of groups ranging from two to four. All included a placebo control. An average of 76.8 patients were randomized, with a range of 40 to 122 patients. Studies'participants received the intervention for an average of 13.3 (range: 12-16) weeks. Some financial assistance for Peet et al.'s first project was provided by the investigators' colleague and by Laxdale Limited, the manufacturer of the EPA product.[58] Fenton et al.'s RCT was supported by a grant from the Stanley Foundation/National Alliance for the Mentally Ill Research Institute.[89] Emsley et al.'s study was supported by a grant from the Medical Research Council of South Africa, with

the study exposure supplied by Laxdale Limited (Stirling, Scotland).[140] Peet and colleagues' second trial received funding from Laxdale Limited, the manufacturer/supplier of their exposure.[87]

Population characteristics. Mean age data across all four included studies could not be calculated given that not all studies reported full sample data while some only provided demographic data for study completers.[58] Participants' ages ranged from approximately 18 to 65 years across the four RCTs.

Age data only from completers were reported for Peet et al.'s study.[58] For these outpatients, mean ages by study group were similar (42-44 years) although a formal statistical test was not performed. Patients' average age in Fenton et al.'s study was 40 years (SD=10; range: 18-65 years).[89] Emsley's et al.'s RCT involved patients between the ages of 18 and 55 years.[140] Baseline demographic were similar for their two study groups (no statistical tests reported). For example, mean ages for the E-EPA (46.2 years; SD=10.6) and placebo groups (43.6 years; SD=13.9) were comparable.[140] Peet and colleagues' patients ranged from 20 to 62 years of age, with study group means making their sample population the youngest of all four trials (34-39 years).[87] In this last RCT, study group mean ages were comparable although no test of statistical significance was reported. At baseline, patients in the 2g/d E-EPA group were slightly younger than those in the other three study groups.

Peet et al. found that males exceeded females in the EPA (67% male) and DHA (75% male) groups, and to a lesser extent in the placebo group (57% male).[58] In their second study, male composition of the study groups ranged from 63% to 71%.[87] Fenton et al.'s study randomized mostly males (61%).[89] Emsley et al. did not report any data regarding sex.[140] Only one study report provided ethnicity/race data,[89] with 84% being Caucasian. In Fenton et al.'s study, 80% were single and 70% were high school graduates.

All studies employed DSM-IV criteria to identify outpatients with schizophrenia, while one study included diagnoses of schizophrenia and schizoaffective disorder.[89] Only three study reports explicitly stated that patients were currently experiencing persistent, residual symptoms despite antipsychotic medication.[87,89,140] Three RCTs used PANSS scores to demonstrate the presence and extent of persistent symptomatology[87,89,140] while a fourth likely used these scores for this purpose.[58] Peet et al. set a criterion PANSS total score of at least 40.[58] No significant between-group baseline differences in PANSS total scores were noted in Peet et al.'s trial, although the mean score was the lowest in the EPA group.[58] Residual symptoms were defined by Fenton et al. as one or more positive and/or negative symptom score(s) greater than 4, or total scores greater than 45 concomitant with a score of 3 or more on at least three PANSS positive or negative items.[89] Emsley established a score of greater than 50 while Peet and colleagues required a total PANSS score of at least 50 in addition to a score of at least 15 on the positive PANSS.[87] In the latter study little difference between study groups was seen for baseline total PANSS or MADRS scores. Baseline scores on the Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS), AIMS, Barnes Akithisia Scale (BAS) and the Simpson-Angus Scale for abnormal movements (SAS) were low and similar across study groups.[87]

In Peet et al.'s study, patients with symptomatic schizophrenia were also selected on the basis of failing to exhibit evidence of significant physical illness or other psychiatric disorders (e.g., mood disorders, learning disability).[58] Substance abuse and significant medical conditions were exclusion criteria in Emsley et al.'s trial.[140] An additional inclusion criterion in the Fenton et al. trial was that there could not be any change in antipsychotic medication in the thirty days preceding the trial, and no on-study change was expected.[89] Exclusion criteria included

diagnoses of substance dependence or mental retardation, bleeding disorders, taking fish oil supplements, anticoagulants, cholestramine or clofibrate antilipemic agents. However, Fenton et al. did not describe statistical tests designed to establish the baseline comparability of patients on key study outcomes.[89] Their ITT group involved those patients with their last observation carried forward (n=87), and to achieve "completer" status patients had to experience no increase in neuroleptics over the study and at least 12 weeks of treatment (n=75; n=37 receiving EPA). As with trial completers and noncompleters, their two study groups did not differ significantly for any patient characteristics, including prestudy/baseline consumption of omega-3 fatty acids in the daily diet, or current smoker status.[89] Prestudy/baseline between-group comparability in terms of dietary intake of omega-3 fatty acids or of omega-6/omega-3 content was not assessed in the remaining three RCTs.[58,87,140]

Few data were reported for key characteristics such as age of onset or time since diagnosis. In Peet and colleagues' RCT, patients were required to exhibit a time since first diagnosis of no more than 20 years and the absence of other important medical conditions.[87] Mean illness durations were similar for Emsley et al.'s two study groups (no statistical tests reported) (E-EPA: 23.1 years, SD=8.5; placebo: 22.1 years, SD=12.4).[140] Patients in Fenton et al.'s study first became ill at a mean age of 20.8 years, were first hospitalized at (mean) age 21.8 years, and had had an average of 10.7 prior hospitalizations.

Intervention/exposure characteristics. While each of the four studies employed an exposure from the same company (Laxdale Limited), only one explicitly stated its exact source (i.e., concentrated fish oil).[58] The other studies referred to E-EPA, a purified form of EPA, yet did not identify its source or describe the process of purification.[87,89,140] Dose contrasts included 3 g/d E-EPA or placebo (liquid paraffin),[140] 3g/d E-EPA or placebo (mineral oil) in addition to 4 mg of vitamin E to retard spoilage,[89] three different doses of E-EPA (4 g/d, 2 g/d, 1g /d) or placebo (liquid paraffin),[87] and 2 g/d EPA enriched oil as opposed to 2g/d DHA enriched oil or placebo (corn oil).[58] However, there were few data allowing us to conclude definitively that these studies were equally able to eliminate the possible confounding influence of having unequal amounts of calories, as energy, provided for their different study groups.

In three RCTS, the omega-3 fatty acid contents were delivered by capsule,[87,89,140] and one study provided their exposure via identical bottles.[58] Of those using capsules, all provided some information suggesting that the appropriate numbers of capsule and amount of placebo content were used to equalize the total daily "intervention" per study group.[87,89,140] Two of these trial reports did not describe whether the capsules were identical[89,140] whereas the third did.[87] Fenton et al.'s tasteless and odourless contents likely contributed to their patients' inability to reliably guess which exposure they were receiving.[89] They also employed capsule counts to assure compliance.

The pourable oils (from identical bottles) used in Peet et al.'s trial[58] were described as being indistinguishable by colour, texture and taste; however, no details were provided as to how the fishy taste or odour were controlled so as to preclude breaching the blind. That the exposure was delivered through pourable bottles raises an issue that was not addressed in Peet et al.'s report;[58] such a poorly controlled approach to delivery typically complicates the interpretation of results (see Discussion).[72]

Three of the four trials employed a high dose, that is, one including at least 3 g/d of omega-3 fatty acids.[87,89,140] As with the three supplemental treatment trials in depression, none of the studies provided omega-6 fatty acids or any other supplement as cointervention, and none attempted to implement a specific on-study ratio of omega-6/omega-3 fatty acid intake through

diet or supplementation. Patients in the four trials were not instructed to maintain their background diet although Emsley et al. had a dietitian review the dietary intake of study participants at baseline and during the study.[140] EPA intake was derived from standard food supplementation tables (South African Medical Research Council). During their study, no between-group differences were observed for the dietary intake of omega-3 fatty acids. A balanced diet (undefined) was attributed to study participants both at baseline and during the trial.[89] Fenton et al. employed the Willett Dietary Survey to estimate baseline fatty acid consumption. Dietary EPA intake was low, ranging from 0.56 g/wk to 1.13 g/wk.[89] For the other RCTs, possible between-or within-group group variability data regarding dietary intake were not provided. Thus, this potential confounder was not controlled for.

Only Fenton et al. used an antioxidant to retard spoilage.[89] None of the trials described efforts to deodorize their exposures to maintain blinding. In the three studies evaluating biomarker data, no notable inappropriate methods to extract, prepare, store or analyze lipids were described.[58,87,89] Purity data regarding the exposure were not provided by any of the trialists. No study report included details as to whether, or how, the presence of methylmercury was tested or eliminated from the omega-3 fatty acid exposure.

Cointervention characteristics. In Peet et al.'s study, patients with symptomatic schizophrenia were receiving various types of antipsychotic medication, including both oral and depot preparations (no data reported).[58] Some required anticholinergic medication to address side effects from the primary medications (no data reported). Fenton et al. reported that all but one patient used a neuroleptic, with 19 taking two neuroleptics, 34 using risperidone, olanzapine or quetiapine, and 24 receiving clozapine.[89] Eight participants required an increased neuroleptic dose (four per study group) and four were terminated by week 12 for nonadherence to study medication protocol (two per study group). Peet and colleagues asked that their participants be maintained on their regular antipsychotic medication and dose for at least one month: clozapine (n=31 in ITT population), novel atypical antipsychotic drugs (i.e., olanzapine, risperidone or quetiapine; n=48 in ITT population) or typical antipsychotic medication (n=36 in ITT population).[87] The proportions of patient on the different antipsychotic medications were similar although fewer individuals were taking standard neuroleptics in the 2 g/d E-EPA group. Antipsychotic doses, expressed as chlorpromazine equivalents in the Emsley et al trial, were slightly different (E-EPA: 1011 mg/d, SD=532; placebo=931 mg/d, SD=652), although results of a statistical test were not reported.[140] Nine patients in each group were receiving clozapine, with the rest taking conventional medication (undefined). The types and doses of antipsychotic medication did not change during the study. No additional medication had to be prescribed during the study except for occasional analgesics for headache or lorazepam for insomnia.

Outcome characteristics. Peet et al. employed the PANSS and assessed RBC PUFA composition.[58] In Fenton et al.'s study, outcomes included the PANSS, the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Rating Scale, MADRS and the CGI.[89] The Repeatable Battery for the Assessment of Neuropsychological Status was used at baseline and 16 weeks. Adverse events were solicited at each study visit using open-ended queries. The fatty acid content of RBCs was also investigated.

PANSS change scores and Extrapyramidal Symptom Rating Scale (total score and subscale scores for dyskinesia, dystonia, akathisia and parkinsonism) were evaluated by Emsley et al.[140] Peet et al. assessed change in scores on the PANSS and its subscales.[58] Other outcomes included the MADRS, the LUNSERS, AIMS, BAS, and SAS.[87] Peet et al.'s ITT population included 115 patients (of 122 randomized) who had had at least one post-baseline assessment, which was then

carried forward.[87] Given that E-EPA appears to act on membrane phospholipids, and different classes of neuroleptic have been seen to act on phospholipids differently, it was argued that patients receiving different antipsychotic medications would respond differently.[87] Data from the three groups of patient receiving different types of antipsychotic were analyzed separately by Peet and colleagues[87] Logistic regression took into consideration center, baseline scores, illness duration and type of antipsychotic medication. Peet and colleagues also assessed the impact on RBC PUFA.

Two additional analyses were conducted with Fenton et al.'s data.[89] The first assessed some of the details defining the strong placebo response observed in the study (see below).[88] The second[60] assessed the impact on RBC fatty acid compositions of current smoker status, as one pro-oxidant factor with known degrading effects on PUFAs.[170] Schizophrenic patients have disproportionately high rates of smoking.[171] Analyses also evaluated the possible impact of another factor with the potential to degrade PUFAs (alcohol[172]), which, for example, was not controlled for by Peet et al.[58] Other variables whose possible impacts were assessed were antipsychotic medication, sex, dietary intake, age, psychopathology, diagnostic subclassification and illness duration. Results from this second additional analysis by Hibbeln et al.[60] could not be used to address the present review's question about the possible association of the fatty acid content of biomarkers and disease states since only schizophrenic patients were a priori selected as study participants. This review required controlled studies to address this question.

Study quality and applicability. The four RCTs received a mean Jadad total quality score of 3.8, indicating sound internal validity. Two each received allocation concealment ratings of Adequate[58,87] or Unclear.[89,140] Two received applicability ratings of II,[58,87] and two received ratings of III.[89,140]

Summary Matrix 14: Study quality and applicability of evidence regarding the supplemental treatment of schizophrenia

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
		Fenton[U]	2001	90						
	II	Author	Year	n	Author	Year	n	Author	Year	n
		Peet[A]	2001	55						
		Peet[A]	2002	122						
	III	Author	Year	n	Author	Year	n	Author	Year	n
					Emsley[U]	2002	40			

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

Qualitative Synthesis of Individual Study Results

Ten of Peet et al.'s schizophrenic patients discontinued treatment (never started, n=3; lost to followup, n=2; felt better, n=1; adverse events described below), leaving data from 45 participants to be entered into the analysis.[58] At study's end, the EPA group's total PANSS score was significantly lower than that in the placebo group. Taking baseline scores into account, repeated measures ANOVA revealed a significant treatment effect in favor of EPA over DHA using positive PANSS scores. EPA produced significantly greater improvement than did DHA

yet the EPA versus placebo difference only approached statistical significance for positive PANSS scores. No significant differences were found for negative symptom scores. When patients were divided on the basis of their type of response (i.e., >25% improvement vs < 25% improvement or unchanged or worse), the groups were significantly different, with EPA patients more likely to show greater than or less than 25% improvement. Additional, pairwise comparisons revealed a significant difference between EPA and either DHA or placebo.

Including data from twelve patients in each of the three groups, analyses of RBC fatty acid levels from Peet et al.'s study showed the largest increases in EPA and DHA in the EPA and DHA groups, respectively.[58] Smaller rises in EPA and DHA were observed in the DHA and EPA groups, respectively. No significant changes were observed for AA. For EPA group participants, patients showing the greatest improvement in total PANSS also had the highest baseline levels of EPA and AA; and, multiple regression identified baseline EPA as a significant predictor of clinical improvement. No similar significant results were found for the DHA group, the placebo group or the full sample.

In Fenton et al.'s study, repeated measures ANOVA showed a small but significant time effect for patients on each of total PANSS, MADRS and CGI scores.[89] Both EPA and placebo patients benefited from their exposures. No time-by-group interaction effect was observed. No significant effects for time or a time-by-group interaction were found for ratings of cognitive impairment, extrapyramidal symptoms or tardive dykinesia. No significant differences were observed for the positive or negative PANSS scores. Results from analyses of data from study completers (n=75) were similar. Dickerson et al.'s followup assessment of the placebo response in the 37 patients receiving placebo revealed that most of the improvement occurred during the first 2 weeks of the study, with no PANSS score (total, positive, negative, general psychopathology) exhibiting significant change from week 2 to week 16.[88]

Analyses of biomarker data were reported by Fenton et al.[89] and Hibbeln et al.[60] No evidence of baseline bimodal distributions of RBC EPA, DHA or AA compositions was found to characterize the schizophrenic patients. By study's end, the EPA group exhibited higher percent compositions of EPA and (omega-3-)DPA, and lower percent compositions of DGLA, AA, and (omega-6-)DPA. A decrease in DHA in the EPA group was observed yet it did not reach statistical significance. EPA increased significantly in the placebo group. The decrease in the AA/EPA ratio over the study was significantly greater for patients receiving EPA.[89] After adjusting for multiple testing, the change in AA/EPA ratio was not significantly associated with any clinical variables. Changes in DHA composition were negatively correlated with changes in positive symptoms and positively associated with changes in involuntary movement.

Of many investigations using various factors (e.g., diagnostic subclassification), only sex and current smoking status were significantly related to fatty acid compositions.[89] The DHA percent was reduced in smokers compared to nonsmokers, and males had lower DHA and EPA percents compared to females. For patients exclusively receiving EPA, neither sex nor smoker status predicted changes in EPA, DHA or AA. Other findings are reported briefly in the Discussion.

With or without controlling for dietary EPA intake, medication, illness duration and sex, total PANSS score decrements were significantly greater in the E-EPA group in Emsley et al.'s trial.[140] This significant difference was observed by week 3. The reduction in E-EPA patients taking clozapine was greater yet it did not achieve statistical significance. The only subscale score that produced a significant difference favored E-EPA patients for percent change in the general psychopathology score (PANSS). The only between-group difference on the dyskinesia scores from the Extrapyramidal Symptom Rating Scale involved a significantly greater reduction

in scores for E-EPA participants at 12 weeks. Yet, ANCOVA with total PANSS change as the dependent variable and change in dyskinesia entered into the analysis revealed no significant between-group differences, suggesting that reduction in total PANSS scores is related to reduction in dyskinesia scores. One participant in the E-EPA group was withdrawn after an overdose of antipsychotic medication.

Peet et al. reported that nine patients experienced an adverse event leading to withdrawal although none were associated with the intervention.[87] Four of these participants had been in the 1 g/d E-EPA group. This active treatment group had the highest number of "failures" other than a protocol violation (n=12/32) although these data included individuals providing more than one reason (data not reported). No demographic or clinical differences were observed for those who dropped out and those who completed the trial. Peet and colleagues observed no or minor reductions in LUNSERS, AIMS, BAS and SAS scores across the study, with no significant between-group differences.[87]

Changes in the total PANSS, its subscales and the MADRS for patients on *typical neuroleptic drugs* indicated that all E-EPA dosing groups improved significantly from baseline on the total PANSS, with the magnitude of the change covarying with the dose size.[87] Only the 2 g/d and 4 g/d E-EPA groups improved significantly on positive PANSS scores, with the magnitude of the change covarying with the dose size. A similar pattern was found for negative PANSS scores although the magnitude did not covary with the dose size. For the general psychopathology subscale of the PANSS, equivalent improvements were seen in the 1 g/d and 4 g/d E-EPA study groups. No significant changes were seen for MADRS scores. However, large placebo effects were found such that significant improvements from baseline were observed for each of these clinical outcomes, including the MADRS. However, when compared to placebo, no significant differences were observed for patients on typical neuroleptics.

Results from patients receiving *atypical neuroleptics* indicated significant within-group improvement for typical neuroleptics for the 1 g/d and 2 g/d E-EPA doses with respect to the total and subscale scores on the PANSS as well as the MADRS, yet the 4 g/d E-EPA did not yield any significant improvement on any of the clinical outcomes.[87] Significant improvements were seen for all clinical outcomes for placebo patients, contributing to the lack of significant between-group differences.

Patients on *clozapine* exhibited a different pattern of results.[87] Results indicated that patients receiving placebo showed no significant improvements from baseline for any clinical outcome. Yet, except for the MADRS and the general psychopathology score on the PANSS, which were characterized by an absence of significant change, all three E-EPA doses showed significant improvements from baseline. The 2 g/d dose exhibited the greatest magnitudes of percent change in scores. Unlike what was found when the other two types of medication were examined, patients on 2 g/d E-EPA added to clozapine improved significantly relative to placebo on the total PANSS scale and the PANSS general psychopathology subscale.

Fatty acid composition data were analyzed by antipsychotic medication.[87] The only significant change in the placebo group was a significant mean increase from baseline in AA within the group of patients taking atypical antipsychotics. In all drug groups except for 1 g/d E-EPA given in addition to clozapine, there were significant dose-related increases in EPA levels from baseline. In patients taking clozapine, a significant increase in AA was observed in the 2 g/d E-EPA group. The increment in DHA in the 2 g/d E-EPA group did not achieve statistical significance. Significant decreases were observed for both DHA and AA levels in the 4 g/d E-

EPA group of patients also taking atypical antipsychotics. No other significant differences were observed.

Mean percentage change data for the total PANSS score as well as PANSS subscale scores and the MADRS from each of the twelve groups of patient (4 treatment levels by 3 types of neuroleptic) were assessed for their possible association with mean percentage change data for each of EPA, DHA and AA RBC levels.[87] Peet et al. found that changes in AA were significantly and positively related to changes in all clinical outcomes. Changes in DHA or EPA were unrelated to changes in clinical outcomes.

A known side effect of clozapine, elevated levels of triglycerides were either prevented (in placebo and 1g/d E-EPA groups) or baseline levels were reduced significantly (2 g/d E-EPA and 4 g/d E-EPA).[87]

Quantitative Synthesis

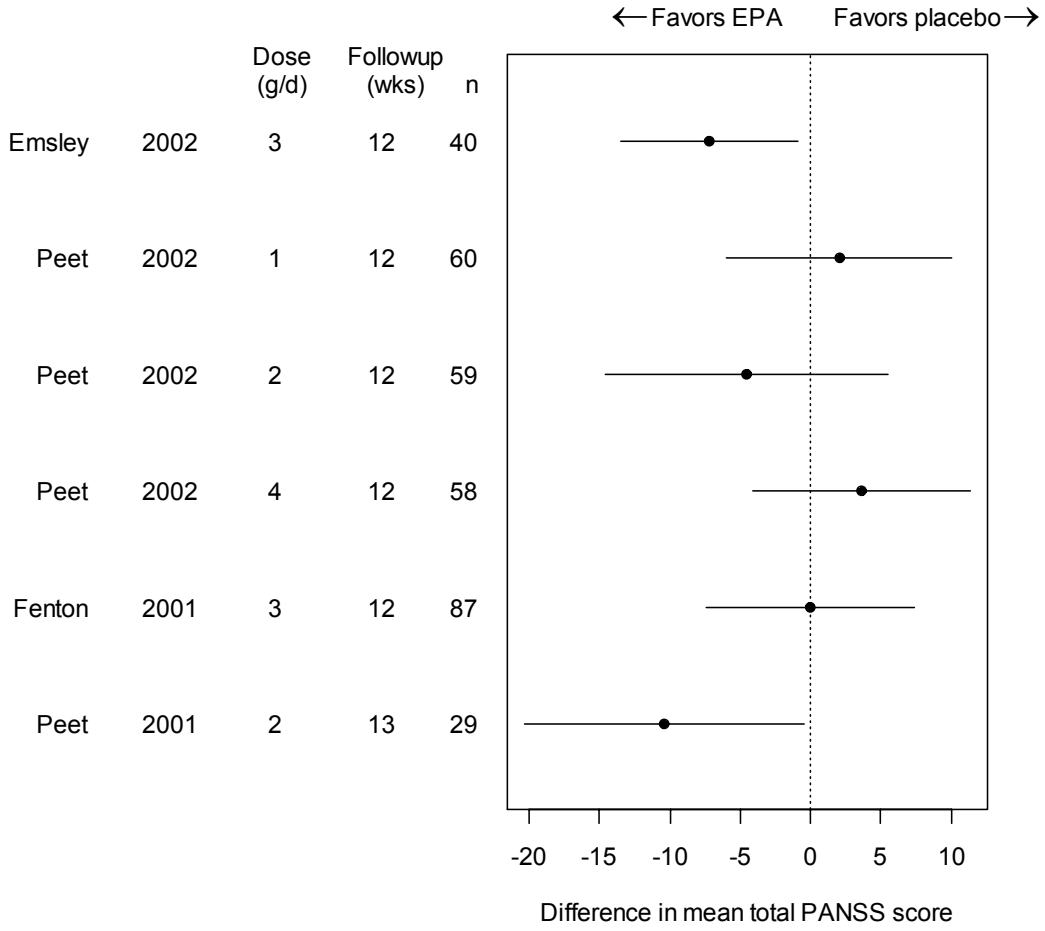
Given the available data, total PANSS score was chosen as the primary outcome measure. Since each of the RCTs measured PANSS at baseline and 12 weeks post-treatment, we aimed to extract the mean change from baseline in PANSS, together with the standard deviation of this change, for each treatment group. Where possible, data for ITT populations were used. Since only one study included more than one dose level of EPA, only placebo-controlled data were analyzed.[87] A single study included one DHA dose,[58] which yielded no benefit when compared to placebo.

In two reports,[58,140] summaries and statistical analyses were reported in terms of percent change. However, percent change has undesirable statistical properties.[173] Thus, the authors of both reports were contacted and change from baseline data were requested.

Only one author provided the requested data.[140] In the Peet et al. report,[58] post-treatment means and standard deviations were used instead of those for change from baseline.[174] In Fenton et al.'s publication,[89] the mean and standard deviation of PANSS were reported at baseline and at followup, but the standard deviation of change from baseline was not provided. The author was contacted but no reply was received, and post-treatment means and standard deviations were used instead of those for change from baseline. In Peet and colleagues' report,[87] results were reported separately by background treatment (typical neuroleptics, atypical neuroleptics, and clozapine), and for four different treatment groups (placebo and three different E-EPA doses). Although the standard deviation of change from baseline was not reported, p-values for change from baseline were provided, enabling us to infer the standard deviation. For each treatment group, the mean change was pooled across primary treatments using a weighted mean, and the standard deviation of the change was pooled across these treatments using a pooled standard deviation.

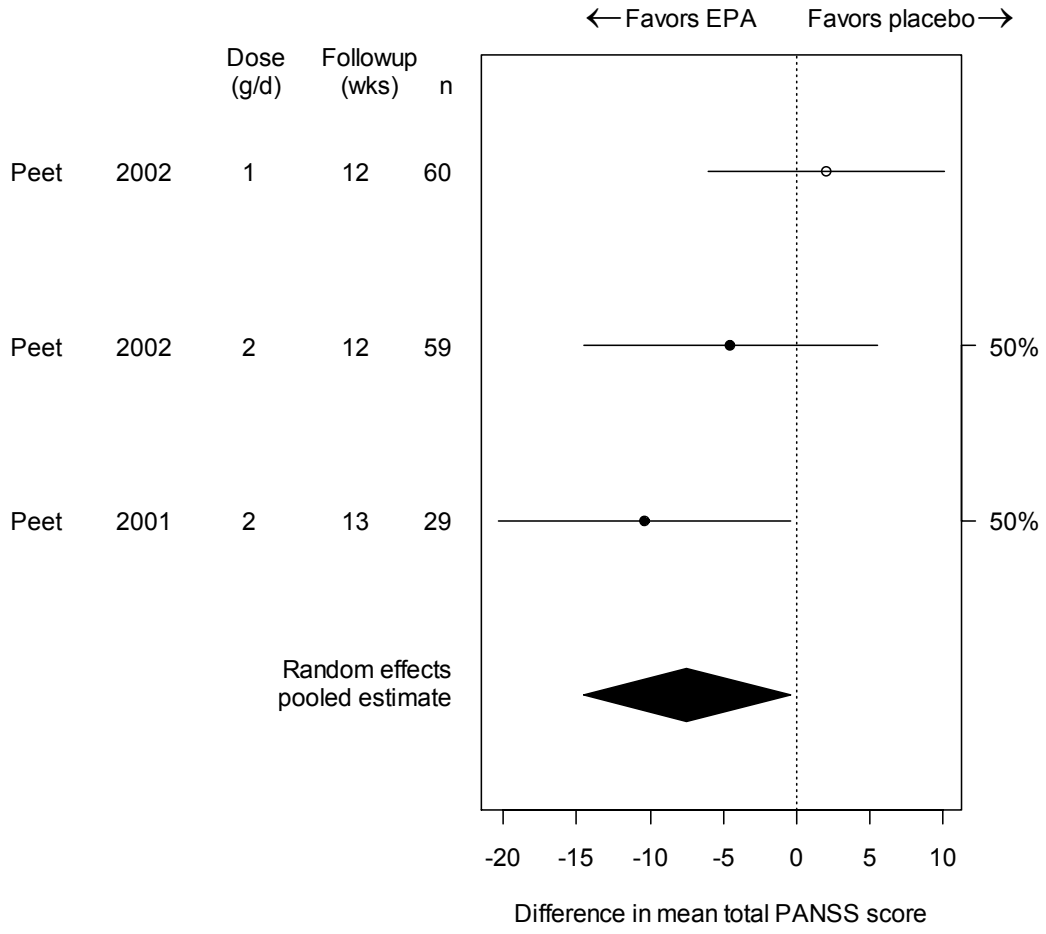
Pooling was conducted using the weighted mean difference approach and the random effects method of DerSimonian and Laird.[175] Statistical heterogeneity was assessed using the chi-square test with a significance level of 0.10. In all but one study,[58] results from ITT analyses were available (using a last-observation-carried-forward strategy).

Figure 4. Estimates of the difference in mean total PANSS score between EPA and placebo groups, by study evaluating the supplemental treatment of schizophrenia



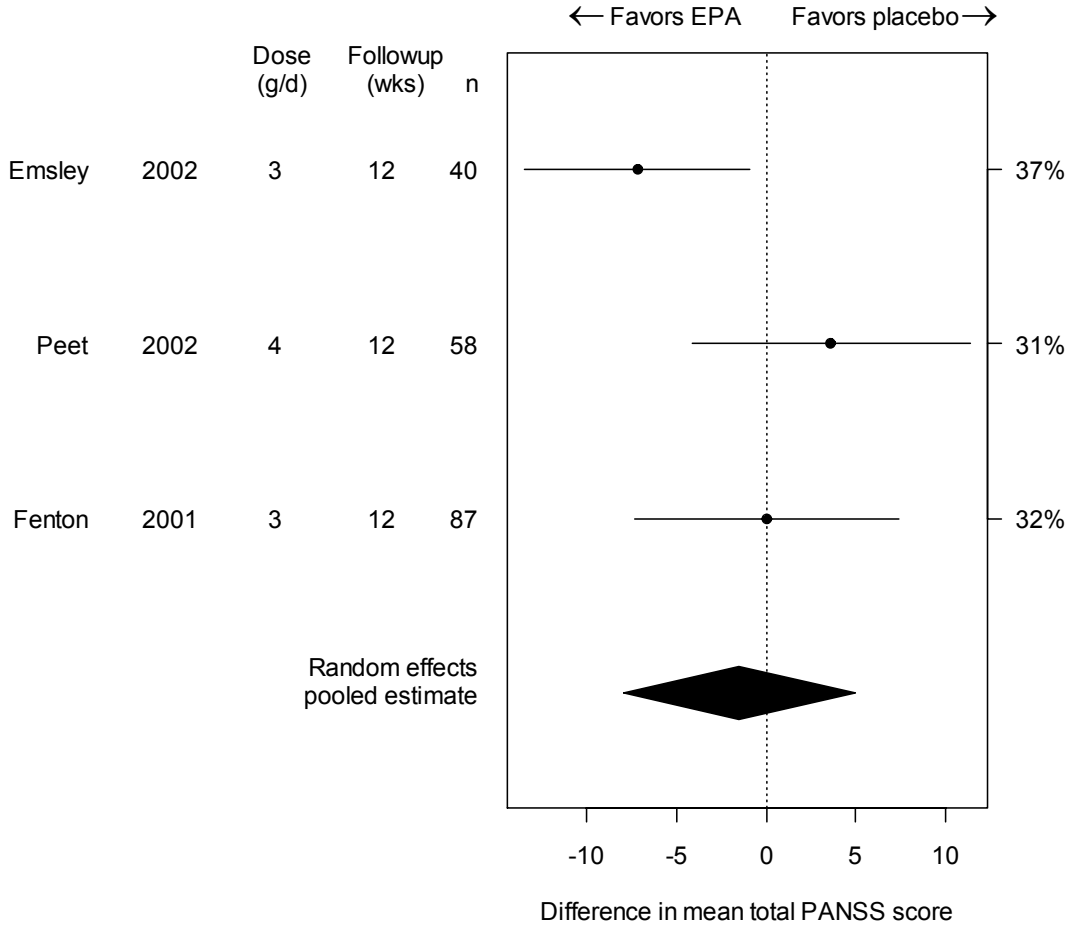
No pooled estimate is shown in Figure 4 because of the variation in dose within and among studies. Additionally, it should be noted that in the Peet and colleagues study[87] the estimates for different doses versus placebo share the same placebo group. It was thus decided to investigate separately the placebo-controlled impacts of high- and low-dose EPA supplementation (i.e. <3 g/d vs ≥3 g/d).

Figure 5. Estimates of the difference in mean total PANSS score between low dose (<3 g/day) EPA and placebo groups. Percentage weights contributed by each study to the pooled estimate are shown on the right-hand side.



Given the number and sizes of the studies, a random effects model was employed. The pooled estimate (-7.5) and its 95% confidence interval (-14.5 to -0.4) are represented by the diamond at the bottom of Figure 5. While the estimate of precision was large, the model revealed significant benefit accruing to a 2 g/d EPA dose.[87] The 1 g/d estimate from the Peet et al. study[87] is shown as an open circle because it was not included in the pooled estimate; the estimate for the 2 g/d dose shares the same placebo group. Statistical heterogeneity was not significant between the two pooled studies (chi-square statistic 0.66 on 1 degree of freedom, p=0.42).

Figure 6. Estimates of the difference in total PANSS score between high dose (3 g/day or greater) EPA and placebo groups. Percentage weights contributed by each study to the pooled estimate are shown on the right-hand side.



Looking at high doses of at least 3 g/d EPA, the pooled estimate (-1.5) and its 95% confidence interval (-8.0 to 4.9) are represented by the diamond at the bottom of Figure 6. No significant benefit was observed in association with high-dose EPA. Statistical heterogeneity between the studies was significant at the 0.10 level (chi-square statistic 4.9 on 2 degrees of freedom, p=0.09).

Impact of Covariates and Confounders

From these preliminary analyses, only 2 g/d, or low-dose, EPA produced a significant benefit. Only one trial employed a 1 g/d dose and hence this definition of a low dose could not be subjected to quantitative synthesis. Since only data from the UK trials were combined statistically in the meta-analysis of low-dose EPA, possible confounding from differences in the background diet was minimized, or even eliminated, in a way that likely would not have

occurred if data from the South African study of Emsley et al. or the American RCT of Fenton et al. had been included in this meta-analysis. It must also be recalled that, in Peet and colleagues' RCT, only those receiving clozapine as primary treatment exhibited a significant benefit associated with E-EPA supplementation.[87]

Is Omega-3 Fatty Acid Intake, Including Diet and/or Supplementation, Associated With the Onset, Continuation or Recurrence of Schizophrenia?

As observed in Summary Tables 37 through 39 (below), derived from Evidence Tables 2 and 3 (Appendix E*), six observational studies and three cross-national ecological analyses met eligibility criteria. Two of the latter have already been described in this report, and so some of their details are not repeated. Since it investigated a single group of patients, the Mellor et al. study did not qualify to address either basic question 1 (i.e., interventional focus) or 3 (i.e., fatty acid content of biomarkers).[91] It did, however, meet eligibility criteria to address the present question. The nine studies were published between 1988 and 2004.

Overview of Relevant Studies

Mother's milk is considered an important dietary source of omega-3 fatty acids, which are essential for the development of the brain.[176] It is thought that schizophrenia may be linked to early brain development,[55] and therefore it is not surprising that the relationship between the early intake of omega-3 fatty acids and the risk of developing schizophrenia has been explored.

Peet et al. conducted a case-control study comparing the infant feeding histories (breastfed vs formula-fed) of DSM-IV diagnosed schizophrenic patients (n=55) and nonpsychiatric controls (n=55) matched for age (mean: 34 years), sex (47 males) and socioeconomic status.[92]

*__Note:__ Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 37: Association between omega-3 fatty acid intake and onset, continuation or recurrence of schizophrenia (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Peet, 1997, UK: case-control study[92]	schizophrenic pts (n=55)	matched nonpsychiatric controls (n=55)	Schizophrenic pts less likely to have been breastfed;$^{+}$ breastfeeders of >4 wk less frequent in schizophrenic pt grp^{+}	Total quality: 3 [Grade: C]	II
McCreadie, 1997, UK: case-control study[143]	schizophrenic pts (n=45)	siblings (n=92)/ national survey data from Scotland (n=1,648 & n=1,718) & Great Britain (n=13,687)	NS lesser breastfeeding in schizophrenic pts than siblings; most pts born in 1940s & 1950s, with breastfeeding incidence in these decades < Scottish national surveys in 1946^{+++} & 1958;$^{+}$ non-breastfed pts had more schizoid & schizoptypal traits^{+++} in childhood than siblings, including poorer social adjustment;$^{++++}$ NS correlations bet breastfeeding length & adjustment	Total quality: 4 [Grade: B]	II
Leask, 2000, UK: case-control study[142]	those developing schizophrenia in 2 national birth cohorts (1946: n=5,362; 1958: n=18,856)	those who do not develop schizophrenia in these 2 national birth cohorts	In both birth cohorts: NS feeding histories of schizophrenic pts & controls, with or without adjustment for offspring's sex & father's social class	Total quality: 5 [Grade: B]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

In McCreadie et al.'s case-control study, mothers of patients with schizophrenia (n=45; 29 males) completed a questionnaire about whether, and for how long, their offspring, including all siblings (n=92), had been breastfed.[143] A census in 1989 identified 146 schizophrenic patients, 61 of whom had living mothers. From these, 51 mothers were interviewed regarding the birth of their children and their subsequent adjustment. The current mental health status of the patients was also assessed (details published elsewhere). In 1995, a questionnaire was sent to the mothers to determine their offspring's breastfeeding history, including its duration. National survey data for Great Britain (1946: n=13,687), Scotland (1958: n=1,648) and Scotland (1980: n=1,718) were used to establish various reference standards.

Leask et al. analyzed prospective data separately from two UK national birth cohorts (1946: n=5,362; 1958: n=18,856) using a nested case-control approach.[142] They compared the feeding histories (including duration) of those individuals who later developed schizophrenia with the rest of the population. The 1946 British National Survey of Health and Development was

devised to survey all births in mainland Britain. A random sample, stratified by social class, comprised a cohort (n=5,362) who were followed up on many occasions (i.e., 20 followups by age 43). The 1958 National Child Development Study included 98% of the births in mainland Britain, and had five followups, ending when individuals were 33 years of age. Mothers provided details about perinatal feeding by interview (1946: when child was age 2; 1958: when child was age 7).

Sasaki et al. examined feeding patterns during the infancy of inpatients and outpatients with schizophrenia (n=100; 60 males; age=32±9 years), their healthy siblings (n=37; 22 males; age=34.6±8.4 years) and age-matched healthy controls (n=200; 92 males; age=31±10 years) (Summary Table 38).[144] Mothers of controls were primarily recruited from hospital staff and a few physicians.

Summary Table 38: Association between omega-3 fatty acid intake and onset, continuation or recurrence of schizophrenia (observational studies)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Sasaki, 2000, Japan: case-control study[144]	schizophrenic inpts & outpts (n=100)	healthy siblings (n=37)/ matched healthy controls (n=200)	no evidence for lesser likelihood of breastfeeding in infancy of patients at 1 or 3 mo	Total quality: 5 [Grade: B]	III
Amore, 2003, Italy: case-control study[141]	hospital admitted schizophrenic pts (n=113)	siblings (n=140)/ normal controls (n=113)	adjusting for age, sex, birth weight, disease severity & birth order, NS breastfeeding incidence; NS age of onset for exclusively breastfed vs others; breastfeeding duration positively correlated with age of onset^{+}	Total quality: 6 [Grade: B]	III
Mellor, 1996, England: 1 wk single prospective cohort study as baseline for a noncomparative before-after study[91]	schizophrenic pts (n=20)		EPA intake negatively associated with total psychopathology;$^{+}$ negative correlations for positive symptoms & ALA intake^{+} & total n-3 fatty intake.$^{+}$ Multiple regression: EPA intake inversely related to total PANSS;$^{+}$ total n-3 intake negatively related to positive symptoms^{+}	Total quality: 4 [Grade: B]	II

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; PANSS = Positive and Negative Symptoms Scale; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Amore et al. conducted a case-control study to compare the incidence and length of breastfeeding in patients with schizophrenia (n=113; n=58 inpatients), their siblings (n=140) and normal (i.e., nonschizophrenic) controls (n=113).[141] The goal was to examine the relationship between the duration of breastfeeding and age of onset of schizophrenia. Schizophrenic patients who were either consecutively admitted to a psychiatric ward or attending an outpatient community health center were enrolled in Bologna. For each patient, a control was selected from the Bologna birth register. The latter were matched for age, sex, singleton status and residential district.

Mellor et al. examined the possible association of both dietary intake and RBC fatty acid status with schizophrenic symptoms in a cohort of schizophrenic patients (mean age: 56.1 years; 13 males) who, after providing prospective data concerning dietary intake, then went on to receive supplementation in a noncomparative before-after study.[91] All patients were receiving neuroleptic medication.

Christensen and Christensen described the statistical association between the course and outcome of schizophrenia using data from eight national centers involved in the WHO's 2-year followup study (Denmark, India, Colombia, Nigeria, UK, the former USSR, US and the former Czechoslovakia), and data regarding the dietary intake of fats from various food sources, including fish and seafood (Summary Table 39).[145] The latter data were obtained from the same FAOSTAT source consulted by Peet in his cross-national ecological analysis.[109]

Summary Table 39: Association between omega-3 fatty acid intake and onset, continuation or recurrence of schizophrenia (cross-national ecological analyses)

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Christensen, 1988, 8 countries: cross-national ecological analysis[145]	n=8 countries		high intake of saturated fat associated with unfavorable schizophrenia course and outcome$^{+- +++}$ NS relationship bet intake of unsaturated fat, including PUFAs, & schizophrenia course or outcome	Total quality: 3 [Grade: C]	III
Noaghiul, 2003, 14 countries: cross-national ecological analysis[90]	n=14 countries		seafood consumption did not predict lifetime prevalence rates	Total quality: 4 [Grade: B]	III
Peet, 2004, 12 countries: cross-national ecological analysis[109]	n=12 countries		fish consumption not associated with specific schizophrenia course or outcome variables	Total quality: 3 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; wt = weight; Δ = change; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Lifetime prevalence rates for schizophrenia, from seven countries, were obtained by Noaghiul and Hibbeln from the Cross-National Collaborative Group epidemiological study in

their cross-national ecological analysis.[90] To these were added prevalence data from seven additional countries (Spain, Israel, Iceland, Australia, UK, Greece and Hong Kong). All rates were reported as cases per 100,000 population. Prevalence rates drawn from the Cross-National Collaborative Group epidemiological study were standardized at each site, with a weight calculated per subject, and stratified for age and sex. Data from other sources could not be weighted in this manner since primary data were unavailable. Socioeconomic status and educational level were not taken into consideration. The female-to-male ratio (age=18-64 years) was roughly equal at all sites, with slightly higher rates seen for Canada, Puerto Rico, Korea and New Zealand. National seafood consumption data, measured as apparent seafood consumption (lb/person/y), were obtained from the National Marine Fisheries Service and the WHO's FAOSTAT database. As a measure of the disappearance of seafood from the economy per year, apparent seafood consumption (lb/person/y) was once again calculated as total catch plus imports minus exports.

Peet's ecological analysis focused on international variations in the prevalence of depression and the outcome of schizophrenia, and their possible prediction by patterns of omega-3 fatty acid intake.[109] Data on food use were taken from the FAOSTAT database, and reflect apparent national food consumption. Two-year outcome data relating to schizophrenia were drawn from the WHO's International Pilot Study of Schizophrenia (IPSS). A second source of schizophrenia outcome data was the Determinants of Outcome of Severe Mental Disorders (DOSMED) study. Additional references to the sources of these data are included earlier in this report.

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Of the five case-control studies, only Peet et al.'s abstract[92] failed to give adequate descriptions of eligibility criteria. Mellor et al.'s description of their patient cohort was sparse.[91] All three cross-national ecological analyses provided sufficient amounts of detail to determine their methods.[90,109,145] While the latter each included data from multiple countries, the observational studies were conducted in Italy,[141] Japan[144] and the UK.[91,92,142,143]

Population characteristics. Given the heterogeneous nature of the included studies' populations it made little sense to synthesize some of the population characteristics such as age or percent male composition. On two occasions, inpatients and outpatients were described as the source of the study population.[141,144] Mellor et al.'s schizophrenic patients had been, or were, longterm inpatients.[91] The remaining reports did not provide similar details.[90,92,109,142,143,145] Diagnoses of schizophrenia were assigned using DSM-IV criteria,[92,141,144] the ICD-9[143] or DSM-III-R for Leask et al.'s 1946 birth cohort and CATEGO criteria for their 1958 birth cohort.[142] Mellor et al. also employed DSM-III-R criteria.[91] Most of Sasaki et al.'s patients had been chronically ill, had had several episodes of exacerbation and had histories of admission to hospital.[144] Other than this case-control study report, none of the other reports described a method used to rule out schizophrenia or other psychopathology from control groups. Comparison subjects and their mothers, in addition to unaffected siblings, were interviewed by Sasaki et al.'s clinicians to establish that none were experiencing major psychoses or other psychiatric disorders. The WHO's international followup study, using its own diagnostic criteria, were implicated in all three cross-national ecological analyses.[90,109,145]

Each observational study report failed to present ethnicity/racial data although Sasaki et al.'s likely involved Asian participants.[144] The cross-national ecological analyses included, by definition, mixed ethnicities/races.[90,109,145] Some active attempts to match controls and patients

were made. Amore et al. matched their groups by age, sex, singleton status and residential district.[141] Peet et al. matched groups based on age, sex and socioeconomic status.[92] The social class of the father at birth, and sex of the child were taken into consideration as potential confounders in Leask et al.'s study.[142] In Amore et al.'s study, the only significant between-group differences were that more patients than siblings were male, and more patients than controls were second-born or more.[141] No significant differences were observed for age of offspring, age of mothers at birth, or age of fathers at birth. Amore et al. divided their patients with schizophrenia into those who had been solely breastfed for at least the first four months of life, those having exclusively received formula, or those having received a mixed feeding within the first four months of life.[141]

Intervention/exposure characteristics. Typically, interviews were employed in case-control studies to gather data concerning the feeding method,[92,142] with some investigators also inquiring about the duration of feeding practices.[141,143] Sasaki et al. employed a written questionnaire to collect their data.[144] Leask et al.'s breastfeeding data were collected from the two cohorts in the same way: prospectively from UK birth registries.[142] Data were not provided in any report on the possible intake of omega-3 fatty acids by mothers during pregnancy or breastfeeding. Mellor et al. collected meal intake data prospectively for one week using a 7-day weighed intake approach.[91] Diet history diary data were also requested to keep track of between-meal intake. Exposure data for all three cross-national analyses were extracted from the United Nations' FAOSTAT database.[90,109,145]

Outcome characteristics. Two case-control studies assessed outcomes pertaining to the course and outcome of schizophrenia.[109,145] Amore et al. evaluated the age of onset of schizophrenia.[141] McCreadie assessed a number of scores based on instruments evaluating adjustment, including the PANSS.[143] Mellor et al. employed the PANSS, AIMS and Research Diagnostic Criteria concerning tardive dyskinesia.[91] All other studies focused on the prevalence of schizophrenia.

Study quality and applicability. The five case-control studies received a mean quality score of 4.6, with three studies assigned an applicability rating of II,[92,142,143] and another two studies receiving an applicability rating of III.[141,144] The single prospective cohort study attained a quality score of 4 and an applicability rating of II.[91] The mean quality score received by the three cross-national ecological analyses was 3.3, and each attained an applicability rating of III.[90,109,145]

Summary Matrix 15: Study quality and applicability of evidence regarding the association between omega-3 fatty acid intake and onset, continuation or recurrence of schizophrenia

		Study Quality								
		A			B			C		
Applicability	I	Author	Year	n	Author	Year	n	Author	Year	n
	II	Author	Year	n	Author McCreadie Leask Mellor	Year 1997 2000 1996	n >13k >23k 20	Author Peet	Year 1997	n 110
	III	Author	Year	n	Author Sasaki Amore Noaghiul	Year 2000 2003 2003	n 337 363 14C	Author Christensen Peet	Year 1988 2004	n 8C 12C

n = number of allocated/selected participants; C = Countries; k = 1,000's

Qualitative Synthesis of Individual Study Results

Peet et al. found that, compared with nonpsychiatric controls (78%), schizophrenic patients (60%) were less likely to have been breastfed.[92] Additional analysis of those individuals who had been breastfed for more than 4 weeks indicated that there were fewer of these individuals in the schizophrenic group (44%) compared with the control group (67%).

McCreadie reported that the incidence of breastfeeding (i.e., breastfed at least once) was lower in schizophrenic patients (29%) than in their siblings (38%).[143] This difference was not statistically significant. Neither mother's age at birth, nor birth order, distinguished between patients and their siblings. Most of the patients had been born in the 1940s and 1950s, with the incidence of breastfeeding in these decades being significantly lower than what was observed in Scottish national surveys in 1946 (33% vs 81%) and 1958 (26% vs 51%), respectively. Those patients who had not been breastfed exhibited more schizoid and schizotypal personality traits (Scale for Assessment of Premorbid Schizoid and Schizotypal Traits) in childhood than did their siblings, including poorer social adjustment (Premorbid Social Adjustment Scale). Breastfed patients did not differ in these ways from their siblings. No significant correlations were observed between length of breastfeeding and any indices of adjustment, including the negative PANSS.

Leask et al. did not find significant differences in the feeding histories of patients with schizophrenia and controls, with or without adjustment for offspring's sex and father's social class.[142] In the 1946 birth cohort, 30 cases of schizophrenia or schizoaffective disorder (n=20 males) had manifested by age 43 years, with 24.1% of cases and 23.6% of controls having exclusively been formula-fed. In addition, 17.3% of cases and 12.3% of controls had been breastfed for less than 1 month. Corresponding data for those breastfed more than one month were 58.6% and 64.1%, respectively. In the 1958 birth cohort, 40 cases of "narrow schizophrenia" (n=14 males) had emerged by age 28 years. Of these, 24.1% of cases had been solely bottle-fed compared with 31.7% of controls. The figures for those breastfed for less than 1 month were 27.6% and 24.9%, respectively. Data for those breastfed longer than 1 month were 48.3% and 43.3%, respectively.

Sasaki et al. found no evidence for a lesser likelihood of schizophrenic patients having been breastfed, either at 1 month or 3 months post-birth (no statistics reported).[144] Nor was there

evidence that a decrease in breastfeeding had occurred during the infancy of schizophrenic patients (no statistics reported).

Amore et al. divided their schizophrenic patients into those who had been solely breastfed for at least the first 4 months of life, those who had exclusively received formula, or those having received "mixed" feeding within the first 4 months of life.[141] Adjusting for age, sex, birth weight, disease severity and birth order, they found no significant between-group differences in the incidence of breastfeeding. As well, there were no between-group sex differences in the type of feeding. Siblings had been breastfed longer than normal controls. Age of onset was later in those exclusively breastfed (22.1±6.3 years) compared with all others (20.8±4.9 years), yet this difference was not statistically significant. However, the duration of breastfeeding was positively and significantly correlated with the age of onset of schizophrenia.[141]

Mellor et al. observed that dietary EPA intake was significantly and negatively associated with PANSS total psychopathology.[91] Significant and negative correlations were likewise found for positive symptoms and both ALA dietary intake and total omega-3 fatty acid intake. Dietary EPA intake was also significantly and negatively associated with tardive dyskinesia scores on the AIMS. Multiple regression revealed that EPA intake was significantly and inversely related to PANSS total scores and to tardive dyskinesia ratings, and that total omega-3 fatty acid intake was significantly and negatively related to PANSS positive symptoms. While these results do not come from a controlled study, RBC total omega-3 fatty acid content was significantly and positively correlated with PANSS negative symptoms.

In their cross-national ecological analysis Christensen and Christensen found that a high total intake of saturated fat was significantly associated with ratings of an unfavorable schizophrenia course and outcome. To be exact, both the percentage energy derived from fat, including saturated fat, and the percentage energy derived predominantly from land animals and birds, containing saturated fat, were: a) significantly and positively associated with the mean percentage of followups spent in psychotic episodes, the percentage of patients with severe social impairment and total overall outcome score; and b) significantly and negatively associated with mean days spent outside hospital. The percentage of energy derived from sources with a relatively high content of unsaturated fat, including PUFAs (i.e., vegetables, fish and seafood), was not significantly associated with any of the aformentioned mental health parameters. Multiple regression revealed that only total outcome score was significantly predicted by both the percentages of intake of saturated (positive correlation) and unsaturated fats (negative correlation). Countries obtaining more of their dietary fat from land animals and fowl and less from vegetable or marine sources exhibited a worse schizophrenia outcome. This scenario accounted for 97% of the variance in outcome between countries. However, the evidence did not exhibit a significant direct relationship between intake of unsaturated fat, including PUFAs, and schizophrenia course or outcome.

Using linear and nonlinear regression models, Noaghiul and Hibbeln found that seafood consumption did not significantly predict lifetime prevalence rates (no data reported).[90] Peet reported that fish consumption was not significantly associated with specific schizophrenia course or outcome variables, including mean days out of hospital, percentage of patients with severe social impairment, total outcome score, hospitalization status, percentage of patients with little social impairment, or total "best outcome" score.

Quantitative Synthesis

Meta-analysis was not considered because of the variability in the study designs (case-control vs single prospective cohort study vs cross-national ecological analysis), the schizophrenia-related outcomes (incidence vs prevalence vs course vs outcome) as well as in the sampling strategies, methods assessing breastfeeding practices and the definitions of cases or controls employed in the case-control studies.

Impact of Covariates and Confounders

The mix of study designs and study outcomes, in addition to the failure of studies to try to experimentally or statistically control for variables with the potential to influence clinical outcomes, made it impossible to assess the impact of extra-exposure factors on study outcomes. At the same time, few studies yielded results indicating a significant association between omega-3 fatty acid intake and the onset, continuation or recurrence of schizophrenia; and, no variables were noted as being potentially responsible for determining this pattern of findings.

Is the Onset, Continuation or Recurrence of Schizophrenia Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Tables 40 through 44 (below), derived from Evidence Table 2 (Appendix E*), 14 cross-sectional studies published between 1979 and 2003 were included.[114,146-158] Two of these studies were conducted at baseline in prospective cohort studies.[157,158]

Overview of Relevant Studies

Obi and Nwanze assessed the RBC and plasma fatty acid compositions of schizophrenic patients (n=6; 30-50 years) compared to age-matched (22-45 years) healthy controls (n=6) drawn from hospital staff and students in Nigeria (Summary Table 40).[153] Horrobin et al. evaluated the fatty acid content in plasma phospholipids in an heterogeneous population of schizophrenic patients from three different cities (n=84; mean age: 40.8 [20-71] years; 72.6 % male), compared with younger healthy controls (n=119; mean age: 35.7 [19-66] years; 51.3 % male).[152] Kaiya et al. examined the plasma fatty acid composition in medicated Japanese schizophrenics (n=59; mean age: 35.7 years; 61% male), patients with an affective or paranoid disorder (n=24; mean age: 36.3 years; 37.5% male) and healthy volunteers recruited from hospital personnel (n=24; mean age: 36.3 years; 37.5% male).[151]

*__Note:__ Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

Summary Table 40: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Obi, 1979, Nigeria: multiple-group cross-sectional study[153]	schizophrenic pts (n=6)	healthy controls (n=6)	↑ % of LA in schizophrenic pts+	Total quality: 1 [Grade: C]	III
Horrobin, 1989, England, Scotland, Ireland: multiple-group cross-sectional study[152]	adult male & female schizophrenic pts (n=84)	adult male & female controls (n=119)	↓ total n-6 levels in pts;+ ↑ n-3 levels in pts;+ ↓ n-6/n-3 in pts;+ ↓ LA & AA in pts;+ ↑ DHA in pts (England & Ireland);++ NS EPA bet grps	Total quality: 2 [Grade: C]	II
Kaiya, 1991, Japan: multiple-group cross-sectional study[151]	adult male & female schizophrenic pts (n=59)	adult male & female affective or paranoid disorders (n=24)/ adult male & female controls (n=24)	NS total n-3 FA; ↑ DGLA in schizophrenic pts;+ ↓ LA in schizophrenic pts;+ ↑ EPA in schizophrenic male pts vs female pts;++ in cholesterol fraction, NS bet schizophrenic pts >40 & <40 y; ↑ AA in inpts vs outpts+	Total quality: 3 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; +p<.05 or significant with 95% confidence interval; ++p<.01; +++p<.001; ++++p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower

Fischer et al. analyzed the fatty acid content in platelets from: German schizophrenic patients treated with "high dose" (n=9; age: 24-42 years, inpatients) or "low dose" (n=7; age: 35-53 years, outpatients) monotherapy of neuroleptic drug (phenothiazine and thioxanthene); untreated schizophrenic patients (n=2); and, untreated healthy controls (n=6; 100% male) (Summary Table 41).[150] Peet et al. examined the RBC fatty acid content in medicated schizophrenic inpatients (n=23; mean age: 55 years; 69.5% male) and in age- and sex-matched healthy controls (n=16).[149] Vaddadi et al. examined the RBC fatty acid content in hospitalized and non-hospitalized medicated schizophrenic patients with or without tardive dyskinesia (n=72), in addition to patients with schizophrenia or schizoaffective disorders (n=72; mean age: 35.4 [18-64] years; 75% male) and age-matched healthy controls (n=39).[157]

Summary Table 41: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Fischer, 1992, Germany: multiple-group cross-sectional study[150]	"high dose" inpts (n=9)/ control males (n=6)	"low dose" outpts (n=7)/ untreated pts (n=2)	↓ LA, AA & DHA "high-dose" vs "low dose" & controls;$^{++}$; ↓ LA, AA & DHA in "low dose" vs untreated;$^{+}$ ↑ ratio of SFA/PUFA in "high dose" vs "low dose" & controls^{+}	Total quality: 1 [Grade: C]	III
Peet, 1995, UK: multiple-group cross-sectional study[149]	medicated inpts (n=23)	age & sex-matched healthy controls (n=16)	↓ EPA & DHA in pts;$^{+++}$ ↓ LA & AA in pts;$^{+++}$ NS correlation bet neuroleptic dosage & FA levels	Total quality: 3 [Grade: C]	III
Vaddadi, 1996, Australia: multiple-group cross-sectional study at baseline of multiple prospective cohort study[157]	adult male & female schizophrenic pts with tardive dyskinesia (n=32)	adult male & female schizophrenic pts without tardive dyskinesia (n=40)/ normal controls (n=39)	↓ LA pts severe TD vs pts without TD;$^{++}$ ↓ LA pts without TD vs control group;$^{++}$ ↑ (n-3-)DPA pts vs controls;$^{+}$ followup at 4.5 y: ↑ RBC (n-6-)DGLA in both pt grps vs controls^{++}	Total quality: 1 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower; SFA = saturated fatty acids; TD = tardive dyskinesia

Mahadik et al.'s sample of 12 schizophrenic patients (n=8 drug-naïve and first episode) and six patients with bipolar mood disorder (n=2 manic first episode) were compared to eight sex-matched control subjects with respect to their fatty acid content in cells extracted from skin biopsies (Summary Table 42).[114] Assies et al. evaluated the RBC fatty acid content in schizophrenics (n=16), one patient with psychoaffective disorder, one with bipolar disorder and one with a brief psychotic disorder according to DSM-IV diagnostic criteria (n=19; mean age: 21.2 years; 89% male), compared with age, sex, height and weight-matched healthy controls (n=14; mean age: 20.9 years; 85.7% male).[148] Yao et al. examined the correlation between RBC fatty acid content and in vivo membrane phospholipid metabolites in first-episode, drug-naïve schizophrenics (n=11; mean age: 26 [17-44] years; 54.5% male) compared to age-, sex- and race-matched normal controls (n=11; mean age: 26 [19-39] years; 54.5% male).[154]

Summary Table 42: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Mahadik, 1996, US: multiple-group cross-sectional study[114]	male & female schizophrenic pts (n=12)	male & female bipolar pts (n=6)/ controls (n=8)	↓ DHA in cell lines of schizophrenic pts vs bipolar pts & controls;$^{+}$ NS DHA bet bipolar & controls; ↓ AA in schizophrenia vs bipolar pts^{+}	Total quality: 5 [Grade: B]	I
Assies, 2001, Holland: multiple-group cross-sectional study[148]	schizophrenia & other diagnoses in young adults (n=19)	matched controls (n=14)	↓ DHA & (n-3-)DPA in pts;$^{++}$ ↓ total n-3 in schizophrenic pts;$^{+++}$ NS n-6 bet grps; ↓ DHA/AA ratio in pts;$^{+}$ NS AA/EPA, DPA/DHA & n-6/n-3; positive correlation bet CPZ equivalents & AA/EPA;$^{+}$ negative correlation for EPA & CPZ dosage;$^{+}$ ↓ n-6/n-3 in cannabis users vs nonusers; no consistent pattern of correlations of FA content & symptomatology	Total quality: 2 [Grade: C]	III
Yao, 2002, US: multiple-group cross-sectional study[154]	drug-naïve, first episode schizophrenic pts (n=11)	normal controls (n=11)	↓ AA in pts;$^{+}$ NS bet-grp differences for rest of FA; positive correlation bet peripheral biomarkers & PLs only in prefrontal brain^{++}	Total quality: 3 [Grade: C]	I

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; $^{+}$p<.05 or significant with 95% confidence interval; $^{++}$p<.01; $^{+++}$p<.001; $^{++++}$p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower;SFA = saturated fatty acids; CPZ = chlorpromazine

Khan et al. enrolled drug-naïve, first episode schizophrenic patients (n=22) drawn from the Army Medical Center in United States, chronically medicated schizophrenic patients from an outpatient clinic (n=30) and age- and sex-matched healthy volunteers (n=16) (Summary Table 43).[147] This study measured plasma and RBC fatty acid contents and their metabolites from peroxidation.

The first Arvindakshan et al. study examined the RBC and plasma fatty acid compositions in medicated schizophrenic patients in India (n=28; mean age: 29.6 years; 64.3% male) and in age- and sex-matched healthy volunteers (n=45; mean age: 30 years; 67% male).[155] This was a before-after study, where only the patients received an intervention (i.e., omega-3 fatty supplementation) for 24 weeks. We assessed the cross-sectional baseline data from schizophrenics and controls. Because the intervention part of the study was uncontrolled, clinical efficacy data were not eligible for inclusion in this review. Arvindakshan et al.'s second study evaluated the RBC membrane content in drug-naïve, first episode schizophrenics (n=20; mean age: 29.4 years; 60% male), medicated patients (n=32; mean age: 31.3 years; 65.6% male) and age-, sex -and race-matched healthy controls (n=45; mean age: 29.2 years; 55.6% male).[146]

Summary Table 43: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Khan, 2002, US: multiple-group cross-sectional study[147]	drug-naïve, first episode schizophrenic pts (n=22)	chronic medicated schizophrenic pts (n=30)/ healthy controls (n=16)	↓ LA, AA & DHA were lower in FE vs chronic pts;$^{+++}$ ↓ LA, AA & DHA in FE & chronic pts vs controls;$^{+++}$ Larger ↓ PUFA levels associated with greater severity of psychosis, indicated by ↑ clinical scores in FE pts vs chronic pts; Δ did not seem to be related to age or smoking	Total quality: 3 [Grade: C]	I
Arvindakshan, 2003, India: multiple-group cross-sectional study at baseline of before-after study[155]	medicated schizophrenic pts (n=28)	healthy controls (n=45)	↓ EPA & DHA in pts (at baseline);$^{+++}$ NS in LA or AA content (at baseline)	Total quality: 4 [Grade: B]	III
Arvindakshan, 2003, India: multiple-group cross-sectional study[146]	drug-naïve, first episode schizophrenic pts (n=20)	medicated schizophrenic pts (n=32)/ healthy controls (n=45)	↓AA, DHA, total n-6 & n-3 FA in FE & MS vs controls;$^{+++}$ NS AA & DHA bet MS vs controls; ↓ AA, DHA, total n-6 & n-3 in FE vs MS;$^{+++}$ negative correlation bet AA & BPRS;$^{+}$ negative correlation bet DHA & PANSS negative symptoms^{+++}	Total quality: 2 [Grade: C]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source;[3] biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower; FE = first episode; MS = medicated schizophrenics; SFA = saturated fatty acids; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Symptom Scale

Evans et al. assessed the RBC fatty acid content in patients with first-episode schizophrenia (n=16) and healthy volunteers (n=25), although the latter group was significantly older and were more highly educated than the schizophrenic group (Summary Table 44).[158] Ranjekar et al. measured the RBC and plasma fatty acid content, as well as the lipid oxidative products, in medicated schizophrenic patients (n=31; mean age: 37.3 years), patients with bipolar mood disorder (n=10; mean age: 40.8 years), and age-, sex- and race-matched healthy controls (n=31).[156]

Summary Table 44: Association between omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Evans, 2003, US: multiple-group cross-sectional study at baseline of single prospective cohort study[158]	first episode schizophrenic pts (n=16)	healthy controls (n=25)	↓ (n-3-)DPA & DHA in FE vs controls;[+] NS AA & LA levels bet grps	Total quality: 1 [Grade: C]	I
Ranjekar, 2003, India: multiple-group cross-sectional study[156]	adult male schizophrenic pts (n=31)	bipolar adult males (n=10)/ healthy controls (n=31)	↓ SOD, CAT & GPx in schizophrenic pts vs controls;[++] ↓ ALA, DHA & EPA in pts vs controls;[+] ↓ SOD, CAT in bipolar pts vs controls;[+]	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; bet = between; grp = group; wk = week(s); mo = month; Δ = change; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; [+]p<.05 or significant with 95% confidence interval; [++]p<.01; [+++]p<.001; [++++]p<.0001; ↑ = increase(d)/higher; ↓ = decrease(d)/reduction/lower;SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; PE = phosphatidylethanolamine

Qualitative Synthesis of Relevant Studies' Key Characteristics

Study characteristics. Fourteen included studies had cross-sectional designs involving at least two groups.[114,146-158] Six studies did not report inclusion criteria,[147,148,150,151,153,155] and seven did not report exclusion criteria.[147,149-153,158] Study sizes ranged from 12[153] to 203 participants.[152] Countries where the studies were conducted included: India,[146,155,156] Holland,[148] Nigeria,[153] Japan,[151] Germany,[150] Australia,[157] the US [114,147,154,158] and the UK.[149,152]

The Arvindakshan et al. studies were supported by the Council of Scientific and Industrial Research, M.L. Vasa, Laxmichand Dayabhai NIH/Fogarty International Center, Interactive Research School for Health Affairs and the Vasa Heart Foundation (India).[146,155] Evans et al. and Khan et al.'s funding source was the NIH/NCCAM[147,158] and the Stanley Foundation.[158] Ranjekar et al.'s work was supported by Mr. M.L. Vasa, Laxmichand Dayabhai (Export) Co.[156] and Vaddadi et al.'s study was funded by Scotia Pharmaceuticals Ltd. (UK).[157] Yao et al.'s study was supported by the NIMH, an NARSAD Young Investigator Award, the Office of Research and Development, Department of Veteran Affairs and Highland Drive Veteran Affairs Pittsburgh Healthcare System.[154] Seven studies did not report a funding source.[114,148-153]

Population characteristics. Studies included only adult participants. Horrobin et al.'s controls were younger than their schizophrenic participants and were not fully sex-matched, although the difference was not significant.[152] Obi and Nwanze's schizophrenic patients were likely well-matched by age (30-50 years).[153] Kaiya et al.'s subjects were matched by age.[151] In Fischer et al.'s study the low-dose antipsychotic therapy group was slightly older than the other

groups.[150] Peet et al. and Assies et al.'s samples were well-matched by age and sex.[149] Vaddadi et al.'s study groups were well-matched by age (18-64 years).[157] Mahadik et al.'s schizophrenic and bipolar patients were well-matched by age and sex, with a preponderance of males taking part in their project.[114] Yao et al.'s work included participants who were matched by age, sex and race.[154] Only Khan et al.'s first-episode psychotic patients and their controls were matched by age.[147] Their chronically medicated-schizophrenics were older. For both of Arvindakshan et al.'s studies, between-group differences were not observed for age or sex.[146,155] Evans et al.'s controls were significantly older than their schizophrenic patients.[158] Ranjekar et al.'s study groups were well-matched by age; and, only males with the same racial origin were included.[156] Few studies described the ethnicity/race of their participants. Three studies included east Indian patients[146,155,156] and one study included Japanese participants.[151]

All studies involved inpatients and/or outpatients with acute and/or chronic schizophrenia of varying degrees of severity and ages of onset. Some studies included heterogeneous subtypes of schizophrenia, namely schizoaffective disorder,[146,148,151,154,157] severe bipolar mood disorder,[114,148,156] schizophreniform disorder[146,154,158] and paranoid disorder.[151] Five studies included neuroleptic-naïve, first episode schizophrenic participants.[114,146,147,154,158] Diagnoses were made on the basis of DSM-III-R[114,149,151,152,157] or DSM-IV diagnostic criteria.[146-148,154-156,158] Only two studies failed to report this information.[150,153] Horrobin et al. also used the Research Diagnostic Criteria for schizophrenia.[152] Assies et al. as well as Khan et al. employed the PANSS.[147,148] Assies et al. utilized the MADRS to identify depressive symptomatology within the context of bipolar mood disorder.[148]

The control groups were composed of "healthy volunteers" who were sometimes screened for mental disorders using the nonpatient version of the SCID.[114,146,154-156] Healthy controls were excluded from four studies if they had a personal or family history of psychiatric disorder, medication use and/or substance abuse.[154-156] Exclusion criteria pertaining to healthy controls were not described in most study reports.

In order to control for possible confounding factors, some studies established exclusion criteria. Vaddadi et al. excluded any subject with a history of established neurological illness, developmental handicap or currently receiving nonsteroidal anti-inflammatory drugs.[157] Mahadik et al.'s patients were excluded if they had a history of substance abuse or dependence, seizure disorder, head injury with loss of consciousness, or positive family history of Huntington's Disease, dementia, or mental retardation in first degree relatives.[114] Assies et al. did not include subjects with a major medical illness, mental retardation, endocrine disorders, or a cholesterol-lowering diet or medication.[148] Yao et al. excluded patients with significant drug or alcohol use within one month of the initial assessment, a history of significant medical illness, hyperlipidemia at baseline, obesity, starvation in the previous two weeks, neurologic disorders, history of psychosis longer than two years, or comorbidity involving a DSM-IV Axis I diagnosis.[154] Both of Arvindakshan et al.'s studies, as well as that conducted by Ranjekar et al., excluded patients with WAIS-R full-scale IQ<80, high levels of dietary supplement use, severe under- or malnourishment, seizure disorder, head injury with loss of consciousness, alcohol and substance abuse or dependence, excessive smoking, type II diabetes, lipid disorders, cardiovascular disease, hypertension or obesity.[146,155,156]

Intervention/exposure characteristics. Thirteen studies did not involve an intervention or exposure. Only one of the Arvindakshan et al.'s studies employed supplementation[155], and Assies et al. assessed dietary intake of omega-3 fatty acids using a questionnaire.[148] Kaiya et al. described the use of a typical Japanese diet rich in rice and seafood by their inpatients residing in

a Geriatric Hospital.[151] No other studies controlled statistically for background diet in their analysis. No study reported inappropriate methods by which lipids were extracted, prepared, stored or analyzed.

Cointervention characteristics. One of the most relevant confounders is the use of medication for the treatment of schizophrenia. Obi and Nwanze did not report the medication used by their participants.[153] Horrobin et al.'s sample from England and Scotland were using neuroleptic drugs.[152] Kaiya et al.'s schizophrenic patients used neuroleptic drugs (i.e., haloperidol), while the participants with affective or paranoid disorders were taking antidepressants.[151] Fischer et al.'s patients were receiving neuroleptics such as phenothiazines (i.e., perazine) or thioxanthenes (i.e., flupentixol).[150] The reports of Peet et al. and Vaddadi et al. mentioned the use of neuroleptic medication by all their patients, but did not provide additional details.[149,157] Assies et al.'s subjects were taking olanzapine (n=11), pimozide (n=4), risperidone (n=3) or clozapine (n=1), combined with other medications such as paroxetine, fluvoxamine, oxazepam, temazepam, alprazolam, biperideen, trihexyfenidyl, dexetimide or lithium carbonate.[148] Some studies also described the use of atypical antipsychotics (i.e., risperidone).[146,147,155,156,158] Ranjekar et al.'s sample took antidepressants as well.[156] In a small number of studies, particularly those including cases of first-episode schizophrenia, the participants did not receive any type of drug prior to the study or during the study assessment period.[114,146,154]

Outcome characteristics. Outcomes included all types of fatty acid, from various sources, and were expressed either as percentages, or fractions (i.e., composition), or concentrations.

Study quality and applicability. The fourteen cross-sectional studies received a mean quality score of 2.5, with all but five studies achieving an applicability rating of III.[146,148-151,153,155-157] Four studies received an applicability rating of I,[114,147,154,158] and one study attained a rating of II.[152]

Summary Matrix 16: Study quality and applicability of evidence regarding the association between the omega-3 or omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of schizophrenia

		Study Quality								
		A			B			C		
Applicability	I	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
					Mahadik	1996	26	Yao	2002	22
								Evans	2003	41
								Kahn	2002	68
	II	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
								Horrobin	1989	203
	III	**Author**	**Year**	**n**	**Author**	**Year**	**n**	**Author**	**Year**	**n**
					Arvindakshan	2003	73	Obi	1979	12
					Ranjekar	2003	72	Kaiya	1991	97
								Fischer	1992	24
								Peet	1995	39
								Vaddadi	1996	111
								Assies	2001	34
								Arvindakshan	2003	97

n = number of allocated/selected participants

Qualitative Synthesis of Individual Study Results

In Obi and Nwanze's study, a significantly higher proportion of LA was found in schizophrenic patients compared with controls.[153] The difference was observed in both the neutral lipids and the phospholipids extracted from plasma and RBCs.

In Horrobin et al.'s study, a separate analysis was performed for data from each of the three countries.[152] There were no significant differences between patients and controls in the total amount of plasma phospholipid present. At all three sites, patients had significantly reduced total omega-6 fatty acid levels compared with controls. The levels of omega-3 fatty acid were significantly increased in the schizophrenic groups. The omega-6/omega-3 fatty acid ratio was significantly reduced in all three patient groups. LA and AA were significantly reduced in all three groups of patient, and DGLA was reduced in two of them. DHA was significantly increased in the schizophrenic patients of England and Ireland compared with controls. EPA levels were not significantly different between groups.

Kaiya et al. found that, with the exception of DGLA which was significantly above normal in the schizophrenic patients, the levels of omega-3 fatty acid in plasma phospholipids were not significantly different between normal Japanese subjects and schizophrenic patients or patients with affective or paranoid disorders.[151] From the analysis of fatty acids in plasma cholesterol esters, LA was significantly lower in schizophrenic patients compared with controls, but not in patients with affective or paranoid disorders. In plasma phospholipids, EPA was significantly higher in schizophrenic males compared with schizophrenic females. In the cholesterol fraction, there were no significant differences between schizophrenics over and under 40 years of age. When data from hospitalized schizophrenics were contrasted with that from outpatients, AA was significantly higher in the inpatients.

Fischer et al. analyzed data regarding the total fatty acid composition of platelets. LA, AA and DHA were significantly lower in schizophrenic patients using high-dose neuroleptics compared with those taking low-dose neuroleptics or with untreated healthy controls.[150] LA, AA and DHA were significantly lower in the group of low dose patients compared to two untreated schizophrenic patients. In general, the ratio of SFAs to PUFAs was significantly higher in the high-dose group compared with the low-dose group or with healthy controls. This ratio was also significantly higher in the low dose group than in the controls.

The medicated and hospitalized schizophrenic patients included in the Peet et al. study exhibited significantly lower RBC EPA and DHA levels compared to healthy controls.[149] LA and AA were also significantly lower than in controls. There was no significant correlation between neuroleptic dosage, expressed as chlorpromazine equivalents, and any of the measures of fatty acid level. Plasma levels of total free fatty acids did not differ between groups.

Based on Vaddadi et al.'s initial assessment, schizophrenic patients were grouped according to their tardive dyskinesia status.[157] The RBC fatty acid compositions from four groups were compared. Patients with severe tardive dyskinesia had significantly lower LA compared to patients without tardive dyskinesia, who in turn had lower levels compared to the control group. All patients had elevated levels of omega-3 fatty acids, but only (omega-3-)DPA was significantly higher when compared to controls. Half of the patients were assessed 4.5 years later, when only RBC (omega-6-)DGLA was found to be significantly elevated, relative to controls, in schizophrenics with and without tardive dyskinesia.

Given that the cell membrane distributions of AA and DHA did not differ in cultured skin fibroblasts from patients with chronic schizophrenia and patients with first-episode

schizophrenia, Mahadik et al. combined data from these two patient groups for analyses.[114] These data were then compared to those obtained from patients with recurrent bipolar mood disorder and sex-matched controls. The DHA composition was found to be significantly lower in cell lines of schizophrenic patients compared with cell lines obtained from either bipolar patients or normal subjects. Data from the two latter groups did not differ. The percent distribution of AA in the cell lines of schizophrenic patients was significantly lower than that in bipolar patients, but the percent distribution of AA from either group did not differ significantly from that seen in normal controls.

In the study of Assies et al., no significant differences were found between schizophrenic patients and normal controls in terms of age, sex, BMI or dietary intake of lipids at baseline in Assies et al.'s study.[148] DHA content and that of its precursor (n-3-)DPA were each significantly reduced in the RBCs of schizophrenic patients compared with controls. Between-group differences for the other omega-3 fatty acids were not observed. Total omega-3 fatty acid content was significantly reduced in the schizophrenic group. No significant between-group differences were found for any of the omega-6 fatty acids. The DHA/AA ratio was lower in schizophrenic patients than in control subjects. The study groups' AA/EPA, DPA/DHA and total omega-6/omega-3 fatty acid content ratios did not differ. There was a significant positive correlation between chlorpromazine equivalents and the AA/EPA ratio. A significant negative correlation linked EPA content and chlorpromazine dosage. By subgroup analysis, the omega-6/omega-3 fatty acid content ratio was significantly lower in cannabis users compared with nonusers. There was no consistent pattern of correlations involving fatty acid contents and measures of symptomatology.

Yao et al.'s population of first-episode, untreated schizophrenics had a significantly lower RBC AA concentration than did normal controls.[154] The remaining fatty acid contents did not differ significantly between groups. There was a significant correlation between the levels of peripheral biomarkers and the level of free phospholipids in the prefrontal region of the brain, as assessed by ^{31}P Spectroscopy.

Khan et al.'s heterogeneous sample of active army personnel consisted of drug-naïve first-episode schizophrenics, chronic medicated schizophrenics and healthy controls. The fatty acid contents of their RBC membranes were compared.[147] The levels of LA, AA and DHA were significantly lower in first episode patients than in chronic patients. Levels were also lower in first-episode patients and in chronic patients compared with controls. The larger reductions in PUFA levels were associated with a greater severity of psychosis assessed in drug-naïve, first-episode patients, compared with chronic medicated schizophrenics, as assessed using the Brief Psychiatric Rating Scale (BPRS), negative PANSS and positive PANSS. These changes did not appear to be related to age or to smoking.

The first Arvindakshan et al. study showed that the schizophrenic patients had a significantly lower RBC membrane concentration of EPA and DHA compared to healthy controls.[155] Significant between-group differences were not observed for LA or AA content.

In the second Arvindakshan et al. study, the RBC membrane AA, DHA, total omega-6 and total omega-3 fatty acid contents were each significantly lower in both patient groups, (medicated and never medicated) when compared to healthy controls.[146] The differences remained significantly different when the never-medicated patients were compared to the normal controls, but neither the AA nor the DHA contents were significantly different when medicated schizophrenics and controls were compared. The AA, DHA, total omega-6 fatty acids and total omega-3 fatty acid levels in RBCs were significantly lower in never medicated patients

compared to medicated schizophrenics. The psychopathologic measures in never medicated subjects were examined for their relationship to PUFA levels. Significantly negative correlations were found for AA levels and BPRS scores, and for DHA levels and PANSS negative symptoms. Never medicated patients appeared to exhibit more severe psychopathology than medicated patients.

Evans et al. showed that RBC (omega-3-)DPA and DHA levels were significantly lower in first episode, untreated schizophrenics compared with controls.[158] Significant between-group differences were not observed for AA or LA levels. RBC antioxidant enzymes were assessed and it was found that the level of superoxide dismutase (SOD) was significantly lower in schizophrenic patients than controls, and catalase (CAT) was significantly elevated in these patients.

Ranjekar et al. evaluated the possible association of levels of RBC antioxidant enzymes (i.e., SOD, CAT, glutathione peroxidase [GPx]), as key indices of oxidative stress, with RBC fatty acid contents for schizophrenics, bipolar mood disorder patients and normal controls.[156] These enzymes were significantly lower in schizophrenics compared with controls. ALA, DHA and EPA levels were also significantly lower in patients compared to controls. When these analyses included data from bipolar patients, only two enzymes—SOD and CAT—were reduced significantly relative to control subjects.

Four studies measured the products of membrane lipid peroxidation utilizing blood levels of thiobarbituric acid reactive substances (TBARS).[146,147,149,155] The results were inconsistent when data from schizophrenics and healthy controls were compared. These data are not reviewed in more detail here since they lie beyond the scope of our report.

Quantitative Synthesis

Although all of the included studies were controlled, only one had a formal followup that included controlled data. Thus, a meta-analysis was not considered.

Impact of Covariates and Confounders

Studies were distinguishable on the basis of whether the sample of schizophrenic patients was currently, or ever had been, medicated with neuroleptics. Comparing the results obtained from studies where patients were, or were not, receiving medication could illumine one possible source controlling variation in biomarker outcomes. All comparisons presented here involve healthy controls; the use of any other types of control was too infrequent and idiosyncratic to specific studies to afford generalization.

In the five studies where at least one set of analyses involved a comparison between patients not on medication and healthy controls,[114,146,147,154,158] all assessed RBC fatty acid content data, four revealed reductions in DHA,[114,146,147,158] three showed reductions in AA content,[146,147,154] one highlighted a reduction in LA,[147] one noted a reduction in (omega-3-)DPA[158] and one found significantly lower levels of total omega-6 fatty acids and total omega-3 fatty acids in never-medicated schizophrenic patients.[146] In this last study, when data from patients who had never been medicated were compared with data from patients who were currently medicated, levels of AA, DHA, total omega-6 fatty acids and total omega-3 fatty acids were significantly lower in never-medicated patients.[146]

In studies where patients were medicated, and RBC data were again compared with those from healthy controls, significant reductions in DHA,[148,149,155,156] AA,[149] LA,[149,157] (omega-3-)DPA,[148] ALA,[156] total omega-3 fatty acids,[148] DHA/AA[148] and EPA[149,155,156] were observed in schizophrenic patients. While there is considerable overlap when these results are contrasted with those from studies where schizophrenic patients were not receiving medication, one notable difference is that, compared to controls, medicated patients were more likely to show reduced levels of EPA in RBCs. Thus, medication status may have an influence on between-group differences in RBC fatty acid content when the comparator is healthy controls.

As with RBC data, when plasma phospholipids were examined, Horrobin et al. reported significantly lower levels of total omega-6 fatty acid content, LA and AA in schizophrenic patients compared with controls.[152] Kaia et al. revealed that LA was significantly reduced in plasma choleterol esters.[151] When Fischer et al. assessed the total fatty acid content of platelets they found that significant reductions in DHA, AA and LA were associated with medicated patients compared with controls as well as with patients receiving high-dose versus low-dose neuroleptic medication.[150] Patients on low dose medication also exhibited significantly lower levels of LA, AA and DHA compared with controls. Those taking high doses of medication also displayed a higher SFA/PUFA value compared with those receiving lower doses. These data suggest that, as with studies investigating RBC content, medication appears to have an impact on biomarker outcomes that may be independent of the disease process.

However, other biomarker data gleaned from a minority of studies provided a picture of effects that are inconsistent with what was found for RBCs. Vaddadi et al. reported that all RBC omega-3 fatty acid levels were significantly higher in schizophrenic patients compared with healthy controls.[157] Horrobin et al. noted the same difference albeit in plasma phospholipids.[152] One final study showed that LA content in either RBCs or plasma phospholipids was actually increased significantly in schizophrenic patients compared with controls.[153]

Is the Onset, Continuation or Recurrence of Autism Associated With Omega-3 or Omega-6/Omega-3 Fatty Acid Content of Biomarkers?

As observed in Summary Table 45 (see below), derived from Evidence Table 2 (Appendix E*), a single cross-sectional study published in 2001 met eligibility criteria.

Overview of Relevant Study's Characteristics and Results

Vancassel et al.'s study was supported by INRA, INSERM U316, INSERM Network and the Fondation France Telecom.[159] It compared the plasma phospholipid fatty acids of mentally retarded children (n=18; 72.2% male; mean age: 8.7 years) and in children having received a diagnosis of autism (n=15; 73.3% male; mean age: 8.3 years), who were attending the Child Psychiatry Day Care Unit in a hospital in France. The diagnoses of autism and mental retardation were based on DSM-III-R and DSM-IV criteria. The entire study population

*Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gvo/clinic/tp/o3menttp.htm.

participated in day care and received the same diet over a 12-hour period. There were no significant between-group differences for height or weight. The aim of the study was to compare the study groups' plasma fatty acid content. No notable inappropriate methods to extract, prepare, store or analyze lipids were described.

Summary Table 45: Association between omega-3 and omega-6/omega-3 fatty acid content of biomarkers and onset, continuation or recurrence of autism

Author, Year, Location: Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Study groups[1] Group 2 (n)/ Group 3 (n)	Notable associations	Internal validity	Applicability
Vancassel, 2001, France: multiple-group cross-sectional study[159]	autistic children (n=15)	mentally retarded children (n=18)	NS plama LA, AA bet grps; NS plasma DHA, ALA; ↓ total n-3 in autism; ↑ n-6/n-3 in autism	Total quality: 4 [Grade: B]	III

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; n-3 = omega-3 fatty acids; n-6 = omega-6 fatty acids; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; N/A = not applicable; pb = placebo; grp = group; wk = week(s); mo = month; RBC = red blood cells; PL = phospholipid; CPG = choline phosphoglycerides; EPG = ethanolamine phosphoglycerides; Jadad total = Jadad total quality score: reporting of randomization, blinding, withdrawals/dropouts (/5); Schulz = reporting of adequacy of allocation concealment (adequate, inadequate, unclear); $^{+}p<.05$ or significant with 95% confidence interval; $^{++}p<.01$; $^{+++}p<.001$; $^{++++}p<.0001$; ↑ = increase; ↓ = decrease/reduction

The results showed that there were no significant between-group differences in the plasma content of omega-6 fatty acids or in ALA and DHA.[159] Yet, autistic children had a significantly lower total omega-3 fatty acid level and a significantly higher omega-6/omega-3 fatty acid ratio compared to the mentally retarded children. This study received an applicability rating of II and a total quality score of 4.

What is the Evidence That, in Review-Relevant Studies Concerning Mental Health, Adverse Events (e.g., Side Effects) or Contraindications are Associated With the Intake of Omega-3 Fatty Acids?

Adverse events are often underreported in study reports; therefore, failure to report any does not constitute evidence that none occurred. That said, a number of study reports explicitly stated that no exposure-related events had been observed;[97-99,115,120,122,131,139,140] since the focus here is on exposure-related events, we had to include event data (e.g., type, consequence) in Summary Tables 46 through 48 when it was unclear as to which circumstances these events could be attributed. On one occasion, a failure of study authors to state that certain events were not directly linked to the expoure did not prevent our review team from suggesting that they were likely related to the disorder and not the exposure (i.e, self-harm [e.g., wrist scratching] in two active treatment patients and one control patient, respectively).[139] At the same time, Peet et al. did not identify the patients or study groups from whom adverse event data were collected.[58]

Finally, multiple adverse events can be experienced concurrently or at different points in time over a study by a single patient. On occasion, included reports failed to explicitly identify these scenarios whereby a small number of study participants contributed many or most of the adverse event data.

Eight treatment RCTs provided some adverse event data.[53,58,87,89,95,96,112,119] Two of the three intervention studies looking at the possible protective effects of omega-3 fatty acids in healthy volunteers also reported safety data.[129,130] The treatment trials included two of the three RCTs and the only RCT investigating the supplemental and primary treatment of depression, respectively. Three of four trials investigating the supplemental treatment of schizophrenia yielded adverse event data.[58,87,89]

Summary Table 46: Studies reporting adverse events (e.g., side effects) or contraindications

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Safety data
DEPRESSION			
Marangell, 2003, US: 6 wk parallel RCT[95]	2g/d DHA (n=18)	pb (source undefined) (n=18)	2g/d DHA (source undefined): fishy aftertaste (n=14 events), belching (n=3), lightheadedness or dizziness (n=3), loose stools (n=2), headache (n=2), insomnia (n=1), continued (n=18/18); pb (source undefined): fatigue (n=3 events), insomnia (n=1), loose stools (n=1), continued (n=18/18)
Peet, 2002, England & Scotland: 12 wk parallel RCT[53]	4g/d E-EPA (n=17)/ liquid paraffin pb (n=18)	2g/d E-EPA (n=18)/ 1g/d E-EPA (n=17)	Musculoskeletal system: 4g/d E-EPA (source undefined) (n=1); 2g/d E-EPA (n=2); central & peripheral nervous system: 4g/d E-EPA (n=1); 1g/d E-EPA (n=1); pb (liquid paraffin) (n=3); visual system: pb (n=1); psychiatric event: 2g/d E-EPA (n=2); 1g/d E-EPA (n=4); pb (n=2); gastrointestinal: 4g/d E-EPA (n=5); 2g/d E-EPA (n=8); 1g/d E-EPA (n=7); pb (n=4); metabolic: 1g/d E-EPA (n=2); pb (n=2); endocrine: 4g/d E-EPA (n=1); respiratory system: 4g/d E-EPA (n=1); 2g/d E-EPA (n=2); 1g/d E-EPA (n=1); pb (n=2); white blood cells: pb (n=1); reproductive system: 2g/d E-EPA (n=1); pb (n=2); whole body: 4g/d E-EPA (n=3); 2g/d E-EPA (n=6); 1g/d E-EPA (n=1); pb (n=4); infections: 4g/d E-EPA (n=3); 2g/d E-EPA (n=3); 1g/d E-EPA (n=2); pb (n=2); diarrhea: 1g/d E-EPA (n=1)
Su, 2003, China: 8 wk parallel RCT[96]	4.4g EPA + 2.2g/d DHA (n=14)	olive oil ethyl ester pb (n=14)	4.4g EPA + 2.2g/d DHA (fish oil): mild excitement (n=1), continued (n=1/1); mild diarrhea (n=1), continued (n=1/1); pb (olive oil ethyl esters): insomnia (n=1), continued (n=1/1)
BIPOLAR DISORDER			
Stoll, 1999, US: 4 mo parallel RCT[112]	9.6g/d EPA+DHA (6.2g/d EPA, 3.4g/d DHA) (n=~22)	olive oil ethyl ester pb (n=~22)	Gastrointestinal (mild): 9.6g/d EPA+DHA (fish oil) (n=8), continued (n=8/8); pb (olive oil ethyl ester) (n=8), continued (n=8/8)

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; *No explicit description that adverse events specifically linked to exposure, only that associated with participants in a specific study group; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; grp = group; wk = week(s); mo = month

In Peet et al.'s supplemental treatment study of depression, no adverse events were reported by placebo group participants, whereas 20 of 52 individuals receiving E-EPA had at least one mild adverse event.[53] One patient dropped out due to a gastrointestinal event (severity undefined). According to the authors, all events in the E-EPA groups were linked to the ingestion of an oily subtance, not the omega-3 fatty acids per se. Adverse event types were evenly distributed across the E-EPA groups. The fewest number of events occurred in the 2 g/d E-EPA group. The exact meaning of some of the events was not transparent to our review team, however. Likely using the same methodology, and again failing to adequately define some of their adverse events, Peet et al.'s study of the supplemental treatment of depression revealed that none of the nine patients withdrawn due to an adverse event (4 g/d E-EPA [n=2]; 2 g/d E-EPA [n=2]; 1 g/d E-EPA[(n=4]; placebo [n=1]) left because of the exposure per se.[87] No between-group difference was observed for exposure-related adverse events. The most common events were mild and transient (i.e., diarrhea, nausea), and only one control patient withdrew for these reasons. It is conceivable that greater numbers of adverse event were reported in these two studies because the investigators used a more comprehensive approach to solicit these data.

Summary Table 47: Studies reporting adverse events (e.g., side effects) or contraindications

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Safety data
SCHIZOPHRENIA			
Peet, 2001, England: 3 mo parallel RCT[58]	2g/d EPA enriched fish oil (n=15 completers)	2g/d DHA enriched oil (source undefined) (n=16 completers)/ corn oil pb (n=14 completers)	Study 1: (full sample, n=55) felt ill and forgetful (n=1), dropped out (n=1/1); nausea, irritable bowel, indigestion (n=3), dropped out (n=3/3)
Fenton, 2001, US: 16 wk parallel RCT[89]	3g/d E-EPA (n=45)	mineral oil pb (n=45)	3g/d E-EPA (source undefined): upper respiratory infection (n=8), continued (n=8/8); diarrhea (n=8), continued (n=8/8)
Peet, 2002, England: 12 wk parallel RCT[87]	4g/d E-EPA (n=27)/ liquid paraffin pb (n=31)	2g/d E-EPA (n=32)/ 1g/d E-EPA (n=32)	Body as a whole: 4g/d E-EPA (source undefined) (n=2); 2g/d E-EPA (n=1); 1g/d E-EPA (n=2); placebo (liquid paraffin) (n=6); cardiovascular/heart: 4g/d E-EPA (n=1); 1g/d E-EPA (n=1); pb (n=1); central & peripheral nervous system: 4g/d E-EPA (n=2); 2g/d E-EPA (n=3); pb (n=3); diarrhea: 4g/d E-EPA (n=3); 2g/d E-EPA (n=1); 1g/d E-EPA (n=7); pb (n=7); nausea: 4g/d E-EPA (n=2); 2g/d E-EPA (n=3); 1g/d E-EPA (n=1); liver & biliary tract: 1g/d E-EPA (n=1); metabolic: 4g/d E-EPA (n=3); 2g/d E-EPA (n=1); 1g/d E-EPA (n=1); pb (n=1); musculoskeletal: pb (n=1); psychiatric: 4g/d E-EPA (n=6); 2g/d E-EPA (n=2); 1g/d E-EPA (n=4); reproductive: 4g/d E-EPA (n=2); pb (n=1); infections & respiratory system: 4g/d E-EPA (n=3); 2g/d E-EPA (n=1); 1g/d E-EPA (n=5); pb (n=5); skin: 4g/d E-EPA (n=1); 2g/d E-EPA (n=1); 1g/d E-EPA (n=2); urinary: 1g/d E-EPA (n=2); pb (n=1); vision: 1g/d E-EPA (n=1); pb (n=1); white cells: 4g/d E-EPA (n=1); pb (n=1); other: 4g/d E-EPA (n=3); 2g/d E-EPA (n=1); 1g/d E-EPA (n=2)

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; *No explicit description that adverse events specifically linked to exposure, only that associated with participants in a specific study group; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; grp = group; wk = week(s); mo = month

Stoll et al. indicated that side effects were associated with their omega-3 fatty acid exposure.[112] Their study delivered, by far, the largest dose of omega-3 fatty acids as an intervention (9.6 g/d). Three patients had to decrease their daily dose from seven capsules twice a day to a minumum of five capsules twice a day from seven capsules twice a day. At the same time, while there was no variability in the types of reported adverse event (i.e., gastrointestinal disorder), at least a third of study participants from each study group experienced gastrointestinal problems. This suggests that the omega-3 fatty acid dose and/or the amount of oil required to deliver it may have been too high. While Su et al.'s omega-3 fatty acid dose was high by standards established earlier, their participants described very few adverse events.[96]

Summary Table 48: Studies reporting adverse events (e.g., side effects) or contraindications

Author, Year, Location: Length & Design	Study groups[1] Group 1 (n)/ Group 4 (n)	Group 2 (n)/ Group 3 (n)	Safety data
TENDENCIES OR BEHAVIOR WITH THE POTENTIAL TO HARM OTHERS			
Hamazaki, 1996, Japan: 3 mo parallel RCT[130]	1.5-1.8g/d DHA (+ some EPA) (n=27)	oil capsules (97% soybean oil + 3% fish oil) pb (n=26)	1.5-1.8g/d DHA (fish oil): trend toward obesity (n=1), continued (n=1/1); pb (97% soybean oil + 3% fish oil): acne (n=2), continued (n=2/2); itching (n=1), continued (n=1/1)
Hamazaki, 1998, Japan: 13 wk parallel RCT[129]	1.5g/d DHA (n=29)	oil capsules (97% soybean oil + 3% fish oil) pb (n=30)	Pb (97% soybean oil + 3% fish oil): gastrointestinal disorder (n=1), dropped out (n=1/1)
ATTENTION DEFICIT/HYPERACTIVITY DISORDER			
Richardson, 2002, UK: 12 wk parallel RCT[119]	186 mg/d EPA, 480mg/d DHA, 96mg/d GLA, 864 mg/d *cis*-linolenic acid, 42 mg/d AA & 8mg/d thyme (n=22)	olive oil pb (n=19)	186mg/d EPA & 480mg/d DHA (source undefined): digestive upset (n=1), dropped out (n=1/1); swallowing problems (n=1), dropped out (n=1/1); pb (olive oil): digestive upset (n=1), dropped out (n=1/1)

[1]Proceeding from highest omega-3, or lowest omega-6/omega-3, fatty acid content of intervention/exposure; [2]biomarker source; [3]biomarkers = EPA, DHA, AA, AA/EPA, AA/DHA, AA/EPA+DHA; *No explicit description that adverse events specifically linked to exposure, only that associated with participants in a specific study group; FA = fatty acids; n-3 = omega-3 FAs; n-6 = omega-6 FAs; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; E-EPA = ethyl eicosapentaenoate; Length = intervention length; Design = research design; n = sample size; pts = study participants; NR = not reported; NS = nonsignificant statistical difference; n/a = not applicable; pb = placebo; grp = group; wk = week(s); mo = month

Fenton et al. noted that two types of adverse event occurred among more than 5% of the EPA-treated patients.[89] Marangell et al. identified the largest number of patients describing a fishy aftertaste or problems related to belching.[95] However, these complaints were not associated with studies using E-EPA, a largely purified exposure with relatively minimal odour and taste.[53,87,89]

In Richardson and Puri's trial examining the primary treatment of children identified with AD/HD and learning difficulties, two active treatment group subjects and one placebo group participant left the study due to adverse events. However, the authors did not report on the seriousness of these events.[119] It is likely not surprising that, of the ten studies that reported adverse events, only the study that included children identified problems with swallowing the capsules, which led to a discontinuation.

Ten subjects from each of the two study groups in Hamazaki et al.'s first trial with healthy volunteers complained of transient and minor adverse effects (no data reported).[130] Of the others noted by the investigators (see Summary Table 46), none were sufficiently serious to warrant

discontinuation from the study. In their second RCT, a gastrointestinal difficulty required that a single volunteer withdraw from the control group.[129]

Chapter 4. Discussion

Overview

A total of 86 reports, describing 79 unique studies, investigated questions pertinent to this systematic review of the evidence concerning the effects of omega-3 fatty acids on mental health. Not all of the mental health disorders or conditions included in this review had evidence addressing all of the first three basic questions posed in this review—primary or supplemental treatment with omega-3 fatty acids (Question 1), or the association between the onset, continuation or recurrence of the disorder or condition and either the intake of omega-3 fatty acids (Question 2) or the omega-3 or omega-6/omega-3 fatty acid content of biomarkers (Question 3). Schizophrenia (n=28 studies) and depression (n=22 studies) were, by far, the most frequently investigated psychiatric disorders. Many possible explanations likely exist for why these two disorders have received the most attention, including the prevalence of depression and the presumed intractability of schizophrenia.

Of the collections of studies on schizophrenia and depression, 50% (n=14/28) and 36.4% (n=8/22) examined the possible association of schizophrenia and depression outcomes, respectively, with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers. These two clinical areas (i.e., schizophrenia and depression) have produced an abundance of animal studies, as well as both animal and human models concerning the etiology of these disorders.[55] This may help explain why we found many more human studies examining biomarkers data (Question 3), as well as the possible association between omega-3 intake and clinical outcomes (Question 2), than studies investigating the treatment of these disorders or conditions (Question 1). It is conceivable that the research community has assumed it was necessary to first use biomarkers and epidemiological data to demonstrate the plausibility of treating these clinical entities with omega-3 fatty acids. Only recently have studies been published concerning the primary or supplemental treatment of depression (n=4 RCTs: 2002 or 2003) or schizophrenia (n=5 RCTs: 2001 or 2002), and this may signal a trend towards an increased emphasis on treatment investigations.

While this review was not initiated to test the specific deficiency hypotheses relating to the etiology of depression or schizophrenia, below we have, nonetheless, examined the evidence to address the possible soundness of these positions. The justification for the study of the remaining psychiatric disorders or conditions for which we reviewed evidence ranged from the view that certain types of individual (e.g., bipolar disorder patients) may also suffer from deficiencies in "mood-regulating" omega-3 fatty acids, to little or no justification based on human or animal models or data (e.g., obsessive-compulsive disorder). Nonetheless, a study was included if it met our eligibility criteria.

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

Evidence Synthesis and Appraisal

Only interventional studies employing omega-3 fatty acids as supplementation provided *safety data*. Some interventional studies, which employed various populations, interventions/exposures and followup durations, did not report either having solicited adverse effects data from study participants or having received such reports. Results from these studies suggest that omega-3 fatty acid exposures were, for the most part, well tolerated. In spite of a small number of discontinuations presumed to have been instigated by an adverse event, it is unlikely that moderate or severe side effects were ever observed in relation to an omega-3 fatty acid exposure. Occasionally, adverse events were linked to the intake of oily substances, rather than to the omega-3 fatty acid contents in the oils.

Reported difficulties tended to be mild and transient, often involving gastrointestinal upset or nausea. Aside from the minor adverse effects associated with Stoll et al.'s very high dose of omega-3 fatty acids (i.e., 3 patients had to decrease the number of capsules swallowed per day, yet with none required to discontinue),[112] no other discernible patterns were seen regarding the impact of dose, type (e.g., DHA vs EPA) or source (e.g., marine, plant, nut) of omega-3 fatty acids on safety. In the study by Richardson and Puri, one AD/HD child in the active treatment group had to leave the study due to problems swallowing the capsules.[119] Few of the events described in two trials by Hamazaki et al., which enrolled healthy volunteers, suggested that the adverse effects had been directly related to the exposure.[129,130] The ability of purified forms of EPA (i.e., E-EPA) to maintain blinding, due in large part to the oil's minimal fishy taste and odor, could not be evaluated because there were too few studies with which to construct meaningful comparisons.

Four RCTs addressed the questions concerning the *primary or supplemental treatment of depression*. One addressed primary treatment,[95] whereas three investigated supplemental treatment.[53,96,97] Marangell et al. found no benefit related to 2 g/d DHA employed as primary treatment despite an increase in the absolute RBC levels of DHA in the active treatment group.[95] Reasons for this null result could include the use of too small a dose, too short an intervention period, the "wrong" omega-3 fatty acid, broken blinding (i.e., unidentified by group, 14 patients experienced a fishy aftertaste) or failure to modify background omega-6 fatty acid intake at the same time. Clearly, more than a single, likely underpowered trial of low quality (i.e., internal validity) and undetermined applicability is required to ascertain the value of omega-3 supplementation as primary treatment for depression. Data from two of the supplemental treatment studies that included a few patients who were not receiving medication could not be used to address the question concerning primary treatment because the study reports did not provide these individuals' results separately.[96,97]

Peet et al.'s dose-ranging study of E-EPA as supplemental treatment for depression found that only 1 g/d for 12 weeks had a significant impact on various clinical outcomes.[53] Two trials of shorter duration also showed significant benefits associated with 2 g/d E-EPA and 6.6 g/d of EPA+DHA, respectively;[96,97] the significant clinical effect reported by Su et al. was associated with a significant increase in RBC EPA exclusively in the active treatment group.[96] However, it was decided to forego meta-analysis due to: variations in dose both within and between studies; variation in the definition of the omega-3 fatty acid interventions; different followup lengths; and, the use of different sources of placebo material. In addition, unlike the other two supplemental treatment trials, Peet et al.'s did not formally identify patients with a depressive

disorder.[53] This last observation may account for Peet et al.'s finding that 1 g/d E-EPA had a beneficial effect on depressive symptomatology.[53] It is conceivable that this low dose would not have helped the treatment-resistent depressive disorders investigated in the other trials. Yet, this likely cannot explain why Peet et al.'s higher doses (2 g/d, 4 g/d) did not likewise ameliorate depressive symptoms, or why more responders (i.e., 50% improvement) were found in the placebo group than in the 2 g/d E-EPA group. It is possible that the study by Su et al. was confounded by uncontrolled combinations of medication.[96]

There were too few included studies to reliably ascertain the impact of extra-interventional variables with the potential to influence clinical results, or the possible covariation of clinical and biomarker effects. Overall, in spite of the sound internal validity of the three included trials, this study collection is too small to permit us to determine whether omega-3 fatty acid supplementation is efficacious as a supplemental treatment for depressive disorders or symptomatology. Moreover, the three studies exhibited weak applicability to even a predominantly female North American population. Yet, these preliminary findings suggest there may be promise in pursuing investigations into the use of omega-3 fatty acids as a supplemental treatment for depression.

All 12 of the studies addressing the question concerning the possible *association between depression outcomes and omega-3 fatty acid intake* could be construed as focusing on whether (foods containing) omega-3 fatty acids might protect against the onset of depressive disorders or symptomatology. No study investigated subquestions relating omega-3 fatty acid intake to either the continuation or recurrence of depressive disorders or symptoms.

The types of research design providing evidence relating to onset varied in terms of their inherent ability to meaningfully investigate this question. Best suited to address this question were three controlled prospective studies; yet, these constituted a minority. Of these three RCTs,[98-100] the study by Wardle et al. merely assessed the impact of diets without distinguishing the exact nature of the role played by oil fish intake within the Mediterranean diet;[99] and, the data generated by Ness et al. confirmed the assumption that advice to eat fish will not guarantee the compliance of study participants.[100] Thus, the results of both "intervention" studies could not meaningfully shed light on the question of onset.[100] The RCT of Llorente et al. examined the use of supplementation to prevent postpartum depression. While well-designed, the study included a narrowly defined population (i.e., breastfeeding women) and did not reveal a significant clinical benefit related to omega-3 fatty acid intake, despite a significant increase in plasma phospholipid DHA. Moreover, most of the women in Llorente et al.'s trial exhibited, at worst, minimal depressive symptomatology. Therefore, in spite of their RCT designs, these three studies did not constitute the best tests of the possibility that omega-3 fatty acids might protect against the onset of depressive disorders or symptomatology.

The observational studies did not contribute much to resolving the question of onset, despite their somewhat consistent picture of a lack of association. The reason is that their designs also did not constitute the best tests of omega-3 fatty acids' protective potential. The 36-month single prospective (uncontrolled) cohort study by Woo et al. found no significant, adjusted association between fish intake and depressive symptoms in an elderly Chinese population.[110] Hakkarainen et al.'s prospective cohort study observed no significant, adjusted association between fish consumption or (calculated) omega-3 fatty acid intake and indices of depression.[111] Edwards et al.'s multiple-group cross-sectional study revealed that none of the dietary omega-3 or omega-6 fatty acid variables were significant predictors of depressive symptomatology.[48] Two single population cross-sectional surveys completed by Tanskanen and colleagues in Finland each

described a significant association between the frequency of fish consumption and depressive symptomatology in females,[81] and in both males and females.[80] It is unclear why the first significant association was observed only for females.[81] Tanskanen et al. employed a single question to assess the exposure, and perhaps a food frequency questionnaire would have been better.[81] Suzuki et al.'s single population cross-sectional survey revealed a nonsignificant association between depression and the intake of fish or seafood despite observations that ALA and total omega-3 fatty acid intake were inversely related to the likelihood of depressive symptomatology.[107]

In cross-sectional designs, the absence of a meaningful temporal separation between the measurement(s) of the exposure (e.g., intake of fish or specific omega-3 fatty acids) and the clinical outcome (e.g., onset of depression) prevents the possible observation of cause and effect, which thereby precludes drawing causal inferences concerning the impact of the exposure on the (likelihood of the) clinical outcome. Cross-sectional surveys are also limited by recall bias. At the same time, five of the six observational studies exhibited the weakest applicability to a North American population.[80,81,107,110,111] Each study took place either in Finland or Asia, where dietary fish intake is considerably higher than it is in North America. It is likely that greater fish intake yields a lower omega-6/omega-3 fatty acid intake ratio in the background diet.

The most consistent picture of an inverse relationship between the exposure and clinical outcomes was observed in the type of study providing the weakest evidence: cross-national ecological analyses.[47,108,109] These provide possible evidence of the covariation of exposure (e.g., apparent national seafood consumption) and outcome (e.g., prevalence of depression) from often large samples of data derived invariably from non-overlapping sources, that is, where a given sample of individuals does not provide both exposure and outcome data. Thus, individual- or patient-level inferences cannot be drawn. Exposure data are at best crude indices of intake, failing to reflect the dietary practices of individuals or even population subgroups;[109] and, these types of study are readily confounded by cultural, economic, social and other factors.[47] An additional barrier to drawing conclusions based on these findings is that their cross-national focus precludes generalization to the North American population of subjects who may be at risk of developing depressive disorders or symptomatology.

Taken together, the inconsistent results, as well as the limitations of both the inherently stronger (i.e., prospective controlled studies) and weaker designs having produced them, suggest that there is currently insufficient evidence to decide whether or not omega-3 fatty acid intake can protect individuals—with or without known predispositions—from developing either depressive disorders or symptomatology. The observation that the risk of depressive symptomatology is inversely related to fish/seafood consumption or omega-3 fatty acid intake was less likely to be produced by research designs that more appropriately permit the drawing of causal inferences regarding the etiologic role of exposure to omega-3 fatty acids in the development of depressive disorders or symptoms. Studies that are prospective, controlled and focused on subject-level data were less likely to demonstrate evidence for a significant protective relationship. Having identified too few of these stronger study designs also made it inappropriate to conduct a quantitative synthesis and impossible to comprehensively assess the possible influence, on clinical outcomes, of extra-exposure variables (i.e., covariates, confounders). As well, too few studies produced results that could be meaningfully extrapolated to North Americans.

Eight controlled studies were identified that had the potential to address Question 3 concerning the possible *association between biomarkers data and the onset of depressive*

disorders or symptomatology.[48,98,101-106] However, only one study was prospective by design.[98] The other seven were multiple-group cross-sectional designs. Therefore, it was impossible to draw causal inferences concerning the onset of depression from the results of the seven weaker designs, or to consider meta-analysis. With respect to the multiple-group cross-sectional studies, we focused solely on comparisons between groups of patient diagnosed with depression and controls, with the latter typically identified as "healthy" and sometimes matched by age and sex. For each study, this contrast established the sharpest differentiation possible between study groups, even though only a few of the study reports described the methods by which they had formally ruled out the presence or risk of depressive disorders or symptomatology in their control subjects. Results are described as they appeared in the literature, with the data from the strongest design (i.e., RCT)[98] providing, at best, a very limited answer to the research question.

The two earliest publications included in the review—one by Ellis and Sanders[105] and the other by Fehily et al.[106]—revealed a pattern of findings that has since been disconfirmed. Each study reported that plasma CPG EPA and DHA levels were higher in those with a diagnosis of endogenous depression than in healthy controls. They also noted that similar between-group differences in RBC CPG levels of EPA, DHA and AA existed although they were less pronounced (no data reported). These results would disconfirm the omega-3 fatty acid deficiency hypothesis introduced in Chapter 1. However, unlike virtually all subsequent studies, their "endogenously depressed" populations exhibited substantial diagnostic heterogeneity to the extent that it would likely be impossible to find the appropriate populations to which the results of these two studies might be meaningfully generalized.

Arguably the two best controlled cross-sectional studies were conducted by Maes and colleagues in Belgium.[101,103] A priori they excluded many potential confounders (e.g., background diet, alcohol use, heavy smoking, medications at assessment, comorbid conditions) in addition to matching for age and sex. Also, like few other other studies,[104] they explicitly described having excluded from the control group, those subjects with notable psychopathology. Maes et al.'s results are thus likely more reliable, but not solely because they were less prone to confounding. They also employed formal research diagnostic criteria. To draw one comparison, Fehily et al.[106] combined data from unipolar, bipolar and adjustment disorder subjects, whereas Maes et al. excluded subjects with bipolar diagnoses and distinguished between subjects with minor and major depression. Peet et al.'s study was less tightly-controlled experimentally yet they also attempted to rule out psychopathology in controls while noting the absence of significant between-group differences for smoker status.[102] Most studies did not control for the likely confounding effects of stress, smoker status or diet.[177] Both studies by Maes et al., as well as the study by Tiemeier et al., admitted patients to hospital to establish a highly controlled environment.[101,103,104]

Maes et al.'s first set of results indicated that levels of ALA, total omega-3 fatty acids and EPA in serum cholesteryl esters, as well as EPA in serum phospholipids, were significantly lower in major depressed patients compared with healthy volunteers.[103] As well, AA/EPA in both cholesteryl esters and phospholipids were significantly higher in the major depressed patient group compared with controls. ALA, EPA and DHA levels collectively discriminated between these two study groups as well as distinguished minor depressed individuals.

Peet et al.[102] reported that the picture of depleted omega-3 fatty acids in serum cholesteryl esters described by Maes et al.[103] was observed in the RBC total omega-3 fatty acids and DHA of drug-free patients compared with healthy controls.[102] Yet, Peet et al. pointed out that the difference in the number of current smokers across their two study groups (i.e., compared with

controls, all but two depressed patients were nonsmokers) constituted a possible source of confounding.[102] They also acknowledged that there may have been prestudy medication in cell membranes, which likewise may have confounded study outcomes. Nevertheless, Edwards et al. reported similar findings of significantly lower RBC total omega-3 fatty acids, DHA and EPA in medicated depressed patients compared with matched healthy controls.[48] Controlling for stress and smoker status had no effect on RBC values in Edwards et al.'s study.[48]

Maes et al.'s second study revealed significantly lower fractions of EPA, DHA, AA and total omega-3 fatty acids in the serum phospholipids of major depressed patients compared with healthy volunteers.[101] As in their first study, they also reported higher AA/EPA fractions in the patient group.[101] Significantly lower fractions and concentrations of ALA, EPA and total omega-3 fatty acids were observed in the serum cholesteryl esters of these patients.[101] Significantly higher AA/EPA and total omega-6/omega-3 fractions were observed in the patient group as well.[101] Tiemeier et al. found that percentages of AA, AA/DHA and total omega-6/omega-3 in plasma phospholipids were significantly higher in depressed patients compared with controls.[104] The percentage of DHA was lower in the depressed patient group.

Correlational data showed significant negative relationships between: HDRS scores and EPA in serum cholesteryl esters[103] or other PUFAs;[101] BDI scores and RBC ALA, DHA and total omega-3 fatty acids, although multiple regression revealed that only ALA levels predicted BDI scores;[48] and, between plasma phospholipid DHA and results on the BDI, EPDS or SCID.[98] These last findings were obtained from Llorente et al.'s RCT.[98] Significant positive relationships defined HDRS scores and both AA/EPA and total omega-6/omega-3 fatty acid levels in the plasma phospholipids of major depressed patients.[103]

Collectively, the between-group differences suggest a possible balance of PUFAs such that significantly decreased levels of omega-3 fatty acid content coexist with increases in some omega-6 fatty acid levels and in some omega-6/omega-3 fatty acid ratios. Medication status did not appear to modify this picture.[101] For example, EFA levels were not affected in those of Edwards et al.'s patients who had antidepressants added prior to a second assessment of their EFA status.[48] Peet et al. reported that, after six weeks of treatment with antidepressants in ten depressed patients, PUFA levels did not change significantly (no data reported).[102]

However, these results were obtained from cross-sectional studies from which causal inferences relating to onset cannot be drawn. Selection bias can also influence study outcomes in these designs. In addition, PUFA status in studies of mental health is likely determined by multiple factors, suggesting that any between-group differences in PUFA content observed in this review may not simply reflect the disease process itself. Other influences include: age; sex; the dietary intake, metabolism and incorporation into cell membranes of various types and amounts of both omega-3 and omega-6 fatty acid content (given their competitive relationship with respect to enzymes, for example); the disease process underlying any possible comorbid conditions; the efficiency of the PUFA metabolic processes, including the availability and effectiveness of enzymes implicated in the processes of desaturation and elongation; the long-lasting effects of psychotropic medication (e.g., mood stabilizers, antipsychotics) on cell membranes; and the ability of protective mechanisms to deal with degradation from oxidation and other sources (e.g., smoking, alcohol consumption).[48,101-103,178-180]

Differences in RBC PUFA content can be attributed to the mechanisms of action of mood stabilizers (i.e., postsynaptic signal transduction processes) or the abnormal psychoimmunology of patients with bipolar disorder.[113] Mood stabilizers can reduce the AA turnover rate;[181] and, smoking has been observed to deplete PUFAs from cell membranes (e.g., DHA, [omega-3-

]DPA, omega-6 fattty acid series).[182] Given that these variables have been highlighted as influences on EFA status requires that they be controlled for experimentally or statistically in studies assessing the possible association between the fatty acid content of biomarkers and clinical outcomes (e.g., onset of depression).

Thus, with only cross-sectional evidence available to address the question of onset there exists the need for more appropriate tests of the deficiency hypothesis. Ideally, these would employ controlled prospective study designs. The available results, at best, suggest the possible definition of the EFA profile that future research might identify as being responsible for the development of depression. Until then we can only speculate that "it is more likely that changes in fatty acid intake in the population influence depression prevalence than vice versa."[53] The possible role played by omega-3 fatty acid intake or the omega-3 or omega-6/omega-3 fatty acid content of biomarkers in the continuation or recurrence of depression could not be assessed given no studies with these foci were identified. Whether PUFAs' influence on mental health also entails, for example, the activation of the inflammatory response system, including the production of eicosanoids, remains to be determined.

Only Question 2 could be addressed with respect to *suicidal ideation or behavior*. Hakkarainen et al. reported no significant associations between either intake of fatty acids or fish consumption and successful suicides.[111] Tanskanen et al. noted that the adjusted risk of suicidal ideation decreased significantly in frequent fish consumers.[80] The evidence base is thus too small, and the designs less than optimal, to permit us to conclude anything with respect to the possible association between omega-3 fatty acid intake and the onset of suicidal ideation or behavior. Their applicability is limited by the fact that both studies were conducted in Finland.

Two controlled studies investigated the *supplemental treatment of bipolar disorder* with omega-3 fatty acid supplementation,[93,112] although only one report gave us an opportunity to systematically assess its study parameters and results. While the Stoll et al. trial had to be stopped prematurely, their very high dose of 9.6 g/d EPA+DHA produced a significantly longer period of remission in the active treatment group compared with controls.[112] Medication status did not alter this finding. Rating scale results, including depressive symptomatology, showed greater improvement in the omega-3 fatty acid intervention group compared with controls. While these pilot observations appear to be promising, there was also evidence that the blind had been broken. Almost 90% of active treatment patients correctly guessed that they had received fish oil capsules, with data from patients indicating that both the clinical response and a fishy aftertaste contributed to their deduction. For the sake of both its promising findings regarding the impact on a subacute course of bipolar disorder, and its limitations (i.e., its loss of power because of its stoppage; broken blind), this study requires replication. It might also be useful to use a lower dose even though the present one did not produce even moderately severe side effects. A lower dose might also better control the fishy aftertaste. At present, the evidence base is too limited to definitively conclude anything about the potential of omega-3 fatty acids as supplemental therapy for bipolar disorder.

The same must be said with respect to the *capacity of omega-3 fatty acids to prevent the onset of bipolar disorder* (Question 2). Evidence suggesting the possibility that seafood consumption plays a protective role was identified by a single, cross-national ecological analysis.[90] Yet, while the investigators employed stratifications for both age and sex, they did not control for socioeconomic status, urban/rural ratio, educational level, marital status, alcohol consumption, smoker status or family history. These are likely significant omissions given that these risk factors can predict the onset of bipolar illness.[90] The authors also recognized that these

data cannot shed light on whether the lifetime risk for bipolar disorder was affected by low seafood consumption in adulthood and/or by nutritional insufficiency in early neurological development.[90] Nutrient deficiencies during the second and third trimester of pregnancy can increase the risk of developmental affective disorders in children.[183] Noaghiul and Hibbeln's results,[90] while parallelling observations obtained from the above-noted cross-national ecological analyses regarding depression, likewise exhibit limited applicability to individuals/patients and to the North American population.

The results from two multiple-group cross-sectional studies did not agree on *whether a diagnosis of bipolar disorder was associated with a specific biomarker profile* when compared with data from controls (Question 3). This divergence may be attributable to the fact that the two studies obtained their PUFA samples from different biomarker sources. Chiu et al. noted significant between-group differences in AA and DHA from RBC membranes.[113] Adding medication did not appreciably change the EFA levels in Chiu et al.'s bipolar patients. They did, however, fail to control for diet. Mahadik et al. assessed AA and DHA compositions of cultured skin fibroblasts, finding no significant between-group differences for small numbers of bipolar patient and controls.[114] Although Mahadik et al. controlled for dietary intake as one key influence on RBC and brain PUFA levels,[114] PUFA levels from skin fibroblasts may not reflect brain PUFA levels.[113] Moreover, the clinical status of their patients (i.e., duration of illness, mood state [mania, depression, mixed], symptom severity) was poorly defined and controlled for; and, no data were reported indicating patterns of mood stabilizer or antipsychotic medication use, which have been found to influence PUFA levels (see above). The studies were conducted in countries varying in terms of their background diet, and likely their omega-6/omega-3 fatty acid content intake ratio, and this factor may have also influenced the results. In any event, the fact that both efforts employed cross-sectional designs precludes deriving casual inferences regarding the onset of bipolar disorder.

Two RCTs yielded data investigating the possible *protective influence* (Question 2) *of omega-3 fatty acid intake and the onset of symptoms but not disorders of anxiety*.[99,100] Both the Wardle et al. and Ness et al. studies failed to find a significant association. As noted with regards to the subject of depression, neither RCT constituted an appropriate assessment of this question.

Fux et al.'s results indicated that E-EPA was ineffective as a *supplemental treatment for obsessive-compulsive disorder*.[115] However, nothing definitive can be concluded from a single, underpowered crossover study, which failed to describe a washout period.

Two cross-sectional studies investigating the possible *association between the onset of anorexia nervosa and the fatty acid content of biomarkers* analyzed plasma phospholipid data.[116,117] Their observations concurred that both ALA and total omega-6 fatty acid levels were significantly lower in anorexic patients than in controls. However, their findings differed in that Holman et al.[116] noted a similar reduction in DHA in anorexic patients while Langan and Farrell found that DHA levels were significantly reduced in controls.[117] Holman et al.[116] noted a significantly lower level of EPA in patients, and Langan and Farrell[117] reported a reduction of LA in these patients compared with controls. Only Holman et al. evaluated the contents of plasma cholesteryl esters, with respect to which they observed no significant between-group differences. However, in plasma triglyceride fractions they did find significantly reduced total omega-3 fatty acid content in their patients. Irrespective of these results, these small studies utilized a design preventing the drawing of causal inferences regarding etiology.

Notwithstanding the noncomparability of interventions, comparators and populations (i.e., with[118,120,121] or without a formal diagnosis of AD/HD;[119] with[120] or without significant comorbidity[119,121]), the results of the three RCTs[118-120] and the comparative before-after study[121] addressing the question about the *primary treatment of AD/HD* were inconsistent at best. They did not show uniform improvement in clinical outcomes, and in some cases, significant improvements were observed only for control children.[120] The studies by Hirayama et al.[120] and Harding et al.[121] failed to report any significant between-group clinical differences. These are the only two studies which clearly distinguished omega-3 fatty acids as the "intervention." Moreover, Harding et al.'s results are likely unreliable given the selection bias that results from having parents chose which intervention their child will receive.

Each of the two studies exhibiting a few significant clinical effects had used a "cocktail," which included much more than omega-3 fatty acids; and the nature of the synergies involving the components comprising the respective "cocktails" was not evaluated.[118,119] In one of these two studies, the research design did not allow the researchers to tease out the possible specific benefit of omega-3 fatty acids.[119] None of the studies employing DSM-IV to identify AD/HD actually distinguished their populations by AD/HD subtype (e.g., Inattentive vs Hyperactive/Impulsive vs Combined), which is an important source of clinical heterogeneity. The different subtypes entail dissimilar clinical pictures given the various clusters of symptom or behavior required to identify their presence.[13]

With respect to the *supplemental treatment of AD/HD*, Voigt et al. observed only nonsignificant between-group clinical differences.[122] These observations were associated with increased plasma phospholipid DHA levels observed exclusively in the DHA study group. Stevens et al. found almost no evidence of clinical benefit for their "cocktail" exposure compared with a very high dose of olive oil as placebo.[123] This was accompanied by observations of no significant between-group differences for fatty acid content in plasma phospholipids. Participants in the Stevens et al. trial were also entered into the study based merely on parental, not professional, confirmation of an AD/HD diagnosis. The clinical features of AD/HD can exist as isolated clusters of symptom insufficient to merit a formal diagnosis of AD/HD and so, there is no guarantee that all children would have received a DSM-IV diagnosis of AD/HD. Brue et al. reported a benefit for problems of inattentiveness yet not for hyperactivity and impulsivity.[118]

Overall, these supplemental treatment RCTs may have employed intervention lengths that were too short. Primary treatment trials lasted longer. It is also conceivable that weight-adjusting doses of omega-3 fatty acids would have produced a different picture of the efficacy of these primary or supplemental interventions, although all elements of the sometimes complex interventions would likely have required similar adjustments.[118,119,123]

While the results of the supplemental treatment studies are more uniformly generalizable to the North American population than those generated by primary treatment studies of AD/HD, there were too few studies whereby the specific effects of omega-3 fatty acids could be isolated, thereby preventing us from concluding one way or the other about the specific efficacy of omega-3 fatty acids as a primary or supplemental treatment.[118,119,123] The only consistent observation is that, contrary to the situation in the trials of depression, where the majority of subjects were female, most of the participants in the two collections of AD/HD study were male. This is not surprising given what has often been observed in clinical practice.

Yang et al.'s multiple-group cross-sectional design was not concerned with trying to establish a link between omega-3 fatty acid intake and the onset of AD/HD.[94] At best, the results

from this study might hint at the possible conditions maintaining AD/HD, although controlled prospective designs are required to determine causality. Nevertheless, Yang et al. found that, relative to healthy controls, AD/HD children consumed significantly lesser amounts of LA and ALA. These observations, while requiring replication, could be suggestive if it turns out that lower LA and ALA content in biomarkers also distinguishes those individuals with AD/HD and healthy controls.

In their first study Mitchell et al. failed to observe any univariate between-group differences for RBC fatty acid content, although multivariate analysis revealed that levels of ALA and AA, along with a few other fatty acids, distinguished hyperactive and control children.[126] Stevens et al. also found significantly lower AA levels in hyperactive boys.[124] In their second study, Mitchell et al. reported that levels of DHA, AA and DGLA in serum phospholipids were significantly reduced in formally diagnosed hyperactive children.[125] Stevens et al. also found significantly reduced AA, EPA, DHA and total omega-3 fatty acids in the plasma phospholipids of hyperactive boys.[124] However, Stevens et al.'s study did not confirm this observation.[124] They noted higher PUFA intake in the diet of hyperactive boys. More work is needed to resolve this divergence of findings.

Only the second Mitchell et al. study employed formal diagnostic criteria (i.e., DSM-III) to identify their hyperactive subjects.[125] However, none of these biomarker studies formally ruled out the presence of psychopathology in the control subjects. The use of cross-sectional designs by so few studies necessitates additional empirical work.

Based on a single observational study, which controlled for age, income, smoking, alcohol consumption and eating patterns, *mental health status* was observed to be lower in those consuming no fish.[127] However, this cross-sectional design precludes inferring that the onset of mental health diffulties is *related to fish consumption*.

Seven studies, including three RCTs enrolling healthy volunteers, investigated the *relationship between omega-3 fatty acid intake and tendencies or behaviors with the potential to harm others*. All but Gesch et al.'s study were designed to address the relationship of intake and the onset of these tendencies or behaviors.[131] Gesch et al.'s trial investigated the possibility of using an exposure to prevent the recurrence of antisocial behavior (i.e., secondary prevention). It is difficult to discern any reliable, significant patterns, or lack thereof, across the various outcomes, populations and designs, however.

Hamazaki et al.'s work with university students showed that, when a stressor was applied, DHA supplementation provided some protection against aggression directed at the external world;[130] however, a subsequent study, involving no stressor component, showed that control oil capsules had a similar beneficial impact on aggression in control subjects.[129] The first observation was associated with no between-group differences for DHA, EPA or AA content in serum phospholipds. The behavioral finding in their second study, in favor of the control subjects, was coupled with significant increases in RBC EPA and DHA content in the DHA group, and a significant increase in RBC LA content in the control group. For Hamazaki et al.'s elderly Thai population, some benefit related to the prevention of extraaggression was observed for university employees yet not for villagers.[128] Appropriate between-group analyses of RBC content data were not performed. No reliable patterns relating clinical and biomarker effects could be discerned across Hamazaki et al.'s trials.

Enrolling very different populations, yet focused on trying to see if omega-3 fatty acid exposures prevent the onset of tendencies or behavior with the potential to harm others, Wardle et al.'s RCT observed no significant benefits for anger/hostility associated with special diets,[99]

Iribarren et al.'s cross-sectional survey found that high intake of DHA and the consumption of fish rich in omega-3 fatty acids may be related to a lesser likelihood of high levels of hostility in young adults,[132] and Hibbeln's cross-national ecological analysis revealed that lower apparent seafood consumption was associated with higher rates of death due to homicide.[133] Gesch et al.'s "cocktail" supplementation provided young adult prisoners with some (secondary) protection against committing new offences.[131]

Overall, these findings are sufficiently inconsistent and involve too few research designs permitting the drawing of causal inferences (i.e., cross-sectional survey,[132] cross-national ecological analysis[133]) and too many different definitions of the exposure, population and outcome[99,128-133] for us to be able to derive an individual/patient-level conclusion regarding the protective benefits of omega-3 fatty acid intake when it comes to tendencies or behavior with the potential to harm others. Moreover, as a whole, the generalizability of their findings to North Americans is limited.

Very few significant between-group differences were observed in the three included studies addressing the *biomarkers question with respect to the onset of tendencies or behavior with the potential to harm others*;[134-136] and, given the differences in the investigated populations, generalizations cannot be made. That said, Hibbeln et al. reported no significant between-group differences for PUFA content when violent and non-violent subjects were compared.[134] The only observation identified in more than one study entailed lower DHA levels in the plasma phospholipids of patients with antisocial personality compared with healthy controls,[135] and in the plasma phospholipids of aggressive cocaine addicts compared with nonaggressive cocaine addicts.[136] However, only the Hibbeln et al. study did not include a small number of participants.[134] The exclusive use of cross-sectional designs precludes drawing any inferences regarding etiology.

The conflicting results regarding reduced *PUFA content in alcoholic patients* reported by Alling et al.[138] and Hibbeln et al.[137] may not simply be attributable to the different biomarker sources that were investigated. The lower levels of LA, DHA, DGLA and AA found by Alling et al.[137] in male chronic alcoholics, compared with healthy male controls, could have been caused by the consumption of alcohol itself.[60] Yet, the fact that Hibbeln et al.'s abstinent alcoholics exhibited higher PUFA concentrations, while also having smoked many more cigarettes per annum than did healthy controls, is not easily explained. Whatever the correct explanation, findings linked to cross-sectional designs again preclude drawing any inferences regarding the etiology of alcoholism.

Zanarini et al.'s RCT examined E-EPA as a *primary treatment for borderline personality disorder* and found that there were significant clinical effects over the course of the study, as the E-EPA group had, at study end, significantly lower mean scores on both the MADRS and MOAS compared with the placebo group.[139] Notwithstanding its strong applicability to the North American population, this was a small study requiring replication.

While the results of the Peet et al. trial[58] indicated placebo-controlled benefits accruing to omega-3 fatty acid supplementation as *primary treatment for schizophrenia*, this was a small and methodologically adequate pilot trial with little applicability to the North American population. More work is required before we can decide anything about omega-3 fatty acids' promise in this context. Considerably more can be said about their role as supplemental treatment for schizophrenia.

Four recently published RCTs, exhibiting sound internal validity, examined omega-3 fatty acids as *supplemental treatment for schizophrenia*.[58,87,89,140] Three of them reported significant

clinical effects in favor of EPA using total PANSS scores,[58,87,140] although Peet et al.'s study observed this effect only for those receiving clozapine as primary treatment.[87] Emsley et al.'s RCT also found that the reduction in PANSS total scores associated with E-EPA supplementation was greater in patients taking conventional antipsychotic medications when compared with those taking clozapine.[140] EPA did not significantly ameliorate negative (PANSS) symptoms in any study, and improvements were rarely seen for positive (PANSS) symptoms.[58] General psychopathology (PANSS) scores were seldom improved significantly (i.e., by E-EPA[140]). In Emsley et al.'s trial, tardive dyskinesia was ameliorated using 3g/d E-EPA.[140] The only study employing DHA as an intervention showed nonsignificant benefits when compared with placebo or EPA.[58]

Results of our meta-analysis of PANSS total data revealed that dose influenced outcome. A significant placebo-controlled effect was identified for 2g/d EPA yet not for doses of at least 3g/d EPA. However, the significant result demonstrated somewhat limited applicability to the North American population although the inclusion of two UK studies meant that the potentially confounding influence of background diet was controlled for. While these findings are suggestive, they are not definitive given that the results subjected to meta-analysis were derived from a small number of trials involving a small number of patients with schizophrenia. Moreover, the effect might have been more pronounced had the data entered into meta-analysis come exclusively from patients taking clozapine as primary treatment. Peet et al. did not distinguish their results by type of primary treatment,[58] and we did not enter data exclusively from patients receiving clozapine in Peet et al.'s second trial.[87]

Peet et al.'s patients who received clozapine were typically switched to this medication because existing pharmacotherapies had failed.[87] This suggests that these patients, for whom a placebo effect was far less likely than for patients receiving other antipsychotic medication, were more impaired than those patients receiving the other pharmacotherapies. Moreover, patients taking clozapine were at best partial responders to this agent given that they still exhibited PANSS total scores of at least 50 at the start of the RCT. Thus, patients on clozapine likely exhibited more "room for improvement" than did patients receiving the other drugs. That said, the positive response to E-EPA in this exploratory trial is quite interesting, and suggests the need to replicate this finding in an adequately-powered trial, which at minimum would need to enrol patients stratified by type of antipsychotic medication. Yet, the Emsley et al. study found a nonsignificant trend towards greater reduction in total PANSS scores in participants taking typical antipsychotic medication, compared with those receiving clozapine.[140]

The overall outcome—a significant impact of low-dose EPA and a nonsignificant effect of high-dose EPA—may have been different if both of Peet et al.'s studies had used E-EPA. Compared with unpurified EPA,[58] E-EPA's processing minimizes its odour and flavor,[87] and this, in turn, should better preserve blinding. Another possible influence on the results relates to Peet et al.'s use of "uncontrolled dosing," which involved pourable oils.[58] That is, the exposure was not delivered via capsules containing controllable amounts of exposure, but rather via prescribed amounts of oil poured from bottles onto or into foods on a daily basis. Uncontrolled dosing might have produced variability both in the daily and the full study intake of omega-3 fatty acids in the active treatment group and/or in the daily and the full study intake of corn oil in the placebo group. This could lead to confounding stemming from changes in the planned, constant between-group difference in omega-3 fatty acid intake and in the planned, constant between-group equivalence for energy/caloric intake. Controlled dosing likely would have substantially improved the experimental control in Peet et al.'s RCT.[58] Other potential

influences on study results were the short intervention periods, small sample sizes and the use of different placebo sources (i.e., liquid paraffin[87] vs corn oil[58]). More evidence is required to replicate these findings.

Having more studies to systematically review might eventually facilitate comprehensive assessments of the possible role of key covariates or confounders (e.g., current smoker status). Biomarker data were not meta-analyzed given the exploratory purpose underlying the inclusion of these observations from treatment studies. Baseline RBC EPA level predicted clinical improvement in response to EPA supplementation, for example.[58]

A completed Cochrane review of PUFA supplementation for schizophrenia did not conduct meta-analysis in the way that we undertook ours, despite the fact that they identified the same placebo-controlled trials investigating the impact of omega-3 fatty acids.[61] They did not evaluate the impact of dose on total PANSS scores in the same fashion; and, they combined data obtained from patients in placebo-controlled RCTs investigating omega-3 fatty acid supplementation as either primary or supplemental treatment. In our view, their approach compromised the meaningful interpretation of their observed effect in favor of omega-3 fatty acids even though this finding parallels what we observed exclusively with respect to a 2g/d dose of omega-3 fatty acids. No other completed systematic reviews investigating the benefits of omega-3 fatty acids in mental health were identified by our review.

As an aside, uncontrolled studies of the effect of omega-3 fatty acid supplementation have shown that 10 g/d of concentrated fish oil (MaxEPA®), including 1.7 g/d EPA and 1.1 g/d DHA, over 6 weeks improved schizophrenic symptoms and tardive dyskinesia in schizophrenic patients (n=20) taking their regular antipyschotic medication.[91] However, Rudin et al. failed to identify a clinical benefit when linseed oil was given as a source of ALA (50% ALA) to a handful of patients with schizophrenia (n=5).[184]

Research designs, which because of their prospective and controlled nature, are most appropriate for addressing the question of the possible *intake of omega-3 fatty acids and the onset of schizophrenia* were not found. Thus, there is little that can be said with confidence with regards to this subject. The only prospective study was not controlled, and its followup was very short.[91] This, along with the observation that the diagnosis of schizophrenia had already been assigned in this study, indicates that its attempt to correlate dietary intake data with schizophrenia symptom scores could not be used to illumine the question of etiology. As well, data indicating a significant inverse association of EPA intake over 1 week with total psychopathology, or a similar, inverse relationship involving both ALA and total omega-3 fatty acid intake with positive symptom scores, do not allow us to respond meaningfully to the question of the exposure's possible impact on the disorder's continuation.[91]

The results from five case-control studies do not permit us to conclude that there is a reliable association between omega-3 fatty acid intake and the onset, course or outcome of schizophrenia. While Peet et al. noted that schizophrenic patients were significantly less likely to have been breastfed,[92] findings from three other studies did not support this observation;[142-144] and, Amore et al.'s only statistically significant association indicated that the longer infants were breastfed, the later was the onset of schizophrenia.[141]

Differences in national or regional feeding patterns might account for differences among studies. At the same time, Sasaki et al. did not adjust or match for key confounders such as sex, maternal age or socioeconomic status.[144] McCreadie[143]did not have access to stratified sampling data whereas Leask et al. did,[142] perhaps leading to differences in observed patterns of breastfeeding. Moreover, less bias may have been associated with Leask's study[142] since their

cases and controls came from the same population at risk, with equal baseline risk of inclusion. Another factor potentially distinguishing the Leask et al. and McCreadie et al. studies is that the former's outcomes[142] were incident cases while the latter obtained prevalence data,[143] which can be biased towards chronic illness. Leask et al.'s finding was likely more reliable for these reasons, although their analyses may have lacked statistical power. In any case, the studies suggested the absence of a significant association.

As well, likely only one case-control study adequately ruled out the possible impact of recall bias. Leask et al. analyzed breastfeeding data from mothers when their children were either two or seven years of age.[142] Mothers in the other studies had to recall events 20-50 years in the past. Some studies have shown that while long-term recall of whether an infant was breastfed is good, the duration of breastfeeding or the timing when other milk products were initiated are recalled less well.[185-187]

While cross-ecological analyses do not highlight data indicating individual/patient-level covariations of exposure and outcome, they nevertheless failed to demonstrate either a significant association of seafood consumption and lifetime prevalence rates of schizophrenia[90] or a significant relationship between fish consumption,[109] or UFA intake,[145] and the course or outcome of schizophrenia. That said, none of these studies attempted to rule out the possibility that (the nature of) early mother-infant contact might just as easily explain any possible association between breastfeeding and schizophrenia.

While medication status may have had somewhat of an influence on between-group differences in RBC or plasma phospholipid fatty acid content when the comparison group was healthy controls, because these data were obtained from cross-sectional studies, no meaningful possibility exists to permit drawing causal inferences regarding *patterns of PUFA content and the onset of schizophrenia*. The same criticism applies to the single study examining biomarkers data with respect to autism.

Clinical Implications

Omega-3 fatty acids in the present review's collection of interventional studies were not associated with moderate or severe adverse events. Supplementation was well-tolerated, with some mild, mostly gastrointestinal events occurring occasionally. Even the highest doses of omega-3 fatty acids did not produce significant side effects requiring patients to withdraw. The lack of variety in the types of omega-3 fatty acid employed in these studies means that this safety profile refers almost exclusively to the intake of either purified (i.e., E-EPA) or unpurified EPA.

The picture pertaining to the remaining evidence is essentially just as unequivocal. For each psychiatric disorder or condition whose evidence we evaluated, it is impossible to definitively conclude anything with respect to omega-3 fatty acids' efficacy as a therapy or prevention. The existing evidence is therefore insufficient to support clinical recommendations regarding the use of omega-3 fatty acids for the treatment or prevention of any specific mental health condition. Although some individual studies have reported some favorable results, trials have tended to be small, results have often been inconsistent, and study quality has been limited. It is likewise impossible to take existing biomarkers data as constituting reliable predictors of the onset, continuation or recurrence of any psychiatric disorder or condition. Too few large, well-controlled prospective studies employing research designs with the greatest inherent potential to

address each of the first three basic research questions were identified in this systematic review. Yet, given their reasonable safety profile, it is likely that the use of (foods containing) omega-3 fatty acids to influence mental health is unlikely to produce notable adverse effects.

While little is known about the primary treatment of schizophrenia, more can be said about its supplemental treatment. A low dose of 2g/d EPA may, in the shortterm, ameliorate symptoms of schizophrenia. High dose (at least 3g/d) EPA did not provide a similar benefit. However, these observations require replication from much larger, longer term studies that also exercise specific experimental and statistical controls. These refinements are described in the next section. Until these studies are conducted we will not feel confident that 2g/d EPA, or any other dose or type of omega-3 fatty acid, can or cannot produce even reliable shortterm symptom improvement in schizophrenia. Similarly, until more appropriate research designs are employed, the existing evidence does not allow us to conclude that either specific patterns of omega-3 fatty acid intake or particular PUFA levels in biomarkers reliably predict the onset, continuation or recurrence of schizophrenia. It is therefore doubtful that the latter observations can be used to unequivocally confirm the PUFA deficiency facet of the membrane phospholipid hypothesis concerning the etiology of schizophrenia.[55]

It has also been suggested that smoker status alone may account for the results indicating between-group differences in PUFA content,[60] although other factors can influence PUFA status as well (e.g., medication use, alcohol consumption: see above). Hibbeln et al.'s additional analysis[60] of RCT data from their investigation of the effect of omega-3 fatty acids as supplemental treatment for schizophrenia[89] revealed some important observations that may raise doubts about the validity of some of the data presumed to support the membrane phospholipid hypothesis regarding the etiology of schizophrenia.[55] They have suggested that failing to account for current smoker status in studies examining the possible depletion of PUFA content may have confounded numerous, if not most, of the results of cross-sectional studies thought to support the hypothesis.[60] Their observations are summarized below.

Peet et al.'s demonstration of the superiority of EPA over DHA as supplemental treatment for schizophrenia was not expected.[58,188,189] The investigators had assumed that DHA's prominent role in neuronal membrane phospholipids, via their capacity to affect the configuration and function of neurotransmitters (e.g., dopamine), might contribute to the amelioration of symptoms. (Others have suggested that DHA has mood stabilizing effects because of its action on serotenergic neurotransmission, altered membrane fluidity and suppressed phosphatidylinositol and protein kinase C signal transduction.[113,188-190]) Peet et al. also expected that EPA's lesser representation in neuronal membranes would mean that it would play a less important role. They argued that any positive clinical effect of EPA would have to occur independent of its direct incorporation into neuronal membrane phospholipids.[58]

That said, they found that schizophrenic patients with the lowest RBC EPA levels exhibited the weakest response to treatment, an observation, they argued, that would not be predicted if EPA treatment merely entailed correcting a membrane deficiency.[58] Given their earlier findings of a bimodal distribution of PUFA levels in schizophrenic patients (i.e., very low vs moderately low EPA reductions when compared with healthy controls[149]), the group with very low EPA levels in their treatment study may have had a more serious metabolic problem that was less amenable to modification by EPA supplementation. On the other hand, further analyses of biomarker data from Fenton et al.'s supplemental treatment RCT[89] found no evidence of baseline bimodal distributions of RBC EPA, DHA or AA compositions in schizophrenic patients.[60]

Mechanisms potentially leading to EPA being more effective than DHA in depression have been reviewed briefly by Peet et al.[53] In depression, the production of PGs from AA by the cyclooxygenase system appears to be elevated; and, EPA but not DHA has been observed to be an effective substrate for cyclooxygenase, and can compete with AA at this point in the metabolic pathway. Also, in some phospholipase A_2 assays, EPA but not DHA has been seen to be an effective inhibitor. Work investigating EPA's possible mode of action has also suggested the possible role of increased phospholipase A_2 enzyme in the etiology of schizophrenia.[55] Although the modulation of background drug pharmacokinetics cannot be ruled out as the mechanism of action of E-EPA, Peet and Horrobin have suggested that it is more likely that its action is on cell membranes and signal transduction systems.[53,190] These different effects of EPA and DHA, which may be characterized both by synergism and antagonism, suggest that the biological effects of fish oils, which contain both EPA and DHA in highly variable proportions, may be difficult to predict.[53]

Overall, we agree with Peet et al. that the biomarkers (Question 3) and intake-outcome association data (Question 2) are likely suggestive enough to justify the conduct of more intervention studies pertaining to schizophrenia and depression.[58] We provide a few details in the next section.

Until data are obtained from more appropriate research designs (i.e., well-controlled prospective designs collecting individual/patient-level data), it is likely impossible to conclude with great confidence that an omega-3 fatty acid deficiency is responsible for the onset of depression (Question 3); or, that these findings, together with data presumed to reflect the "protective potential" of omega-3 fatty acid intake (Question 2), can readily be taken to justify the use of omega-3 fatty acids as either prevention or therapy. Testing the omega-3 fatty acid deficiency hypothesis also requires control of variables with the potential to influence PUFA status. Suggestive results from the small number of typically underpowered RCTs likely cannot be used to confirm or disconfirm the value of using omega-3 fatty acids as a primary or supplemental therapeutic for depressive disorders or symptomatology (Question 1). More evidence is required.

Even less, or nothing, can be concluded about the value of omega-3 fatty acids as (primary or supplemental) treatment or (primary or secondary) prevention for bipolar disorder, suicidal ideation or behavior, symptoms of anxiety, obsessive-compulsive disorder, anorexia nervosa or other eating disorders, AD/HD, tendencies or behavior with the potential to harm others, alcoholism, borderline personality disorder, autism and mental health difficulties in general. The same may be said about the value of PUFA biomarker profiles as reliable predictors of the onset, continuation or recurrence of these disorders. Even if apparently consistent findings were noted, for example when a greater intake of (foods containing) omega-3 fatty acids was associated with lower prevalence rates of both depression and bipolar disorder, these observations came from designs exhibiting the weakest ability to illumine individual/patient-level associations (i.e., cross-national ecological analyses). Furthermore, much of the included research evidence lacked strong applicability to North Americans. Recommendations for further research stem from the identication of limitations characterizing existing studies and are highlighted in the next section.

Research Implications and Directions

One overarching finding revealed by our review is that not all psychiatric disorders have been investigated for their clinical response to primary or supplemental treatment with omega-3 fatty acids (Question 1) or for their possible association (e.g., prevention) with either omega-3 fatty acid intake (Question 2) or the omega-3 or omega-6/omega-3 fatty acid content of biomarkers (Question 3). Some studies have also focused exclusively on psychiatric conditions (e.g., symptoms of anxiety) that are necessary yet insufficient to merit a formal clinical diagnosis.

The primary targets of mostly recent research endeavors have been schizophrenia and depression. Studies examining the association between these psychiatric disorders or conditions and the PUFA content in biomarkers (Question 3) have outnumbered those investigations evaluating their association with the intake of omega-3 fatty acids (Question 2), and have far outnumbered studies assessing treatment of these disorders or conditions with omega-3 fatty acids (Question 1). In intervention studies, the emphasis has been almost exclusively on the supplemental treatment of these disorders or conditions.

The lack of studies pertaining to some psychiatric disorders or conditions (e.g., eating disorders other than anorexia nervosa) means that nothing can be concluded other than the need for multiple research investigations, employing appropriately-controlled designs of sufficient size (i.e., to afford detection of a meaningful effect/association) and incorporating sound methodologies (e.g., reliable and valid outcome measurements). For those psychiatric disorders or conditions for which fewer than all of the first three basic questions were found to have been examined with empirical evidence (e.g., borderline personality disorder), the unstudied questions likewise require research embodying multiple, appropriately-controlled designs of sufficient size, and implementing sound methodologies.

Yet, even for those questions investigated by numerous studies (i.e., associations between the PUFA content of biomarkers or the intake of omega-3 fatty acids *and* schizophrenia or depression), limited sample sizes, designs (e.g., cross-sectional studies examining associations between biomarkers and the onset of schizophrenia or depression) and methodologies (e.g., using apparent seafood consumption to measure intake of sources containing omega-3 fatty acids in cross-national ecological analyses) highlight the need for studies incorporating modifications to each of these study parameters. Finally, for those few topic areas where studies implementing appropriately-controlled research designs and sound methodologies yielded somewhat suggestive (i.e., supplemental treatment of schizophrenia) or potentially promising results (i.e., supplemental treatment of depression), more, similarly well-designed studies need to be completed, which enroll/allocate larger sample populations and implement additional or refined research design or methodologic characteristics (e.g., account more extensively for covariates and confounders). Given that only minor safety issues were noted in the included studies—despite their likely under-reporting— treatment and prevention trials are justifiable. We now highlight some of the possible directions these investigations might take. While we focus considerable attention on schizophrenia and depression, given their prominence in our review, many of the basic issues apply equally to other psychiatric disorders or conditions.

One possible approach to developing future research avenues is to encourage the collection of data (e.g., animal or human) and the construction of models (e.g., mechanisms of action) suggesting the (e.g., biological) plausibility of clinical treatment effects associated with omega-3

fatty acid supplementation before needlessly embarking upon the expense of studies examining the utility of these treatments for mental health problems (Question 1). From this vantage point, it could be argued that, for those psychiatric disorders or conditions for which few or no empirical treatment data have yet been obtained, the next step would be to establish some degree of plausibility regarding treatment based on empirical evidence addressing other, purportedly more "basic" research questions.

Two such questions, albeit exclusively focused on human data, were addressed in our review: the association between the the onset, continuation or recurrence of psychiatric disorders or conditions and the intake of omega-3 fatty acids (Question 2), or their association with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers (Question 3). Empirical answers to these two questions could suggest important roles (e.g., risk factors) for omega-3 fatty acid contents in mental health, observed in terms of their dietary intake and/or their levels (e.g., composition, concentration) present within blood lipid biomarkers. In turn, these data could serve to justify the use of omega-3 fatty acids as a treatment.

In the present collection of studies, answers to Questions 2 and 3 were too limited, either design-wise or methodologically, to provide support for the deficiency hypotheses relating to either depression or schizophrenia. For the reasons described earlier, both cross-sectional studies and cross-national ecological analyses cannot produce answers that meaningfully identify those omega-3 fatty acid intake or biomarker profiles that may influence the onset of depression or schizophrenia. As well, studies employing other designs did not provide unequivocal support for these hypotheses. Thus, investigators in the domain of inquiry of interest to the present systematic review have at least two options: either wait for these "basic" data to be collected before conducting treatment studies, or find some other rationale supporting the design of new treatment trials. One such raison d'être might be to improve upon the designs and methodologies of studies that have already been completed. We suggest that this option may be especially relevant with regards to the foci of schizophrenia and depression. Moreover, it has also been said that data from epidemiological studies observing the association between fish consumption and psychiatric disorders (e.g., depression), or data from cross-sectional studies observing the association between the PUFA content of biomarkers and clinical outcomes (e.g., presence/absence of a diagnosis of major depressive disorder), each constitute, at best, indirect lines of evidence supporting a role for omega-3 fatty acids in the etiology, pathogenesis and treatment of such disorders.[191]

What, then, are the directions that these treatment studies might take? After we focus on this question, we highlight briefly some avenues that studies addressing the other two basic questions (i.e., intake, biomarkers) might follow. Many of the issues we raise are pertinent to all questions, given that they reflect the need to exercise tighter control of variables (e.g., population) with the potential to confound results. At present, despite the suggestive picture of efficacy of a 2g/d dose as supplemental treatment for schizophrenia, nothing conclusive can be said about the nature of the impact of any of the confounders (e.g., smoking; alcohol use; omega-3 fatty acid dose) on clinical or biomarker outcomes with respect to any of the questions or disorders/conditions whose studies we systematically reviewed.

With respect to the question of the efficacy of omega-3 fatty acids as primary or supplemental treatment for any psychiatric disorder or condition, there have been too few well-controlled RCTs of sufficient size and intervention length to permit drawing any meaningful conclusions about shortterm symptom relief. Moreover, only one study each examined the primary treatment of depression or schizophrenia. More, larger and adequately powered studies

are required.[53] As well, three months of omega-3 fatty acid supplementation in the life of a patient with schizophrenia or with treatment-resistant depression likely cannot be considered, in clinical terms, to be a shortterm intervention. Intervention lengths in the studies investigating the supplemental treatment of depression or schizophrenia lasted no longer than 13 weeks; often, patients seen in clinical practice with either of these disorders will receive medication for years or even decades.

Therefore, especially because of the somewhat suggestive evidence pertaining to 2g/d EPA as supplemental treatment for schizophrenia, additional studies need to replicate this shortterm finding over longer investigative periods. These studies should resolve whether or not omega-3 fatty acid supplementation, when provided as a supplemental intervention, can provide (e.g., additional) shortterm and longer term symptom relief. Then, if ever reliable longterm symptom relief is demonstrated, future studies could be conducted to see whether omega-3 fatty acid supplementation can alter the progression of psychiatric disorders or conditions. The effects of certain conditions associated with schizophrenia and/or the medications given to schizophrenic patients might be lessened, or even prevented. One focus could be tardive dyskinesia, whose incidence, severity or progression could be studied as potentially modifiable outcomes. Likewise, for some patients diagnosed with major depression, suicidal ideation or behavior may become less likely or less intense. Dysphoric feelings might also be "prevented" from becoming full-fledged disorders. In addition, patients with "rapid cycling" forms of bipolar disorder could experience a lengthening of the time between major shifts in mood.

To return to the topic of schizophrenia, if ever its symptoms or clinical course are demonstrated to be improved by omega-3 fatty acid supplementation, especially in the longterm, then "medication-sparing" research designs could be used to test whether adding a specific dose of omega-3 fatty acids—which typically exhibits a relatively benign safety profile—to a lower-than-usual dose of antipsychotic medication can maintain at least the same level of clinical improvement (e.g., symptom control) typically associated with a traditional dose of this antipsychotic medication. This is potentially clinically significant since, at full-dose, antipsychotic medications often exhibit a notable safety profile (i.e., moderate-to-severe adverse effects). In this way, patients might be "spared" the likelihood, or a particular intensity, of side effects associated with their regular antipsychotic medication (e.g., extrapyramidal symptoms).[140] This type of study design is often employed in studies examining health problems (e.g., asthma) where it may be best to reduce doses of medication (e.g., oral corticosteroids), which especially in the longterm, can have negative health consequences.

In such a dose-sparing study, the exact amount of the (absolute or percent) dose reduction could be defined either before the RCT begins or established during the course of the study. In either design, patients selected would include those schizophrenic individuals whose symptoms are well-controlled by their regular antipsychotic medication. If these participants vary on the basis of the type of prestudy medication, stratification by medication type could be undertaken. The types and severities of prestudy adverse effect related to their antipsychotic medication would be noted prior to the commencement of the trial.

In the type of RCT where the dose reduction is defined before the study begins, patients would be randomized to one of two conditions: a) an (absolute or percent) reduction in the dose of their regular antipsychotic medication in addition to receiving a daily dose of omega-3 fatty acid supplementation; or b) continuing to receive their regular antipsychotic medication in addition to a placebo to control for the other group's receipt of supplementation. While other design or analytic controls would be required (e.g., adding placebo material to the first group's

antipsychotic medication in order to mask the dose reduction; determining whether the degree of symptom control at study baseline for both groups was indeed the same), the outcomes of interest would be whether or not: a) the same degree of symptom control (e.g., PANSS total) was observed in both groups; and b) adverse effects related to the antipsychotic medication occurred less often, or were less severe, in the dose reduction group.

In the second type of RCT, dose reduction in one of the study groups would be conducted on a patient-by-patient basis, and in a predefined and uniformly stepwise fashion, until evidence for a loss of symptom control would signal a halt to the reductions. While implementing all of the aforementioned controls, the outcomes of interest would be: a) the mean (or maximal) percent dose reduction that permits symptom control; and, b) the pattern (i.e., frequency or severity) of adverse effects.

These studies might identify, in empirical fashion, the specific types(s) of patient or medication for which dose reductions are beneficial on the basis of both outcomes. The first type of RCT would typically precede conduct of the second type. A final followup would need to take place no earlier than at six months, to be able to establish the stability of any benefits.

For each disorder or condition, including schizophrenia and depression, much more work needs to be done to identify the exact sources (e.g., marine), types and doses of omega-3 fatty acids, and combinations thereof, which reliably produce clinical effects. Both DHA and ALA were underrepresented in the present evidence base. Whether or not specific doses of EPA and DHA should be combined, and how, and for which disorders or conditions, remains to be determined. Whether or not different types and doses of omega-3 fatty acid are required to treat disorders (e.g., major depressive disorder), compared with psychiatric conditions (e.g., feelings of dysphoria), is unknown. Likewise, whether or not different types and doses of omega-3 fatty acid are required to treat disorders of varying degress of severity, or associated with various types (and severities) of comorbid condition, are unresolved questions. Additionally, with respect to each of these questions, there remains the issue of which combinations of omega-3 fatty acid types and doses are both efficacious and safe, that is, where they minimize the likelihood of even mild, transient adverse events.

There are also a number of questions that need to be addressed further regarding dosage. For example, is one RCT enough to determine that 1 g/d E-EPA yields significant clinical improvement in populations experiencing depressive symptomatology?[53] Would such a low dose produce the same kind of effect in those formally diagnosed with a depressive disorder? It is our view that we need more research evidence before we can conclude anything about the utility of this dose for any psychiatric disorder or condition, not just for those individuals exhibiting depressive symptomatology.

At the same time, is 9.6 g/d EPA+DHA too high a dose for patients with bipolar disorder[112] or any other disorder? Stoll et al. did not report even moderate adverse events associated with this dose.[112] Again, we likely need more than a single study (which was stopped prematurely) before we can conclude anything about this dose's clinical utility. Additional research might reveal that the definition of an "effective dose" is disorder-specific, that doses should be weight-adjusted especially in studies with children, or that doses should be adjusted to fit individuals, and not vice versa.[53,190]

While dose-ranging studies may be helpful in determining answers to some of these unresolved issues, it may be wise, however, to avoid situations such as those encountered in the two supplemental treatment RCTs conducted by Peet and colleagues. By having four levels define their intervention (i.e., 4g/d vs 2g/d vs 1g/d vs placebo) in studies examining depression[53]

and schizophrenia,[87] these investigators made it difficult to power each study sufficiently to afford detection of significant clinical effects. It may be better to design less complicated studies with respect to levels of the intervention, while instead instituting greater experimental control of variables with the potential to confound clinical outcomes. More about this topic is discussed below.

That said, in designing future trials, we will likely need to select doses which allow us to make sense of why only patients receiving a low dose (1g/d) E-EPA in Peet et al.'s investigation of the supplemental treatment for depression benefited clinically.[53] The investigators themselves offered no cogent explanation, yet we suggest that the effect might eventually be found to have been produced by hormesis, or to have been influenced by certain changes—which were unrelated to the intervention—in the clinical status or background diet (e.g., omega-6/omega-3 fatty acid intake ratio) of patients receiving the 1g/d dose of E-EPA.

If the goal is to be able to readily interpret study results aimed at determining the clinical utility of omega-3 fatty acids as an intervention, researchers likely need to satisfy a number of requirements. Studies should likely avoid using uncontrolled dosing methods (e.g., oils poured from bottles), since this approach makes it difficult for studies employing controlled research designs to achieve two key controls typically preferred in supplementation studies; each control is intended to minimize the influence of confounding. For example, requests to pour specific amounts (or ranges) of oil from bottles on a per-meal or a per-day basis, can make it difficult to assure that study subjects consistently pour the prespecified amounts of oil and thereby maintain the planned on-study between-group difference in the intake of omega-3 fatty acids (e.g., 3 g/d EPA vs 0 g/d EPA) as well as the planned on-study between-group equivalence of energy/caloric intake (e.g., 3g/d of oil for each study group).[58] Failure to maintain these two between-group constants would confound study results.[72] Then, at the end of the study, when clinical results following uncontrolled dosing require interpretation, it may be impossible to specify, with much precision or confidence, the "daily dose" to which a significant or nonsignificant between-group difference might be attributed.

Uncontrolled interventional studies can also be plagued by this consequence of uncontrolled dosing. It is likely easier to control "doses" when the exposure is delivered via prespecified numbers of swallowable capsules containing finite amounts of omega-3 fatty acid content. Compliance data may someday help to evaluate the present hypothesis regarding the benefits of controlled dosing. For now, the nature of the impact of Peet et al.'s uncontrolled dosing scheme[58] on the significant clinical effect identified by our meta-analysis, assessing the value of low-dose EPA as a supplemental treatment for schizophrenia, remains unknown.

If the goal is to be able to readily interpret study results aimed at determining the clinical utility of omega-3 fatty acids as an intervention, it is also likely wise to avoid using complex interventions, or "cocktails," which contain omega-3 fatty acids combined with many other active ingredients. Otherwise, it will be impossible to account for the exact contribution of omega-3 fatty acids to any clinical effects. The issue of complex exposures is discussed further below.

One type of ingredient in omega-3 fatty acid exposures that is likely useful is one which can maintain the freshness of the exposure and thereby prevent the type of rancidity that would allow patients to determine, from the increasingly strong taste or odour of especially fish oils especially, which exposure they are receiving.[190,191] Failure to maintain freshness can jeopardize blinding. Several interventional studies added, for example, the antioxidants tertiary butylhydroquinone and tocopherals, to what *all* study groups received as their exposure so as to

maintain the exposure's freshness, but also to avoid any possible confounding were these ingredients ever found to have a psychoactive effect.[96,192] Other studies added flavoring to what all study groups received, or even vacuum-deodorized the exposures in order to maintain blinding.[96,191] Still others employed purified EPA, or E-EPA, which purportedly eliminates much of an oil's original taste and odour.[53,87,115,139]

Future research probably needs to carefully examine the impact of using E-EPA, compared with EPA, both to maintain blinding and to influence study outcomes. Processing EPA may change its therapeutic (or preventive) potential, but research assessing its role in mental health is needed to ascertain this possibility. At the same time, the actual purity of all exposures should likely be established.[191] Otherwise, unknown elements already contained within fish oil, for example, might somehow mitigate the effects of the oil itself. Only studies that employed E-EPA even broached this subject, meaning that the exposures in the other interventional studies could have included agents that potentially affected their therapeutic (or preventive) value. No study report addressing any of the basic questions described having assessed the possible presence of, or having eliminated, methylmercury from marine sources of omega-3 fatty acids.

The choice of placebo may also affect study results. While the need for a standard placebo format in research on the therapeutic or preventive role of omega-3 fatty acids in mental health has yet to be established, there is preliminary evidence suggesting that investigators might want to consider steering away from the use of olive oil as a placebo in interventional studies of mental health.[119,120] Olive oil is a source of oleic acid, from which the psychoactive lipid oleamide can be biosynthesized in mammals;[193] and, oleamide has psychoactive properties, including the induction of sleep and the modulation of serotonin receptor-mediated signaling.[194] Thus, olive oil may actually affect mood disorders, which might diminish between-group differences in certain clinical outcomes.[195] Stevens et al. has recommended that liquid paraffin oil be used as placebo in supplementation studies.[123] Liquid paraffin oil was the choice of various intervention studies reviewed in our report.[53,87,115,140] Whatever the true influence of placebo contents on clinical outcomes turns out to be, it has been recommended that one way to minimize the placebo response seen on a few occasions in our review may be to include a 2-week placebo run-in period in trials.[88]

To revisit the subject of complex interventions, given the primarily competitive inter-relationships between omega-3 and omega-6 fatty acids, and their respective metabolites—both within the metabolic pathway and within membranes—future research could potentially end up identifying that specific types and quantities of both omega-3 and omega-6 fatty acids require simultaneous modification to reliably produce clinical benefits for some or all psychiatric disorders or conditions. This research might also point out that these significant clinical effects are brought about by changes in levels of specific types of PUFA in specific biomarker sources (e.g., RBCs). That is, significant clinical benefits could result from the subtraction, from the background diet, of specific types and amounts of omega-6 fatty acids, concomitant with the addition of omega-3 fatty acid content. This strategy could essentially lower the omega-6/omega-3 fatty acid intake ratio. It might also decrease the omega-6/omega-3 fatty acid content ratio in certain biomarkers, although, as pointed out earlier, PUFA status has multiple determinants. However, no study identified by our review employed this dual approach.

Given that a high omega-6/omega-3 fatty acid intake ratio has been thought to be associated with patterns of disease,[33-45] the possible success of a strategy to reduce the omega-6/omega-3 fatty acid ratio might not be unexpected. Variables such as the magnitude of the change in each PUFA's content, the intake ratio's actual value, the intervention length, or the timing of these

changes in (or prior to) a disease process might determine the success of such a therapeutic (or preventive) strategy.

There is some suggestion that the omega-6/omega-3 intake ratio in the background diet may predict the likelihood of observing significant clinical effects. It comes not from the present review, since there were too few studies per psychiatric disorder or condition with which to assess the impact of this possible confounder. Rather, we shared these observations in a recent report examining the impact of omega-3 fatty acids in asthma.[72] While we did not feel it was appropriate to perform a meta-analysis of these results concerning asthma, an impressionistic analysis suggested that studies examining the effects of omega-3 fatty acid supplementation conducted within Asian countries—where the omega-6/omega-3 fatty acid intake ratio in the background diet is considerably reduced compared with the omega-6/omega-3 fatty acid intake ratio in the background diet of populations selected from non-Asian countries—were more likely to produce significant clinical improvements in respiratory outcomes.[72] With less competition for enzymes in the metabolic pathway, and for positions in cell membranes, it is conceivable that in populations eating considerable amounts of fish or seafood, their lower levels of omega-6 fatty acid intake and higher levels of omega-3 fatty acid intake in the prestudy and on-study background diets may make it "easier" for additional omega-3 fatty acid supplementation to make a clinical difference. This speculation may pertain especially (or exclusively) to DHA, given its likely function(s) in cell membranes. Yet, an alternative hypothesis could suggest that significant clinical benefits are less likely when the omega-6/omega-3 fatty acid intake ratio is already reduced prior to a study because cell membranes already contain "enough" omega-3 fatty acid content, and adding typically small amounts of omega-3 fatty acid content via supplementation may not make an appreciable difference.

Whichever hypothesis is confirmed by future research, both perspectives rest on the assumption that clinical effects are brought about by changes in the PUFA levels observed within blood lipid biomarkers. More research could indicate that this is not the case. While PUFA status is influenced by more than just the intake of omega-3 fatty acids, the mechanism promoting clinical changes could actually be even more complicated, implicating the availability of enzymes to, for example, desaturate or elongate PUFA metabolites, or entailing the production or activities of eicosanoids or cytokines. The LC PUFAs especially may be found to directly influence synaptic function through effects on membrane structure and/or indirectly through the production of eicosanoids (PGs, LTs, TXs) or via immune system/cytokine interactions.[122,190] It is therefore likely appropriate to continue examining PUFA content levels in biomarkers within studies evaluating the impact of omega-3 fatty acids on mental health.

In the present review, we could not investigate either directly or indirectly (e.g., using the country in which a study was conducted as a surrogate measure of the omega-6/omega-3 fatty acid intake ratio) the impact on clinical outcomes of the omega-6/omega-3 fatty acid intake ratio of: a) the prestudy/baseline background diet, b) the on-study background diet (i.e., excluding the supplementation), or c) the complete on-study diet (i.e., background diet plus supplementation). Moreover, few investigators conducting interventional studies controlled for this possible confounder either by mandating that patients maintain their prestudy/baseline background diet during the study or by performing a covariate analysis.

Researchers in future interventional studies (i.e., treatment, prevention) will likely need to account analytically (e.g., covariate analysis), if not experimentally (e.g., subject selection criteria; stratification), for prestudy and on-study background definitions of diet, and their inherent omega-6/omega-3 intake ratios, if only because they *may* influence/predict clinical

outcomes. At the same time, it may be premature to assert that given the likely inter-relationships between omega-3 and omega-6 fatty acid contents both in the diet and in blood lipid biomarkers, the questions examined in this review could benefit in the future from an expanded scope, that is, to include a co-focus on the influence of omega-6 fatty acids in mental health.

Future research also needs to assure full knowledge of the details defining study populations so that this source of clinical heterogeneity can be taken into account when analyzing and interpreting the results of interventional or observational studies. Many study reports included in our review failed to specify many of the details pertaining to population variables with the potential to confound study outcomes. These include the possible between-group differences observed at study baseline in controlled studies, which relate to the severity and historical course of the primary disorder (e.g., age of onset, number of episodes, timing of intervention relative to the disease process [e.g., first-episode vs chronic schizophrenia]) or the presence and nature (e.g., severity, age of onset) of comorbid conditions (see Chapter 2). Occasionally, full sample descriptions of these variables were not provided. Failing to have these details made it impossible for us to informally assess their possible impact on study results.

However, this was not always the case in individual studies. In their RCT examining the supplemental treatment of schizophrenia, Hibbeln et al. were concerned that the long duration of illness in their patient population, reflected in notable symptoms despite treatment with newer neuroleptics (e.g., clozapine), may have contributed to the failure to find a significant clinical effect for their full sample.[60,88] Patients in other supplemental treatment studies had been younger and exhibited a shorter illness duration. However, additional analyses revealed that duration of illness was not associated with changes in clinical outcomes or in changes in EPA, DHA, AA, or AA/EPA fatty acid contents following EPA supplementation.[60] Analytic "control" for this possible confounder was achieved, and afforded a clearer interpretation of study outcomes.

Other possible, population sources of confounding may be observed in circumstances where on-study life events unrelated to the exposure (e.g., job loss) can influence subjects' psychiatric status and, in turn, their response to treatment. But, these events need to be measured in order to to statistically control for them. Seldom did the present collection of interventional studies identify the occurrence, or noted absence, of important life events other than those few presumed to be the reason for a discontinuation.

Successful control for population sources of confounding can also be achieved through experimental means. For example, an interventional or an observational study might only include patients exhibiting a single diagnostic subtype, or a minimal or maximal severity level for a particular disorder. They might also exclude patients exhibiting certain types or severities of a particular comorbid condition. While such restrictive conditions limit the possible "breadth" of the population to which study results can be generalized, these experimental controls maximize the specificity of populations to which the evidence can be extrapolated. Ultimately, this could benefit the practice of mental health care.

One final population source of confounding was highlighted in a recent meta-analysis investigating the impact of short-acting Ritalin® in the treatment of AD/HD.[13] The basic premise is that, while patients or populations may share a given diagnostic label (e.g., AD/HD) assigned using stringent clinical approaches, even sophisticated diagnostic classification approaches (e.g., DSM) can lead to an obfuscation of individual differences when it comes to

understanding what each of these individuals is experiencing clinically and, in turn, selecting an appropriate treatment strategy. We focus here on the first observation.

To use AD/HD as an example, three major subtypes of AD/HD are identified by DSM-IV (i.e., predominantly Inattentive subtye vs predominantly Hyperactive subtype vs Combined subtype). Thus, the "AD/HD" label can refer to three different clinical scenarios. In the AD/HD studies included in our review, seldom were the exact subtypes specified or was this source of clinical heterogeneity controlled for analytically. To compound matters, the method employed to assign any one of these subtype diagnoses allows for important variability in the numbers, and combinations of symptom that can be taken to indicate the presence of a single diagnostic subtype. For example, for problems with inattention, DSM-IV asks clinicians to select 6 of 9 possible items, and the same request for 6 items is made with respect to 9 possibilities concerning problems with hyperactivity/impulsivity. Thus, there are several different combinations of symptom referred to by a single diagnostic label; this might be thought of as a homogeneous population in an interventional or observational study, when in fact, it is not. Individuals could vary widely on the basis of their clinical pictures of symptoms. Furthermore, this heterogeneity could influence responses to treatment even in RCTs, where different distributions of clinical picture could characterize different study groups. Such uncontrolled population variability is likely undesirable, and it is further complicated when and if controls are not put in place to deal with similar problems relating to variability in comorbid conditions.

Finally, as introduced in Chapter 1, one other population source of clinical heterogeneity—most important when different studies are compared, as is the case in systematic reviews—stems from relevant studies having used different diagnostic systems, or even different versions of a constantly evolving system (e.g., DSM-III published in 1980, DSM-III-R in 1987 and DSM-IV in 1994), to identify their study populations. Since the diagnostic criteria of these systems can vary, even slightly, then the study populations, or subpopulations, they identify can also vary.[13] This additional definition of "diagnosis heterogeneity" could account for differences in outcomes observed in different studies. Systematic reviews relating to mental health should therefore consider evaluating the impact of diagnostic systems on study outcomes. However, in our review, having too few studies included per psychiatric disorder prevented us from achieving this task.

Other types of control are likewise required to maximize the interpretability of results of interventional or observational studies involving omega-3 fatty acids. Here, we distinguish between three types of variable based on their possible influence on outcomes. They include: those that have the potential to impact clinical (mental health) outcomes; those that can influence the fatty acid content of biomarkers (and which may turn out to be responsible for specific clinical effects); and, those that appear to affect both types of outcome.

There were too few studies per psychiatric disorder or condition to permit the identification of the nature or extent of the influences of effect modifiers on clinical outcomes relating to any of the basic research questions we investigated. Examples of influences on mental health observed in clinical practice include: illicit drug use, general health status, stressors, social support, exercise, quality of sleep, marital status, education, income and employment status. In both controlled and uncontrolled studies, these factors can independently, or in combination, influence mental health outcomes and thereby confound study results. These influences can be observed, for example, where their on-study status changes in ways unrelated to the intervention/exposure (e.g., an unexpected death in the family). In controlled studies, these variables (e.g., disease severity; comorbid conditions) can also affect study outcomes when

study groups differ in their prestudy/baseline status. Either scenario has the potential to mask or artificially inflate the actual benefits of an omega-3 fatty acid intervention/exposure. As a result, future studies relating omega-3 fatty acids and mental health should consider controlling, either experimentally or analytically, for the possible impact of these variables.

Influences on PUFA status include: the disease process itself; dietary intake, metabolism and incorporation into cell membranes of various types and amounts of both omega-3 and omega-6 fatty acid content; efficiency of the PUFA metabolic processes, including the availability and effectiveness of enzymes implicated in the processes of desaturation and elongation; and the ability of protective mechanisms to deal with degradation from oxidation and other sources.[48,101-103,178-180] While the impact of these variables could not be ascertained in our review, future studies which assume that beneficial effects on clinical outcomes might be mediated by changes in the PUFA status of biomarkers likely need to account for these factors.

Variables with the potential to influence both clinical (e.g., control of psychiatric symptomatology) and PUFA (e.g., omega-6/omega-3 fatty acid content in RBCs) status/outcomes include: age; sex; the disease process underlying any possible comorbid conditions; psychotropic medication, including type, dose and duration of use; (e.g., prestudy/baseline and on-study) background diet; alcohol consumption; and current smoker status.[60,180] But, other than those data indicating the positive impact of omega-3 fatty acid supplementation on symptoms of schizophrenia in patients taking clozapine,[87] little can be said about the actual roles of these variables within our evidence base. While the impact of medication status on the PUFA levels of biomarkers could be informally assessed with respect to schizophrenia, little that is meaningful can be concluded since the preponderance of cross-sectional designs prevents drawing inferences about etiology. As stated earlier, the impact of background diet, or of the country in which the study was conducted as a possible surrogate measure of the omega-6/omega-3 fatty acid content thereof, could not be evaluated.

Overall, there were too few studies per psychiatric disorder or condition to permit the identification of the nature or extent of the influences of these or other effect modifiers on outcomes relating to any of the basic research questions we investigated. It is therefore difficult to definitively rule out the possible impacts that these variables may have had on study outcomes. New research should consider routinely accounting for these factors. As was presented above, one interventional study did pursue this ideal regarding the variable of "illness duration."

Hibbeln et al. also argued, based on additional analyses of interventional data,[89] that sex and current smoking status are important confounders in studies examining the interventional or observational relationships between omega-3 fatty acids and schizophrenia outcomes.[60] Each variable was significantly related to fatty acid compositions. DHA was reduced in smokers compared with nonsmokers, and males had lower DHA and EPA fractions compared with females. MANOVA revealed that, of all subgroups, nonsmoking women had the highest EPA and DHA levels while AA did not vary by smoker status or sex.[60] For females, nonsmokers exhibited a greater RBC EPA and DHA percentages compared with smokers. For males, no significant differences for EPA, DHA or AA were noted when smoker status was evaluated. Both EPA and DHA compositions were higher in female nonsmokers compared with male nonsmokers. Neither fatty acid compositions nor the number of cigarettes smoked per day differed significantly for male and female smokers. Thus, the sex specificity of the smoker status effect is likely not attributable to differences in smoking intensity (i.e., daily number of

cigarettes smoked). Smoking intensity was not significantly associated with either absolute or relative amounts of EPA, DHA or AA in RBCs.

Hibbeln et al. then reported that, when they assessed the effects of sex and smoker status on the dietary intake of omega-3 (ALA, EPA, DHA) and omega-6 fatty acids (LA, AA), dietary intakes did not differ by sex or current smoker status when data were expressed as absolute amounts of daily intake.[60] When intake data were observed as percentages of total fat intake, nonsmokers consumed more ALA, although no other significant differences were observed. The consumption of EPA and DHA, expressed as percentages of total fat intake, were greater in females compared with male patients. Differences in AA were not found when either smoker status or sex were taken into consideration. Dietary EPA intake (as percentage of total fat intake) predicted the RBC EPA composition for all patients, for male patients alone, and for nonsmoking males.[60] Dietary DHA intake predicted the RBC DHA composition for males and for nonsmoking male patients. All correlations were significant and positive. Hibbeln et al. concluded that sex and current smoking status should be accounted for in research since they are strongly related to the intake of omega-3 fatty acids and to fatty acid compositions.[60] Finally, while our review could not determine whether PUFA levels indeed reflect the mechanism responsible for clinical effects, in no small part because we remain uncertain that reliable or robust clinical benefits actually exist for any psychiatric disorder or condition, we believe that their *possible* role in producing clinical benefits behooves researchers to assess their possible influences in new studies.

Turning our attention to the issue of outcomes, investigators conducting future research likely need to identify all of the most clinically pertinent outcomes for a given disorder or condition. The reason is that significant clinical benefits observed in mental health research can be outcome-dependent. A recent meta-analysis demonstrated this with respect to treatment studies examining the impact of short-acting Ritalin® on AD/HD.[13] Significant clinical benefits were seen only for a subset of the central problems defining the presence of various forms of AD/HD. This observation suggests that each of the key symptoms defining a psychiatric disorder should likely be measured in new research.

To adequately investigate questions concerning the association between omega-3 fatty acid intake or the PUFA content of biomarkers and the onset, continuation or recurrence of psychiatric disorders or conditions, many of the controls discussed thus far are indicated. The ideal design to permit drawing causal inferences about etiology is a prospective and controlled one.

Primary prevention RCTs may be the best way to examine the possible protective role of omega-3 fatty acid intake, although the length of followup required to establish meaningful effects may necessitate studies that are exceptionally long and too expensive to conduct. Prospective cohort studies investigating the possible association between clinical outcomes and omega-3 fatty aid intake or PUFA status of biomarkers are likely a good choice yet they, too, might be too costly given the exposure period required to permit the detection of incident cases. When it comes to the question relating the intake of omega-3 fatty acids and review-pertinent clinical outcomes (e.g., onset), while prevention RCTs could implement precisely defined interventions, involving capsule-based supplementation, prospective cohort studies are more likely to assess patterns of consumption of foods containing omega-3 fatty acid content. The latter studies, while perhaps demonstrating greater ecological validity, nevertheless suffer from difficulties in precisely delineating the types and amounts of omega-3 fatty acid content associated with clinical outcomes.

A question that would need to be resolved likely prior to undertaking any of these studies relates to the timing of the intervention or exposure period. That is, when should a study with either a treatment or prevention focus begin, and end? The answer is likely disorder-specific, and should be based on what is known from clinical practice and research regarding the age of onset for the disorder. It probably makes little sense to state, without distinction, that these studies should all begin shortly after birth, with followups to occur every 2 years, for 20 years or more.

What may be more useful is to think somewhat outside the box. For example, it may make some sense to "piggyback" the assessment of mental health outcomes in well-controlled and adequately-powered studies that initially aim to assess the impact of omega-3 fatty acid supplementation, via formula feeding, on growth, visual, neurodevelopmental or cognitive outcomes. With time, and and further assessments of these outcomes, what began as an RCT could eventually become a less-expensive, single group observational study designed to identify the development of possible problems in mental health. Five-year telephone followups could be conducted to assess recent intake of (foods or supplements containing) omega-3 fatty acids and mental health status, such that if there is evidence that psychiatric symptoms or disorders may have emerged since the last followup, the individual could be seen and assessed formally. What this approach could offer is an opportunity to relate the intake of omega-3 fatty acids both early and later in life with the development of psychiatric disorders or conditions. Moreover, the inter-relationships among the various outcomes assessed in the study could reveal the broadest developmental context possible within which to understand, at the very least, the etiology of psychiatric disorders or conditions. As in most early intervention studies of formula supplementation involving PUFAs, a reference group of breastfed offspring could be followed in parallel. Assessments of the fatty acid content of biomarkers could be included in such an endeavor, including during pregnancy and at various times post-delivery.

That said, where the questions regarding the association between the onset, continuation or recurrence of psychiatric disorders or conditions and the intake of omega-3 fatty acids or the fatty acid content of biomarkers are concerned, it may be sufficient to avoid both cross-sectional studies and cross-national ecological analyses. Neither design generates data that allow us to resolve either of these questions. Case-control studies constitute an option,[109] although this design likely better suits the question examining the relationship between omega-3 fatty acid intake and the onset, continuation or recurrence of psychiatric disorder or conditions.

What also needs to be determined via new research is whether patterns of omega-3 fatty acid intake or patterns in the fatty acid content of biomarkers can prevent a psychiatric symptom (e.g., feelings of dysphoria) from developing into a full-fledged disorder. As well, what remains to be seen is whether patterns of omega-3 fatty acid intake or patterns in the fatty acid content of biomarkers can predict and perhaps prevent the continuation or recurrence of psychiatric disorders or conditions. It is conceivable that additional research could someday illumine the secondary preventive value of the intake of omega-3 fatty acids, for example.

In general, if researchers ever hoped to establish or reinforce the plausibility of employing omega-3 fatty acids as a treatment for any psychiatric disorder or condition using evidence from studies examining the associations between clinical outcomes and the intake of omega-3 fatty acids as well as the fatty acid content of biomarkers, it is our view that this has not been achieved. Therefore, the recent publication of treatment studies directed at depression, and especially schizophrenia, may suggest either that researchers have interpreted these data in ways

that diverge greatly from our interpretation or, that they have perceived some other, inherent value in undertaking treatment trials.

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

Limitations of the Review

While there are some limitations characterizing the present systematic review, almost none could likely be considered a serious impediment to the interpretation of the evidence we identified and synthesized. Overall, we found too few studies investigating a given question, and employing an appropriate research design of sufficient size and sound methodology, to have these limitations alter the view that, at present, we cannot conclude anything definitive about the disorder/condition-specific or overarching roles of omega-3 fatty acids in mental health. As well, the possible roles played by likely covariates and confounders could hardly be evaluated at all. We were limited in what we could observe because of the paucity of relevant studies per question and because many studies did not specifically investigate the influence of these variables. This is unfortunate since alcohol consumption, for example, like current smoker status, appears to influence both mental health and PUFA status.

The only limitations of possible significance concern the meta-analysis conducted with data obtained from RCTs investigating the efficacious use of omega-3 fatty acids as supplemental treatment for schizophrenia. It was less than ideal to use post-treatment means from Peet et al.'s study[58] when data indicating changes from baseline in outcomes are preferred. Another study report by Peet and colleagues, also used in the meta-analysis, did provide these data.[87] Unfortunately, our request for change from baseline data from the Peet et al. study[58] did not yield a successful response. Furthermore, what remains unknown at this time are the independent or combined impacts of combining data from studies failing to distinguish outcome data from patients receiving different primary medications,[58,87] and using different interventions (i.e., purified[87] versus unpurified EPA;[58] controlled[87] versus uncontrolled dosing[58]), on the meta-analytic estimate or its precision. It should be recalled that there is, for example, limited empirical evidence indicating that low-dose (2 g/d) EPA yielded a clinical benefit solely for those patients receiving clozapine.[87] Replication efforts are required, however, before we can feel confident in the reliability of this observation.

Knowing, in advance, that data from cross-sectional designs could not possibly permit drawing causal inferences about the etiology of psychiatric disorders or conditions, from data reflecting either the dietary intake of omega-3 fatty acids or the PUFA content of biomarkers, might have afforded a decision to a priori exclude these studies from the review. However, this would have left us with few studies to review; and, while the purpose of our review did not include testing the deficiency hypotheses regarding the onset of depression or schizophrenia, reviewing these studies (or cross-national ecological analyses) nevertheless allowed us to highlight the evidence typically used to support these etiologic explanations.

At the same time, it is unlikely that expanding our focus with respect to PUFA metabolism beyond the compositions or concentrations of PUFA metabolites (e.g., to include data regarding the possible presence or activity of enzymes involved in the processes of desaturation or elongation within the metabolic pathway) would have produced results revealing a less unclear picture concerning the association between the PUFA content of biomarkers and the onset, continuation or recurrence of a psychiatric disorder or condition. These relationships were typically investigated in similarly limited, cross-sectional designs.

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

Time constraints made it impossible to complete dual-assessor appraisals of the quality (i.e., internal validity) of studies employing designs other than an RCT, or the applicability of all the included studies. One experienced quality assessor conducted these evaluations. At the same time, we conducted these quality assessments of designs other than RCTs using items we either modified from existing instruments or which we had to develop outright because no similar tools existed (e.g., cross-national ecological analyses). A design-specific, total quality score was then generated for each study, from which a single summary value was derived (i.e., A, B, C). This simplification permitted the entry of these values into summary matrices. However, the design-specific cutpoints used to assign these values were established without any validational basis, and so their value is likely extremely limited. The applicability indices, while continuing the work we did when we systematically reviewed the evidence for the health effects of omega-3 fatty acids on asthma,[72] also did not receive any validational support. Nevertheless, given the limited number of studies addressing a specific question, and using a design whose data could meaningfully elucidate it, it is unlikely that these shortcomings could have had a meaningful impact on the "take home messages" highlighted by our review. Formal statistical assessments of the impacts of study quality or applicability on study outcomes could not be conducted. Finally, with a very limited number of studies entered into meta-analysis, an examination of the possible presence and impact of publiation bias could not be conducted.

Conclusion

Studies investigating omega-3 fatty acids employed as an intervention revealed the absence of a notable safety profile associated with any type or dose of omega-3 fatty acids represented in the review. Only with respect to the supplemental treatment of schizophrenia is the evidence even somewhat suggestive of omega-3 fatty acids' potential as a shortterm intervention. Even then, these results pertaining to 2g/d, or low-dose, EPA[58,87] need to be replicated using larger sample populations, longer investigative periods and instituting various methodologic (i.e., experimental or analytic) controls. The observed failure of high-dose (i.e., $\geq$3 g/d) EPA supplementation to produce a clinical benefit likewise requires replication with similar design modifications.

Data regarding the supplemental treatment of depression suggest a focus where considerable additional, clarifying research might eventually reveal the shortterm or longterm therapeutic

value of omega-3 fatty acid supplementation. One study demonstrating a significant placebo-controlled clinical effect related to 1 g/d E-EPA given, over 12 weeks, to 17 patients with depressive symptoms—rather than depressive disorders—cannot be taken to support the view of the utility of this exposure as a supplemental treatment for depressive symptomatology or disorders.[53] Equally inadequate to establish the efficacy of omega-3 fatty acids as a supplemental treatment for depression are two other trials,[96,97] which lasted 4 or 8 weeks and employed active exposures and exposure-placebo contrasts that distinguish them from the study which highlighted the efficacy of 1g/d E-EPA.[53]

Nothing can yet be concluded concerning the clinical utility of omega-3 fatty acids provided as a supplemental treatment for any other psychiatric disorder or condition, or as a primary treatment for all psychiatric disorders or conditions, examined in our review. Primary treatment studies were rare. Much more research is needed before we can begin to ascertain the possible utility of (foods or supplements containing) omega-3 fatty acids as a primary prevention for psychiatric disorders or conditions. From both an economic and scientific point of view, it might be worthwhile to "piggyback" studies of the primary protective potential of omega-3 fatty acids in mental health onto controlled, longitudinal studies of their impact on general health and developmental outcomes (e.g., growth; neurodevelopment; visual and cognitive development). Requisite modifications for treatment or prevention studies include well-defined and appropriately sampled populations, followup periods of suitable lengths, key experimental or analytic controls (e.g., for confounders) and individual/patient-level data. Overall, almost nothing is known about the therapeutic or preventive potential of each source, type, dose or combination of omega-3 fatty acids.

Because of limited study designs, little is known about the relationship between PUFA biomarker profiles and the onset of any psychiatric disorder or condition. Studies examining the possible association between the intake of omega-3 fatty acids, or the PUFA content of biomarkers, and the continuation or recurrence of psychiatric disorders or conditions were virtually nonexistent.

If future research is going to produce data that are unequivocally applicable to North Americans, it will likely need to enroll either North American populations or populations exhibiting a high omega-6/omega-3 fatty acid intake ratio similar to what has been observed in the diet of North Americans. Furthermore, if a reasonable view is that omega-3 fatty acids may play a role in mental health, then given the observed or proposed inter-relationships between omega-3 and omega-6 fatty acid contents both in the regular diet and in the human biosystem, it may behoove researchers to investigate the possible therapeutic or preventive value of the dietary omega-6/omega-3 fatty acid intake ratio.

To this end, interventional studies could concurrently modify the intake of omega-3 and omega-6 fatty acids, and thereby manipulate experimentally the omega-6/omega-3 fatty acid intake ratio. Prospective observational studies could trace the possible links between the omega-6/omega-3 fatty acid intake ratio and the development, course or outcome of psychiatric disorders or conditions. Finally, any notable causal or correlational relationships observed between the omega-6/omega-3 fatty acid intake ratio and the development, course or outcome of psychiatric disorders or conditions might then be "explained" by observed patterns of omega-6/omega-3 fatty acid content in peripheral, or even brain, biomarkers.

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Alling C, Aspenstrom G, Dencker S J et al. Essential fatty acids in chronic alcoholism. Acta Medica Scandinavica - Supplementum 1979;631(1):-38. Uncontrolled study.

Assies J, Lok A, Bockting C L et al. Fatty acids and homocysteine levels in patients with recurrent depression: An explorative pilot study. Prostaglandins Leukotrienes & Essential Fatty Acids 2004;70(4):349-356. Uncontrolled study.

Bell J G, Sargent J R, Tocher D R et al. Red blood cell fatty acid compositions in a patient with autistic spectrum disorder: A characteristic abnormality in neurodevelopmental disorders? Prostaglandins Leukotrienes & Essential Fatty Acids 2000;63(1-2):21-25. Uncontrolled study.

Buydens-Branchey M, McMakin D L, Hibbeln J R. Polyunsaturated fatty acid status and relapse vulnerability in cocaine addicts. Psychiatry Res 2003;120(1):29-35. Uncontrolled study.

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De Vriese S R, Christophe A B, Maes M. Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: Further evidence that lowered n-PUFAs are related to major depression. Life Sci 2003;73(25):3181-3187. Uncontrolled study.

Holman R T, Johnson S. Changes in essential fatty acid profile of serum phospholipids in human disease. Prog Lipid Res 1981;20(67):-73. Uncontrolled study.

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of schizophrenia. Schizophr Res 1998;29(158):158. Uncontrolled study.

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Wright Jonathan. Treatment of chronic anxiety and associated physical complaints with niacinamide and essential fatty acids: Two cases. Journal of Orthomolecular Medicine 1992;7(3):182-186. Uncontrolled study.

Table of Studies Investigating Each Question: organized by the order of presentation in the text

Question	INCLUDED STUDIES (i.e., THE PRIMARY REPORT REFERRED TO IN TEXT)
• **Primary Treatment for Depression**	• Marangell et al., 2003:[95] Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. Am J Psychiatry 2003;160(5):996-998.
• **Supplemental Treatment for Depression**	• Peet & Horrobin, 2002:[53] Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry 2002;59(10):913-919. • Nemets et al., 2002:[97] Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159(3):477-479. • Su et al., 2003:[96] Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol 2003;13(4):267-271.
• **Intake Associated with Onset of Depression (i.e., Primary Prevention)**	• Llorente et al., 2003:[98] Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. Am J Obstet Gynecol 2003;188(5):1348-1353. • Wardle et al., 2000:[99] Wardle J, Rogers P, Judd P, Taylor MA, Rapoport L, Green M et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am J Med 2000;108(7):547-553. • Ness et al., 2003:[100] Ness AR, Gallacher JEJ, Bennett PD, Gunnell DJ, Rogers PJ, Kessler D et al. Advice to eat fish and mood: A randomised controlled trial in men with angina. Nutr Neurosci 2003;6(1):63-65. • Hakkarainen et al., 2004:[111] Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? Am J Psychiatry 2004;161(3):567-569. • Tanskanen et al., 2001:[81] Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamaki H et al. Fish consumption and depressive symptoms in the general population in Finland. Psychiatr Serv 2001;52(4):529-531. • Tanskanen et al., 2001:[80] Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression, and suicidality in a general population.[comment]. Arch Gen Psychiatry 2001;58(5):512-513. • Woo et al., 2002:[110] Woo J, Ho SC, Yu ALM. Lifestyle factors and health outcomes in elderly Hong Kong Chinese aged 70 years and over. Gerontology 2002;48(4):234-240. • Suzuki et al., 2004:[107] Suzuki S, Akechi T, Kobayashi M, Taniguchi K, Goto K, Sasaki S et al. Daily omega-3 fatty acid intake and depression in Japanese patients with newly diagnosed lung cancer. Br J Cancer 2004;90(4):787-793. • Edwards et al., 1998:[48] Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J Affect Disord 1998;48(2-3):149-155. • Hibbeln, 1998:[47] Hibbeln JR. Fish consumption and major depression.[comment]. Lancet 1998;351(9110):1213. • Hibbeln, 2002:[108] Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J Affect Disord 2002;69(1-3):15-29. • Peet, 2004:[109] Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. Br J Psychiatry 2004;184:404-408.
• **Biomarker Content Associated with Onset of Depression**	• Ellis & Sanders, 1977:[105] Ellis FR, Sanders TAB. Long chain polyunsaturated fatty acids in endogenous depression. J Neurol Neurosurg Psychiatry 1977;40(2):168-169. • Fehily et al., 1981:[106] Fehily AMA, Bowey OAM, Ellis FR, Meade BW. Plasma and erythrocyte membrane long chain polyunsaturated fatty acids in

	endogenous depression. Neurochem Int 1981;3(1):37-42. • Maes et al., 1996:[103] Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. J Affect Disord 1996;38(1):35-46. • Peet et al., 1998:[102] Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry 1998;43(5):315-319. • Edwards et al., 1998:[48] Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J Affect Disord 1998;48(2-3):149-155. • Maes et al., 1999:[101] Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. Psychiatry Res 1999;85(3):275-291. • Tiemeier et al., 2003:[104] Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MMB. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. Am J Clin Nutr 2003;78(1):40-46. • Llorente et al., 2003:[98] Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. Am J Obstet Gynecol 2003;188(5):1348-1353.
• **Intake Associated with Onset of Suicidal Ideation or Behavior (i.e., Primary Prevention)**	• Hakkarainen et al., 2004:[111] Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? Am J Psychiatry 2004;161(3):567-569. • Tanskanen et al., 2001:[80] Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression, and suicidality in a general population.[comment]. Arch Gen Psychiatry 2001;58(5):512-513.
• **Supplemental Treatment for Bipolar Disorder**	• Stoll et al., 1999:[112] Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial.[comment]. Arch Gen Psychiatry 1999;56(5):407-412. • Akkerhuis & Nolen, 2003:[93] Akkerhuis GW, Nolen WA. Lithium-associated psoriasis and omega-3 fatty acids. Am J Psychiatry 2003;160(7):1355.
• **Intake Associated with Onset of Bipolar Disorder (i.e., Primary Prevention)**	• Noaghiul & Hibbeln, 2003:[90] Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am J Psychiatry 2003;160(12):2222-2227.
• **Biomarker Content Associated with Onset of Bipolar Disorder**	• Mahadik et al., 1996:[114] Mahadik SP, Mukherjee S, Horrobin DF, Jenkins K, Correnti EE, Scheffer RE. Plasma membrane phospholipid fatty acid composition of cultured skin fibroblasts from schizophrenic patients: comparison with bipolar patients and normal subjects. Psychiatry Res 1996;63(2-3):133-142. • Chiu et al., 2003:[113] Chiu CC, Huang SY, Su KP, Lu ML, Huang MC, Chen CC et al. Polyunsaturated fatty acid deficit in patients with bipolar mania. Eur Neuropsychopharmacol 2003;13(2):99-103.
• **Intake Associated with Onset of Anxiety (i.e., Primary Prevention)**	• Wardle et al., 2000:[99] Wardle J, Rogers P, Judd P, Taylor MA, Rapoport L, Green M et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am J Med 2000;108(7):547-553. • Ness et al., 2003:[100] Ness AR, Gallacher JEJ, Bennett PD, Gunnell DJ, Rogers PJ, Kessler D et al. Advice to eat fish and mood: A randomised controlled trial in men with angina. Nutr Neurosci 2003;6(1):63-65.
• **Supplemental Treatment for Obsessive-Compulsive**	• Fux et al., 2004:[115] Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. J Psychiatr Res 2004;38(3):323-325.

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• **Biomarker Content Associated with Onset of Anorexia Nervosa**	• Langan & Farrell, 1985:[117] Langan SM, Farrell PM. Vitamin E, vitamin A and essential fatty acid status of patients hospitalized for anorexia nervosa. Am J Clin Nutr 1985;41(5):1054-1060. • Holman et al., 1995:[116] Holman RT, Adams CE, Nelson RA, Grater SJ, Jaskiewicz JA, Johnson SB et al. Patients with anorexia nervosa demonstrate deficiencies of selected essential fatty acids, compensatory changes in nonessential fatty acids and decreased fluidity of plasma lipids. J Nutr 1995;125(4):901-907.
• **Primary Treatment for Attention Deficit/ Hyperactivity Disorder**	• Richardson & Puri, 2002:[119] Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. Prog Neuropsychopharmacol Biol Psychiatry 2002;26(2):233-239. • Hirayama et al., 2004:[120] Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - A placebo-controlled double-blind study. Eur J Clin Nutr 2004;58(3):467-473. • Brue et al., 2001:[118] Brue AW, Oakland TD, Evans RA. The use of a dietary supplement combination and an essential fatty acid as an alternative and complementary treatment for children with attention-deficit/hyperactivity disorder. Sci Rev Altern Med 2001;5(4):187-194. • Harding et al., 2003:[121] Harding KL, Judah RD, Gant CE. Outcome-based comparison of Ritalin versus food-supplement treated children with AD/HD. Altern Med Rev 2003;8(3):319-330.
• **Supplemental Treatment for Attention Deficit/ Hyperactivity Disorder**	• Brue et al., 2001:[118] Brue AW, Oakland TD, Evans RA. The use of a dietary supplement combination and an essential fatty acid as an alternative and complementary treatment for children with attention-deficit/hyperactivity disorder. Sci Rev Altern Med 2001;5(4):187-194. • Voight et al., 2001:[122] Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder.[comment]. J Pediatr 2001;139(2):189-196. • Stevens et al., 2003:[123] Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A et al. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 2003;38(10):1007-1021.
• **Intake Associated with Onset of Attention Deficit/ Hyperactivity Disorder (i.e., Primary Prevention)**	• Yang et al., 1999:[94] Yang S-C, Chiu W-C, Chen J-R, Lee J-C, Shieh M-J. Dietary intakes of 4-8 years old children with attention-deficit hyperactivity disorder. Nutr Sci J 1999;24(2):153-165.
• **Biomarker Content Associated with Onset of Attention Deficit/ Hyperactivity Disorder**	• Mitchell et al., 1983:[126] Mitchell EA, Lewis S, Cutler DR. Essential fatty acids and maladjusted behaviour in children. Prostaglandins Leukot Med 1983;12(3):281-287. • Mitchell et al., 1987:[125] Mitchell EA, Aman MG, Turbott SH, Manku M. Clinical characteristics and serum essential fatty acid levels in hyperactive children. Clin Pediatr (Phila) 1987;26(8):406-411. • Stevens et al., 1995:[124] Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR et al. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. Am J Clin Nutr 1995;62(4):761-768.
• **Intake Associated with Onset of Mental Health Difficulties (i.e., Primary Prevention)**	• Silvers & Scott., 2002:[127] Silvers KM, Scott KM. Fish consumption and self-reported physical and mental health status. Public Health Nutr 2002;5(3):427-431.

• **Intake Associated with Onset or Continuation of Tendencies or Behaviors with the Potential to Harm Others (i.e., Primary or Secondary Prevention)**	• Hamazaki et al., 1996:[130] Hamazaki T, Sawazaki S, Itomura M, Asaoka E, Nagao Y, Nishimura N et al. The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. J Clin Invest 1996;97(4):1129-1133. • Hamazaki et al., 1998:[129] Hamazaki T, Sawazaki S, Nagao Y, Kuwamori T, Yazawa K, Mizushima Y et al. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. Lipids 1998;33(7):663-667. • Hamazaki et al., 2002:[128] Hamazaki T, Thienprasert A, Kheovichai K, Samuhaseneetoo S, Nagasawa T, Watanabe S. The effect of docosahexaenoic acid on aggression in elderly Thai subjects--a placebo-controlled double-blind study. Nutr Neurosci 2002;5(1):37-41. • Wardle et al., 2000:[99] Wardle J, Rogers P, Judd P, Taylor MA, Rapoport L, Green M et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am J Med 2000;108(7):547-553. • Iribarren et al., 2004:[132] Iribarren C, Markovitz JH, Jacobs Jr DR, Schreiner PJ, Daviglus M, Hibbeln JR. Dietary intake of n-3, n-6 fatty acids and fish: Relationship with hostility in young adults - The CARDIA study. Eur J Clin Nutr 2004;58(1):24-31. • Gesch et al., 2002:[131] Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. Br J Psychiatry 2002;181:22-28. [Secondary Prevention] • Hibbeln, 2001:[133] Hibbeln JR. Seafood consumption and homicide mortality: A cross-national ecological analysis. 4th Congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL 2000). World Rev Nutr Diet 2001;88:41-46.
• **Biomarker Content Associated with Onset of Tendencies or Behaviors with the Potential to Harm Others**	• Virkkunen et al., 1987:[135] Virkkunen ME, Horrobin DF, Jenkins DK, Manku MS. Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. Biol Psychiatry 1987;22(9):1087-1096. • Hibbeln et al., 1998:[134] Hibbeln JR, Umhau JC, Linnoila M, George DT, Ragan PW, Shoaf SE et al. A replication study of violent and nonviolent subjects: cerebrospinal fluid metabolites of serotonin and dopamine are predicted by plasma essential fatty acids. Biol Psychiatry 1998;44(4):243-249. • Buydens-Branchey et al., 2003:[136] Buydens-Branchey L, Branchey M, McMakin DL, Hibbeln JR. Polyunsaturated fatty acid status and aggression in cocaine addicts. Drug Alcohol Depend 2003;71(3):319-323.
• **Biomarker Content Associated with Onset of Alcoholism**	• Alling et al., 1984:[138] Alling C, Gustavsson L, Kristensson-Aas A, Wallerstedt S. Changes in fatty acid composition of major glycerophospholipids in erythrocyte membranes from chronic alcoholics during withdrawal. Scand J Clin Lab Invest 1984;44(4):283-289. • Hibbeln et al., 1998:[137] Hibbeln JR, Linnoila M, Umhau JC, Rawlings R, George DT, Salem N, Jr. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. Biol Psychiatry 1998;44(4):235-242.
• **Primary Treatment for Borderline Personality Disorder**	• Zanarini et al., 2003:[139] Zanarini MC, Frankenburg FR. omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry 2003;160(1):167-169.
• **Primary Treatment for Schizophrenia**	• Peet et al., 2001:[58] Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res 2001;49(3):243-251.
• **Supplemental Treatment for Schizophrenia**	• Peet et al., 2001:[58] Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophr Res 2001;49(3):243-251. • Fenton et al., 2001:[89] Fenton WS, Dickerson F, Boronow J, Hibbeln JR, Knable M. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in

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• **Intake Associated with Onset of Schizophrenia (i.e., Primary Prevention)**	• Peet et al., 1997:[92] Peet M, Poole J, Laugharne J. Infant feeding and the development of schizophrenia. Schizophr Res 1997;24:255-256. • McCreadie, 1997:[143] McCreadie RG. The Nithsdale Schizophrenia Surveys. 16. Breast-feeding and schizophrenia: preliminary results and hypotheses. Br J Psychiatry 1997;170:334-337. • Leask et al., 2000:[142] Leask SJ, Done DJ, Crow TJ, Richards M, Jones PB. No association between breast-feeding and adult psychosis in two national birth cohorts. Br J Psychiatry 2000;177:218-221. • Sasaki et al., 2000:[144] Sasaki T, Okazaki Y, Akaho R, Masui K, Harada S, Lee I et al. Type of feeding during infancy and later development of schizophrenia. Schizophr Res 2000;42(1):79-82. • Amore et al., 2003:[141] Amore M, Balista C, McCreadie RG, Cimmino C, Pisani F, Bevilacqua G et al. Can breast-feeding protect against schizophrenia? Case-control Study. Biol Neonate 2003;83(2):97-101. • Mellor et al., 1996:[91] Mellor JE, Laugharne JDE, Peet M. Omega-3 fatty acid supplementation in schizophrenic patients. Hum Psychopharm 1996;11(1):39-46. • Christensen & Christensen, 1988:[145] Christensen O, Christensen E. Fat consumption and schizophrenia. Acta Psychiatr Scand 1988;78(5):587-591. • Noaghiul & Hibbeln, 2003:[90] Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am J Psychiatry 2003;160(12):2222-2227. • Peet, 2004:[109] Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. Br J Psychiatry 2004;184:404-408.
• **Biomarker Content Associated with Onset of Schizophrenia**	• Obi & Nwanze, 1979:[153] Obi FO, Nwanze EA. Fatty acid profiles in mental disease. Part 1. Linolenate variations in schizophrenia. J Neurol Sci 1979;43(3):447-454. • Horrobin et al., 1989:[152] Horrobin DF, Manku MS, Morse-Fisher N, Vaddadi KS, Courtney P, Glen AI et al. Essential fatty acids in plasma phospholipids in schizophrenics. Biol Psychiatry 1989;25(5):562-568. • Kaiya et al., 1991:[151] Kaiya H, Horrobin DF, Manku MS, Fisher NM. Essential and other fatty acids in plasma in schizophrenics and normal individuals from Japan. Biol Psychiatry 1991;30(4):357-362. • Fischer et al., 1992:[150] Fischer S, Kissling W, Kuss HJ. Schizophrenic patients treated with high dose phenothiazine or thioxanthene become deficient in polyunsaturated fatty acids in their thrombocytes. Biochem Pharmacol 1992;44(2):317-323. • Peet et al., 1995:[149] Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. J Psychiatr Res 1995;29(3):227-232. • Vaddadi et al., 1996:[157] Vaddadi KS, Gilleard CJ, Soosai E, Polonowita AK, Gibson RA, Burrows GD. Schizophrenia, tardive dyskinesia and essential fatty acids. Schizophr Res 1996;20(3):287-294. • Mahadik et al., 1996:[114] Mahadik SP, Mukherjee S, Horrobin DF, Jenkins K, Correnti EE, Scheffer RE. Plasma membrane phospholipid fatty acid composition of cultured skin fibroblasts from schizophrenic patients: comparison with bipolar patients and normal subjects. Psychiatry Res 1996;63(2-3):133-142. • Assies et al., 2001:[148] Assies J, Lieverse R, Vreken P, Wanders RJ, Dingemans PM, Linszen DH. Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. Biol

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Abbreviations

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

Appendix A. Search Strategies

Search Strategy 1

Ovid interface for Medline, Embase, PsycInfo, Cochrane Central Register of Controlled Trials
1.exp mental disorders/
2. exp mental disease/
3. suicide attempt/
4. attempted suicide/
5. exp suicide/
6. suicid$.mp.
7. exp Aggression/
8. Aggressiveness/
9. Aggressive behavior/
10. exp Impulsive Behavior/
11. Impulsiveness/
12. exp Impulse Control Disorders/
13. or/1-12
14. exp fatty acids, omega-3/
15. fatty acids, essential/
16. Dietary Fats, Unsaturated/
17. linolenic acids/
18. exp fish oils/
19. (n 3 fatty acid$ or omega 3).tw.
20. docosahexa?noic.tw,hw,rw.
21. eicosapenta?noic.tw,hw,rw.
22. alpha linolenic.tw,hw,rw.
23. (linolenate or cervonic or timnodonic).tw,hw,rw.
24. menhaden oil$.tw,hw,rw.
25. (mediterranean adj diet$).tw.
26. ((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$).tw.
27. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
28. (fish adj2 oil$).tw.
29. (cod liver oil$ or marine oil$ or marine fat$).tw.
30. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
31. (fish consumption or fish intake or (fish adj2 diet$)).tw.
32. diet$ fatty acid$.tw.
33. or/14-32
34. dietary fats/
35. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
36. random$.tw.
37. exp clinical trials/ or evaluation studies/
38. follow-up studies/ or prospective studies/
39. or/35-38
40. 34 and 39
41. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
42. (omega 3 or n 3).mp.
43. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
44. 42 and 43
45. 33 or 40 or 41 or 44
46. 13 and 45

Search Strategy 2

Mental Health with free text supplement
Ovid interface for CDSR
1. exp mental disorders/
2. exp mental disease/
3. suicide attempt/
4. attempted suicide/
5. exp suicide/
6. suicid$.mp.
7. exp Aggression/
8. Aggressiveness/
9. Aggressive behavior/
10. exp Impulsive Behavior/
11. Impulsiveness/
12. exp Impulse Control Disorders/
13. or/1-12
14. exp fatty acids, omega-3/
15. fatty acids, essential/
16. Dietary Fats, Unsaturated/
17. linolenic acids/
18. exp fish oils/
19. (n 3 fatty acid$ or omega 3).tw.
20. docosahexa?noic.tw,hw,rw.
21. eicosapenta?noic.tw,hw,rw.
22. alpha linolenic.tw,hw,rw.
23. (linolenate or cervonic or timnodonic).tw,hw,rw.
24. menhaden oil$.tw,hw,rw.
25. (mediterranean adj diet$).tw.
26. ((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$).tw.
27. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
28. (fish adj2 oil$).tw.
29. (cod liver oil$ or marine oil$ or marine fat$).tw.
30. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
31. (fish consumption or fish intake or (fish adj2 diet$)).tw.
32. diet$ fatty acid$.tw.
33. or/14-32
34. dietary fats/
35. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
36. random$.tw.
37. exp clinical trials/ or evaluation studies/
38. follow-up studies/ or prospective studies/
39. or/35-38
40. 34 and 39
41. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
42. (omega 3 or n 3).mp.
43. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
44. 42 and 43
45. 33 or 40 or 41 or 44
46. 13 and 45
47. remove duplicates from 46
48. mental health.mp.

49. psychiat$.mp.
50. schizophr$.mp.
51. bipolar$.mp.
52. depressi$.mp.
53. (mania$ or hypomani$).mp.
54. unipolar$.mp.
55. (psychotic$ or psychosis$).mp.
56. (schizoaffective or schizo-affective).mp.
57. (aggressi$ and behav$).mp.
58. Aggression.mp.
59. aggressivity.mp.
60. impulsiv$.mp.
61. Impulse Control$.mp.
62. or/48-61
63. 45 and 62
64. 47 or 63

Search Strategy 3

Mental Health with freetext supplement
Silverplatter interface for CAB Health
#1. "mental-disorders" in SU
#2. "depression-" in SU
#3. "neuroses-" in SU
#4. "mental-health" in SU
#5. "suicide-" in SU
#6. mental health in ti,ab,su
#7. psychiat* in ti,ab,su
#8. schizophr* in ti,ab,su
#9. bipolar* in ti,ab,su
#10. depressi* in ti,ab,su
#11. (mania* or hypomani*) in ti,ab,su
#12. unipolar* in ti,ab,su
#13. (psychotic* or psychosis*) in ti,ab,su
#14. (schizoaffective or schizo-affective) in ti,ab,su
#15. (aggressi* near10 behav*) in ti,ab,su
#16. aggression in ti,ab,su
#17. aggressivity in ti,ab,su
#18. impulsiv* in ti,ab,su
#19. impulse control* in ti,ab,su
#20. ("delusory-parasitoses" in SU) or ("psychoses-" in SU) or ("schizophrenia-" in SU)
#21. ("aggression-" in SU) or ("aggressive-behaviour" in SU) or ("fighting-" in SU)
#22. #1 or #2, #3, #4, #5, #6, #7, #8, #9, #10, #11, #12, #13, #14, #15, #16, #17, #18, #19, #20, #21
#23. omega 3
#24. ("essential-fatty-acids" in SU) or ("linolenic-acid" in SU)
#25. ("docosahexaenoic-acid" in SU) or ("eicosapentaenoic-acid" in SU)
#26. explode "plant-oils" in SU
#27. explode "fish-oils" in SU
#28. "fish-consumption" in SU
#29. "polyenoic-fatty-acids" in SU
#30. "polyunsaturated-fats" in SU
#31. "dietary-fat" in SU
#32. (n 3 fatty acid* or omega 3) in ti,ab,su
#33. (docosahexanoic or docosahexaenoic) in ti,ab,su

#34. (eicosapentanoic or eicosapentaenoic) in ti,ab,su
#35. (alpha linolenic)in ti,ab,su
#36. (linolenate or cervonic or timnodonic) in ti,ab,su
#37. (mediterranean diet) in ti,ab,su
#38. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or menhaden) and oil*) in ti,ab,su
#39. (walnut* or butternut* or soybean* or pumpkin seed*) in ti,ab,su
#40. (fish oil* or cod liver oil* or marine oil* or marine fat*) in ti,ab,su
#41. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*) in ti,ab,su
#42. (fish consumption or fish intake) in ti,ab,su
#43. (diet* fatty acid*) in ti,ab,su
#44. (ropufa or maxepa or omacor or efamed or resq or epagis or almarin or coromega) in ti,ab,su
#45. ((omega 3 or n 3) and (polyunsaturated fat* or pufa or dha or epa or long chain or longchain or lc*)) in ti,ab,su
#46. "long-chain-fatty-acids" in SU
#47. (fish and diet) in ti,ab,su
#48. (explode "essential-oils" in SU) or (explode "olive-oil" in SU) or (explode "palm-oils" in SU) or (explode "plant-oils" in SU) or (explode "seed-oils" in SU)
#49. explode "fish-liver-oils" in SU
#50. ("long-chain-fatty-acids" in SU) or (((omega 3 or n 3) and (polyunsaturated fat* or pufa or dha or epa or long chain or longchain or lc*)) in ti,ab,id) or ((ropufa or maxepa or omacor or efamed or resq or epagis or almarin or coromega) in ti,ab,id) or ((diet* fatty acid*) in ti,ab,id) or ((n 3 fatty acid* or omega 3) in ti,ab,id) or ("dietary-fat" in SU) or ("polyunsaturated-fats" in SU) or ("polyenoic-fatty-acids" in SU) or ("fish-consumption" in SU) or (explode "fish-oils" in SU) or (explode "plant-oils" in SU) or (("docosahexaenoic-acid" in SU) or ("eicosapentaenoic-acid" in SU)) or (("essential-fatty-acids" in SU) or ("linolenic-acid" in SU)) or (omega 3) or ((fish consumption or fish intake) in ti,ab,id) or ((salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*) in ti,ab,id) or ((fish oil* or cod liver oil* or marine oil* or marine fat*) in ti,ab,id) or ((walnut* or butternut* or soybean* or pumpkin seed*) in ti,ab,id) or (((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or menhaden) and oil*) in ti,ab,id) or ((mediterranean diet) in ti,ab,id) or ((linolenate or cervonic or timnodonic) in ti,ab,id) or ((alpha linolenic)in ti,ab,id) or ((eicosapentanoic or eicosapentaenoic) in ti,ab,id) or ((docosahexanoic or docosahexaenoic) in ti,ab,id) or (explode "fish-liver-oils" in SU) or ((explode "essential-oils" in SU) or (explode "olive-oil" in SU) or (explode "palm-oils" in SU) or (explode "plant-oils" in SU) or (explode "seed-oils" in SU)) or ((fish and diet) in ti,ab,id)
#51. ((explode "almond-oil" in SU) or (explode "castor-oil" in SU) or (explode "coconut-oil" in SU) or (explode "cottonseed-oil" in SU) or (explode "groundnut-oil" in SU) or (explode "jojoba-oil" in SU) or (explode "linseed-oil" in SU) or (explode "maize-oil" in SU) or (explode "melon-seed-oil" in SU) or (explode "mustard-oil" in SU) or (explode "palm-kernel-oil" in SU) or (explode "rapeseed-oil" in SU) or (explode "rice-oil" in SU) or (explode "safflower-oil" in SU) or (explode "sesame-oil" in SU) or (explode "soyabean-oil" in SU) or (explode "sunflower-oil" in SU) or (explode "tung-oil" in SU) or (explode "wheat-germ-oil" in SU)) or (("cod-liver-oil" in SU) or ("menhaden-oil" in SU))
#52. #50 or #51
#53. #22 and #52

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

May 2, 2003

Dear _____,

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

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

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

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

Best regards,

Catherine MacLean, M.D., Ph.D.
RAND1700 Main Street, M 23-C
Santa Monica, CA 90407-2138
Voice: 310 393-0411, x6364
Fax: 310-451-6930
maclean@rand.org

Relevance Assessment Form

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

a. **Inclusion criteria**:

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

2. Does this study evaluate the role of: a. omega-3 fatty acid intake (diet and/or supplementation) as an intervention/exposure; or b. omega-3 or omega-6/omega-3 fatty acid content of biomarkers?
   YES Can't Tell NO

3. Is the purpose of the study to investigate: a. the effect (e.g., efficacy, effectiveness) of omega-3 fatty acid intake (diet and/or supplementation) as (primary or supplemental) treatment for --or the association of their intake *with* the onset, continuation or recurrence of-- psychiatric disorders or symptoms/behaviors (e.g., depressive, bipolar, anxiety or eating disorders; ad/hd; schizophrenia; anxiety, depression, aggression/hostility, impulsivity or suicidal behavior); or b. the association of the omega-3 or omega-6/omega-3 fatty acid content of biomarkers with the onset, continuation or recurrence of these psychiatric conditions?
   YES Can't Tell NO

4. If this is a study investigating the evidence concerning the efficacious use of omega-3 fatty acids as a primary or supplemental treatment for psychiatric disorders or symptoms/behaviors, or a study investigating the association of the omega-3 or omega-6/omega-3 fatty acid content of biomarkers with the onset, continuation or recurrence of psychiatric disorders or symptoms/behaviors, what type of research design was employed?*

   CONTROLLED (or addresses Question 2) Can't Tell UNCONTROLLED

b. **Exclusion criterion**:

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

c. **Context**:

6. The study appears to *also or instead* concern omega-3 fatty acids as an intervention/exposure associated with the following human health/disease domains *(select at least one option; click on all that apply)*:

__transplantation
__cancer
__child/maternal health
__neurology
__eye health
__none of the above

7. Is this report written in English?
   YES NO

8. Comments box

*Question 4 alone was used at level 3 screening; screening levels 1 and 2 each employed questions 1-3 and 5-8.

Data Abstraction Form

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

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

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

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

BOX = single box at end of list
All abstractors access each level, for verification possibilities.
Each abstractor assigned level(s), and Refids

Initials of reviewer: **BOX**

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

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

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

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

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

Internet document/material
Other
BOX

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

Question(s) addressed (*select all that apply*):

a. Are omega-3 fatty acids efficacious as primary treatment for _____?
b. Are omega-3 fatty acids efficacious as supplemental treatment for _____?
c. Is omega-3 fatty acid intake, including diet and/or supplementation, associated with the onset of _____?
d. Is omega-3 fatty acid intake, including diet and/or supplementation, associated with the continuation of _____?
e. Is omega-3 fatty acid intake, including diet and/or supplementation, associated with the recurrence of _____?
f. Is the onset of _____ associated with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers?
g. Is the continuation of _____ associated with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers?
h. Is the recurrence of _____ associated with the omega-3 or omega-6/omega-3 fatty acid content of biomarkers?
i. Are adverse events/side effects or contraindications associated with the intake of specific sources (e.g., marine, plant), types (e.g., DHA, EPA, ALA) or doses of omega-3 fatty acids, including in specific subpopulations such as diabetics?

Psychiatric disorder(s)/symptom(s)/sign(s)/behavior(s) investigated as primary or exclusive focus of the study (*select all that apply*):

a. Anxiety
b. Depression/unipolar
c. Bipolar/manic depression
d. Eating
e. ADHD or key symptoms/signs (e.g., impulsivity)
f. Antisocial personality
g. Aggression/violence
h. Stress
i. Alcoholism or other drug abuse
j. Borderline personality
k. Schizophrenia/schizoaffective
l. Autism
m. Suicide
n. Other: **BOX**

Study design (*select one*):

a. RCT parallel design
b. RCT crossover design

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

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

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

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

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

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

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

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

Adequacy of eligibility criteria:

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

Sample sizes (*complete all*):

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

completers (= final followup)/total (full; per group) (e.g., group 1: n=4/5; group 2: n=6/7): **BOX**

Settings (*complete both*):

Type(s) of setting (e.g., tertiary care hospital vs community facility) (full; by group): **BOX**

Proportion of participants in relatively controlled (e.g., inpatients) settings during study (full; by group): **BOX**

Study period (*complete all*):

Intervention length (d, wk, mo, y) (*by group only if it varies*): **BOX**

Study duration, including units (h, d, wk, mo) (includes intervention length plus run-in period duration, washout duration[s], etc.): **BOX**

Run-in duration/protocol: **BOX**

Washout duration/protocol: **BOX**

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

a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable (e.g., a cross-sectional survey)

Was the same study procedure employed with reference to each study group? (*select one*)

a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable

Were participants in each study group assessed at the same number of followups, and with the same timing, during the study (*select one*)?

a. Yes
b. No
c. Unclear
d. Not reported
e. Not applicable (e.g., a cross-sectional survey)

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

Adverse events, and losses to followup (*complete both*):

withdrawals vs # dropouts, with reasons (full; by group): **BOX**

Adverse events/side effects and contraindications (full; by group): **BOX**

Basic population characteristics (*complete all*):

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

Psychiatric status (*complete all*):
At/by baseline, the 'primary diagnosis/condition (with diagnostic subtype) and concurrent diagnosis/condition' [i.e., condition = symptom(s)/signs(s), yet no formal diagnosis] (proportions/% in full; by group) (e.g., 100% major depressive disorder [recurrent], no concurrent conditions): **BOX**
Severity of key defining features/symptoms/signs (full; by group): **BOX**
Prominent features/symptoms/signs at study onset e.g., (e.g., bipolar patients in manic phase) (full; by group): **BOX**
Current episode duration (full; by group): **BOX**
Age of onset (full; by group): **BOX**
Duration (i.e., time since diagnosis) (full; by group): **BOX**
Number of previous episodes (full; by group): **BOX**
Diagnostic method (e.g., interview), and classification system (e.g., DSM-IV): **BOX**
Method (e.g., scales) to determine severity: **BOX**
Pre-study medications, with daily dose (full; by group): **BOX**
Pre-study response to medications (e.g., symptoms well-controlled vs symptomatic) (full; by group): **BOX**
Pre-study psychologic interventions (full; by group): **BOX**
Likely etiology (full; by group): **BOX**

Pre-study/baseline comparability of groups regarding the definition of the primary diagnosis/subtype:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups regarding the definition of the primary/concurrent diagnosis/condition combinations:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data

Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline definition of the population (i.e., primary diagnosis/condition or primary/concurrent diagnosis/condition combinations) handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups regarding the severity of key features/symptoms/signs:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline severity of key defining features/symptoms/signs handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Comparability of groups regarding the prominent features/symptoms/signs at study onset (e.g., bipolar patients in manic phase):

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences regarding the prominent features/symptoms/signs at study onset (e.g., bipolar patients in manic phase) handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Comparability of groups regarding the current episode duration:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences regarding the current episode duration handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported

Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups regarding the age of onset:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the age of onset handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups regarding duration (time since diagnosis):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in duration (time since diagnosis): handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Comparability of groups regarding the number of previous episodes:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences regarding the number of previous episodes handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups regarding medication types/daily doses:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study

BOX

How were any between-group differences in the pre-study/baseline medication types/daily doses handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study

BOX

Pre-study/baseline comparability of groups regarding the response to medication (e.g., symptoms well-controlled vs symptomatic):

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study

BOX

How were any between-group differences in the pre-study/baseline response to medication (e.g., well-controlled vs symptomatic) handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study

BOX

Pre-study/baseline comparability of groups regarding psychologic interventions:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported

Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline psychologic interventions handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

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

Pre-study/baseline comparability of groups in the total amount of dietary n-3 intake:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type (EPA, DHA, ALA), and source (e.g., fish oil capsules) (*by group*) (e.g., group 1: 1.8g/d EPA, 1.2g/d DHA, from 3 fish oil capsules/d; group 2: 0g/d EPA, 0g/d DHA, water placebo): **BOX**

Pre-study/baseline comparability of groups in the total amount of n-3 intake from supplementation:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline (daily, weekly or monthly) total n-3 intake *via all sources* (diet +supplementation), per n-3 type (*by group*): **BOX**

Pre-study/baseline comparability of groups in the total amount of n-3 intake from diet and supplementation:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

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

Pre-study/baseline comparability of groups in dietary n-6/n-3 intake:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study

BOX

How were any between-group differences in the pre-study/baseline n-3 or n-6/n-3 intake handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

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

Pre-study/baseline comparability of groups in % caloric/energy intake from fat:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline % caloric/energy intake from fat handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

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

High fish diet
Fish-vegetarian diet
Low fish diet
Low fat diet
High fat diet

Mediterranean diet
Other
Unclear
Not reported
BOX

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

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

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

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

Pre-study/baseline use of other licit (prescription and non-prescription) drugs (full; by group): **BOX**

Pre-study/baseline comparability of groups in use of other licit (prescription and non-prescription) drugs:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline use of other licit (prescription and non-prescription) drugs handled in the study analysis?

Adequately = taken into consideration in the analysis

Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline use of other supplements (e.g., vitamins, minerals), including dose/frequency (full; by group): **BOX**

Pre-study/baseline comparability of groups in use of other supplements (e.g., vitamins, minerals), including dose/frequency:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline use of other supplements (e.g., vitamins, minerals), including dose/frequency, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline use of other complementary/alternative therapies, including dose/frequency (full; by group): **BOX**

Pre-study/baseline comparability of groups in use of other complementary/alternative therapies, including dose/frequency:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data

Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline use of other complementary/alternative therapies, including dose/frequency, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline (ab)use of alcohol (full; by group): **BOX**

Pre-study/baseline comparability of groups in (ab)use of alcohol:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline (ab)use of alcohol handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline use of illicit drugs (full; by group): **BOX**

Pre-study/baseline comparability of groups in use of illicit drugs:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline use of illicit drugs handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline use of smoking tobacco (full; by group): **BOX**

Pre-study/baseline comparability of groups in use of smoking tobacco:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline use of smoking tobacco handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline general health status (full; by group): **BOX**

Pre-study/baseline comparability of groups in general health status:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline general health status handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline status of other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) (full; by group): **BOX**

Pre-study/baseline comparability of groups regarding the status of other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported

Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline status of other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline family history of psychiatric problems, including known diagnoses (full; by group): **BOX**

Pre-study/baseline comparability of groups in terms of a family history of psychiatric problems, including known diagnoses:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline family history of psychiatric problems, including known diagnoses, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis

Not applicable = e.g., a single group study
BOX

Pre-study/baseline employment status (full; by group): **BOX**

Pre-study/baseline comparability of groups in terms of employment status:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline employment status handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline income (full; by group): **BOX**

Pre-study/baseline comparability of groups in terms of income:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline income handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline education (full; by group): **BOX**

Pre-study/baseline comparability of groups in terms of education:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline education handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

Pre-study/baseline marital status (full; by group): **BOX**

Pre-study/baseline comparability of groups in terms of marital status:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported

Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline marital status handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

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

Pre-study/baseline comparability of groups in terms of DHA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups in terms of EPA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data

Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups in terms of EPA+DHA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups in terms of AA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups in terms of AA/DHA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study

BOX

Pre-study/baseline comparability of groups in terms of AA/EPA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

Pre-study/baseline comparability of groups in terms of AA/EPA+DHA status (per biomarker):
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., a single group study
BOX

How were any between-group differences in the pre-study/baseline biomarker EFA status handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for these in the analysis
Not reported = no description of whether/how accounted for in the analysis
Not applicable = e.g., a single group study
BOX

ON-STUDY

Was the n-3 exposure provided/received as primary or supplemental intervention? **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

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

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

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

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

total (daily, weekly or monthly) n-3 exposure *via diet*, with amount per n-3 type, source, frequency and timing of delivery (e.g., NR, likely EPA or DHA, from 2 0.5oz oily fish

servings/wk, as dinner; e.g., NR, likely ALA, from 8-10oz/wk flaxseed oil as salad dressing, NR): **BOX**

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

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

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

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

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

total (daily, weekly or monthly) n-3 dose *via supplementation*, with amount per n-3 type; source, frequency and timing of delivery; other active ingredients (e.g., 1.8g/d EPA, 1.2g/d DHA, from 3 [1g vegan outer] fish oil capsules/d, with breakfast, NR; e.g., 3g/d EPA+DHA [NBD], from 3 [1g gelcap] fish oil capsules/d, NR, 50mg Vitamin E per capsule; e.g., 0g/d, from 3 [1g gelcap] olive oil capsules/d, with breakfast, NR): **BOX**

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

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

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

total (daily, weekly or monthly) n-6/n-3 intake: **BOX** (e.g., 10:1 g/d): **BOX**

type, source and total (daily, weekly or monthly) intake of other mandated or permitted exposures, with dose/serving/frequency: **BOX**

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

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

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

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

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

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

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

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

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

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

Between-group comparability of within-group changes in the primary/concurrent diagnosis/condition combination[s] (i.e., population definition) from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Single group study, adequate = statistically nonsignificant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly adequate = no notable change in reported data in this group yet no reported result of statistical test of significance
Single group study, inadequate = statistically significant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly inadequate = notable change in reported data in this group yet no reported result of statistical test of significance
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the primary/concurrent diagnosis/condition combination[s] (i.e., population definition) from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data

Single group study, adequate = statistically nonsignificant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly adequate = no notable change in reported data in this group yet no reported result of statistical test of significance
Single group study, inadequate = statistically significant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly inadequate = notable change in reported data in this group yet no reported result of statistical test of significance
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

How were any between-group differences in the within-group change(s) in the primary/concurrent diagnosis/condition combinations (i.e., population definition) from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the primary/concurrent diagnosis/condition combinations (i.e., population definition) from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the severity of key defining features/symptoms/signs (e.g., leading to a change in medication type/dose) from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Single group study, adequate = statistically nonsignificant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly adequate = no notable change in reported data in this group yet no reported result of statistical test of significance
Single group study, inadequate = statistically significant change in this group (e.g., p-value; stated result of statistical test)

Single group study, possibly inadequate = notable change in reported data in this group yet no reported result of statistical test of significance
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the severity of key defining features/symptoms/signs (e.g., leading to a change in medication type/dose) from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
Possibly inadequate = no result of statistical test of significance reported, yet at least one notable difference in reported data
Single group study, adequate = statistically nonsignificant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly adequate = no notable change in reported data in this group yet no reported result of statistical test of significance
Single group study, inadequate = statistically significant change in this group (e.g., p-value; stated result of statistical test)
Single group study, possibly inadequate = notable change in reported data in this group yet no reported result of statistical test of significance
Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported
Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

How were any between-group differences in the within-group change(s) in the severity of key defining features/symptoms/signs (e.g., leading to a change in medication type/dose) from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the severity of key defining features/symptoms/signs (e.g., leading to a change in medication type/dose) from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the prominent features/symptoms/signs observed at study onset/baseline (e.g., bipolar patients in manic phase), to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
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Single group study, adequate = statistically nonsignificant change in this group (e.g., p-value; stated result of statistical test)
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the prominent features/symptoms/signs observed at study onset/baseline (e.g., bipolar patients in manic phase), to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
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Unclear = no result of statistical test of significance reported, and, incomplete or conflicting data reported

Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

How were any between-group differences in the within-group change(s) in the prominent features/symptoms/signs observed at study onset/baseline (e.g., bipolar patients in manic phase), to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the prominent features/symptoms/signs observed at study onset/baseline (e.g., bipolar patients in manic phase), to each followup in each group: **BOX**

Between-group comparability of within-group changes in the medication types/daily doses from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the medication types/daily doses from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

How were any between-group differences in the within-group change(s) in the medication types/daily doses from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the medication types/daily doses from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the response to medication (symptoms well-controlled vs symptomatic) from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
Inadequate = statistically significant difference(s) reported
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the response to medication (symptoms well-controlled vs symptomatic) from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

How were any between-group differences in the within-group change(s) in the response to medication (symptoms well-controlled vs symptomatic) from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis

Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the response to medication (symptoms well-controlled vs symptomatic) from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the psychologic interventions from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Between-group comparability of within-group changes in the psychologic interventions from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
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How were any between-group differences in the within-group change(s) in the psychologic interventions from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
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No differences = no differences reported
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Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the psychologic interventions from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the use of other licit (prescription and non-prescription) drugs from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

Between-group comparability of within-group changes in the use of other licit (prescription and non-prescription) drugs from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

How were any between-group differences in the within-group change(s) in the use of other licit (prescription and non-prescription) drugs from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?

Adequately = taken into consideration in the analysis
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the use of other licit (prescription and non-prescription) drugs from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in other supplement use (vitamins; minerals), including dose/frequency, from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)

Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

Between-group comparability of within-group changes in other supplement use (vitamins; minerals), including dose/frequency, from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

How were any between-group differences in the within-group change(s) in other supplement use (vitamins; minerals), including dose/frequency, from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?

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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in other supplement use (vitamins; minerals), including dose/frequency, from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in other complementary/alternative therapies from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
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Between-group comparability of within-group changes in other complementary/alternative therapies from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
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How were any between-group differences in the within-group change(s) in other complementary/alternative therapies from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in other complementary/alternative therapies from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the (ab)use of alcohol from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in the (ab)use of alcohol from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

How were any between-group differences in the within-group change(s) in the (ab)use of alcohol from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
Adequately = taken into consideration in the analysis
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the (ab)use of alcohol from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in illicit drug use from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not reported = no reported data or result of a statistical test of significance
Not applicable = e.g., no followup, as in a cross-sectional study
BOX

Between-group comparability of within-group changes in illicit drug use from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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How were any between-group differences in the within-group change(s) in illicit drug use from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?

Adequately = taken into consideration in the analysis
Inadequately = not taken into consideration in the analysis
No differences = no differences reported
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Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in illicit drug use from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in smoking tobacco from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

Between-group comparability of within-group changes in smoking tobacco from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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How were any between-group differences in the within-group change(s) in smoking tobacco from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in smoking tobacco from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in general health status from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Between-group comparability of within-group changes in general health status from baseline, to final followup:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

How were any between-group differences in the within-group change(s) in general health status from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
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Not applicable = a single group study
BOX

Briefly describe the nature of the change in general health status from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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BOX

Between-group comparability of within-group changes in the other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) from baseline, to final followup:

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BOX

How were any between-group differences in the within-group change(s) in other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?
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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in other factors affecting (and affected by) mental health (e.g., stressors; exercise; quality of sleep; social support) from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in the family history of psychiatric problems, including known diagnoses, from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
Possibly adequate = no result of statistical test of significance reported, yet no notable difference(s) in reported data
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Not applicable = e.g., no followup, as in a cross-sectional study

BOX

Between-group comparability of within-group changes in the family history of psychiatric problems, including known diagnoses, from baseline, to final followup:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
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BOX

How were any between-group differences in the within-group change(s) in the family history of psychiatric problems, including known diagnoses, from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?

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No differences = no differences reported
Unclear = not enough information to rule out possibility that did not account for it in the analysis
Not reported = no description of whether/how accounted for it in the analysis
Not applicable = a single group study
BOX

Briefly describe the nature of the change in the family history of psychiatric problems, including known diagnoses, from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in employment status from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)

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How were any between-group differences in the within-group change(s) in employment status from baseline, to each followup, handled in the study analysis? Or, if a single group study, how was any within-group change in this variable from baseline, to each followup, handled in the study analysis?

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Not applicable = a single group study
BOX

Briefly describe the nature of the change in employment status from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in income from baseline, to the followup required to observe an/no effect:
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Not applicable = a single group study
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Briefly describe the nature of the change in income from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in education from baseline, to the followup required to observe an/no effect:
Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
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BOX

Briefly describe the nature of the change in education from baseline, to each followup in each group: **BOX**

Between-group comparability of within-group changes in marital status from baseline, to the followup required to observe an/no effect:

Adequate = statistically nonsignificant difference(s) reported (e.g., p-value; stated result of statistical test)
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Between-group comparability of within-group changes in marital status from baseline, to final followup:

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Briefly describe the nature of the change in marital status from baseline, to each followup in each group: **BOX**

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

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

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

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

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

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

Adequacy of method to deodorize smell of especially fish oil exposure (*select one*):
Adequate = reported that study participants could not reliably guess which exposure they received
Inadequate = reported that participants could reliably guess which exposure they received

Unclear = incomplete or conflicting data reported
Not reported = no method reported, or method reported but no data reported
Not applicable = did not use an exposure requiring or permitting such a method (e.g., flaxseed; full fish servings)

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

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

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

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

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

Quality Assessment Form—Randomized Controlled Trials

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

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

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

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

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

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

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

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

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

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

JADAD TOTAL SCORE = ___

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

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

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

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

Quality Assessment (Internal Validity) Forms—Designs Other than an RCT

Controlled Study Designs

DESIGN: COMPARATIVE BEFORE-AFTER STUDY

1. Description of validated method(s) to identify the target population

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

2. Control for selection bias

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

3. Description of withdrawals/dropouts

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

4. Comparability of study groups on the basis of the design or analysis: age and sex

a. Study controls for age and sex at baseline = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

5. Comparability of study groups on the basis of the design or analysis: background diet

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

6. Comparability of study groups on the basis of the design or analysis: caloric/energy intake

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

7. Comparability of study groups on the basis of the design or analysis: the severity of the psychiatric disorder/condition

a. Study controls for the severity of the psychiatric disorder/condition at baseline and in light of possible changes unrelated to the exposure during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

8. Comparability of study groups on the basis of the design or analysis: psychotropic medication

a. Study controls for psychotropic medication at baseline and in light of possible changes unrelated to the exposure during intervention period = 1
b. Study fails to control for this confounding influence = 0
c. Unable to determine = 0

9. Description of a validated primary clinical outcome measure(s)

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

10. Blind assessments of outcome

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

11. Description of type and amount of omega-3 fatty acid content in the intervention/exposure

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

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

1. Is the case definition adequate?

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

2. Representativeness of the cases

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

3. Selection of controls

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

4. Definition of controls

a. no history of disease (requires clinical/research diagnostic criteria to determine this) (1 point)
b. no description of source

5. Comparability of cases and controls on the basis of the design or analysis: smoker status

a. study controls for smoker status at baseline and in possible changes unrelated to the exposure during "intervening period" (1 point)
b. study fails to control for this confounding influence

6. Comparability of cases and controls on the basis of the design or analysis: type and dose of psychotropic medication

a. study controls for type and dose of psychotropic medication at baseline and in possible changes unrelated to the exposure during "intervening period" (1 point)
b. study fails to control for this confounding influence

7. Comparability of cases and controls on the basis of the design or analysis: omega-6 fatty acid intake

a. study controls for omega-6 fatty acid intake at baseline and in possible changes unrelated to the exposure during "intervening period" (1 point)
b. study fails to control for this confounding influence

8. Ascertainment of exposure

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

9. Same method of ascertainment for cases and controls

a. yes (1 point)
b. no

10. Non-response rate

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

DESIGN: (MULTIPLE-GROUP) CROSS-SECTIONAL STUDY

1. Control for selection bias

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

2. Description of the same validated method to distinguish the study populations (i.e., to confirm/diagnose the presence and absence of psychiatric disorder/condition in the target and control population(s), respectively)

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

3. Homogeneity of the target psychiatric population: psychiatric diagnosis/condition

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

4. Homogeneity of the target psychiatric population: psychotropic medication(s) and dose(s)

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

5. Comparability of study groups on the basis of the design or analysis: age and sex

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

6. Comparability of study groups on the basis of the design or analysis: current amount of omega-3 fatty acid intake in background diet

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

7. Comparability of study groups on the basis of the design or analysis: current amount of omega-6 fatty acid intake, or omega-6/omega-3 fatty acid intake, in background diet

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

8. Comparability of study groups on the basis of the design or analysis: current smoker status

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

9. Description of a validated primary clinical outcome measure(s)

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

10. Description of the same appropriate methods used to extract, prepare, store and analyze lipid data from all study populations

a. No inappropriate descriptions = 1
b. At least one inappropriate description = 0
c. Different methods used for different study groups = 0
d. Unable to determine for one or more of the methods = 0

Uncontrolled Study Designs

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

1. Representativeness of the exposed cohort

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

2. Ascertainment of exposure

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

3. Demonstration that outcome of interest was not present at start of study

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

4. Description of a validated method to quantify the amount, per type, of omega-3 fatty acids

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

5. Assessment of outcome

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

6. Was followup long enough for outcomes to occur?

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

7. Adequacy of followup of cohort

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

8. Analytic control for confounding: age and sex

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

9. Analytic control for confounding: omega-6 fatty acid intake or omega-6/omega-3 fatty acid intake ratio

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

10. Analytic control for confounding: smoking history

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

DESIGN: CROSS-SECTIONAL SURVEY

1. Description of appropriate sampling technique(s) to identify the sample population

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

2. Description of a validated method to identify/diagnose the target psychiatric disorder/condition

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

3. Description of a validated method to identify the current intake of (foods or supplements containing) omega-3 fatty acids

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

4. Description of a validated method to quantify the amount, per type, of omega-3 fatty acids

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

5. Analytic control for confounding: age and sex

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

6. Analytic control for confounding: smoking history/status

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

7. Analytic control for confounding: severity of psychiatric disorder/condition

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

8. Analytic control for confounding: current intake of (foods or supplements containing) omega-6 fatty acids or omega-6/omega-3 fatty acids

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

9. Response rate (at least 75%):

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

DESIGN: CROSS-NATIONAL ECOLOGICAL ANALYSIS

1. Description of the same validated method to identify all of the target study populations

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

2. Description of the same validated method to identify intake of omega-3 fatty acids (from foods known to contain them) from all of the target study populations

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

3. Description of appropriate sampling techniques to identify all of the target populations

a. Yes = 1 (random sampling; stratified sampling to represent key population elements; large enough)
b. No = 0
c. Unable to determine = 0

4. Description of sampling or analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): age and sex

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

5. Description of sampling or analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): other social factors (e.g., education)

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

6. Description of sampling or analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): economic factors

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

7. Description of sampling or analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): omega-6 fatty acid intake, or omega-6/omega-3 fatty acid intake ratio

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

8. Description of sampling or analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): smoking history/status

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

9. Description of analytic techniques to control for possible confounding (i.e., factors that can influence diet or mental health): re-analysis excluding outlier data

a. Yes = 1
b. No outlier data identified = 1
c. No = 0
d. Unable to determine = 0

Applicability Indices

For studies involving at least one target population identified with a psychiatric disorder or condition (i.e., symptom/behavior):[1]

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

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

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

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

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

For studies involving a target population with or without a known elevated risk for a psychiatric disorder or condition (i.e., symptom/behavior):

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

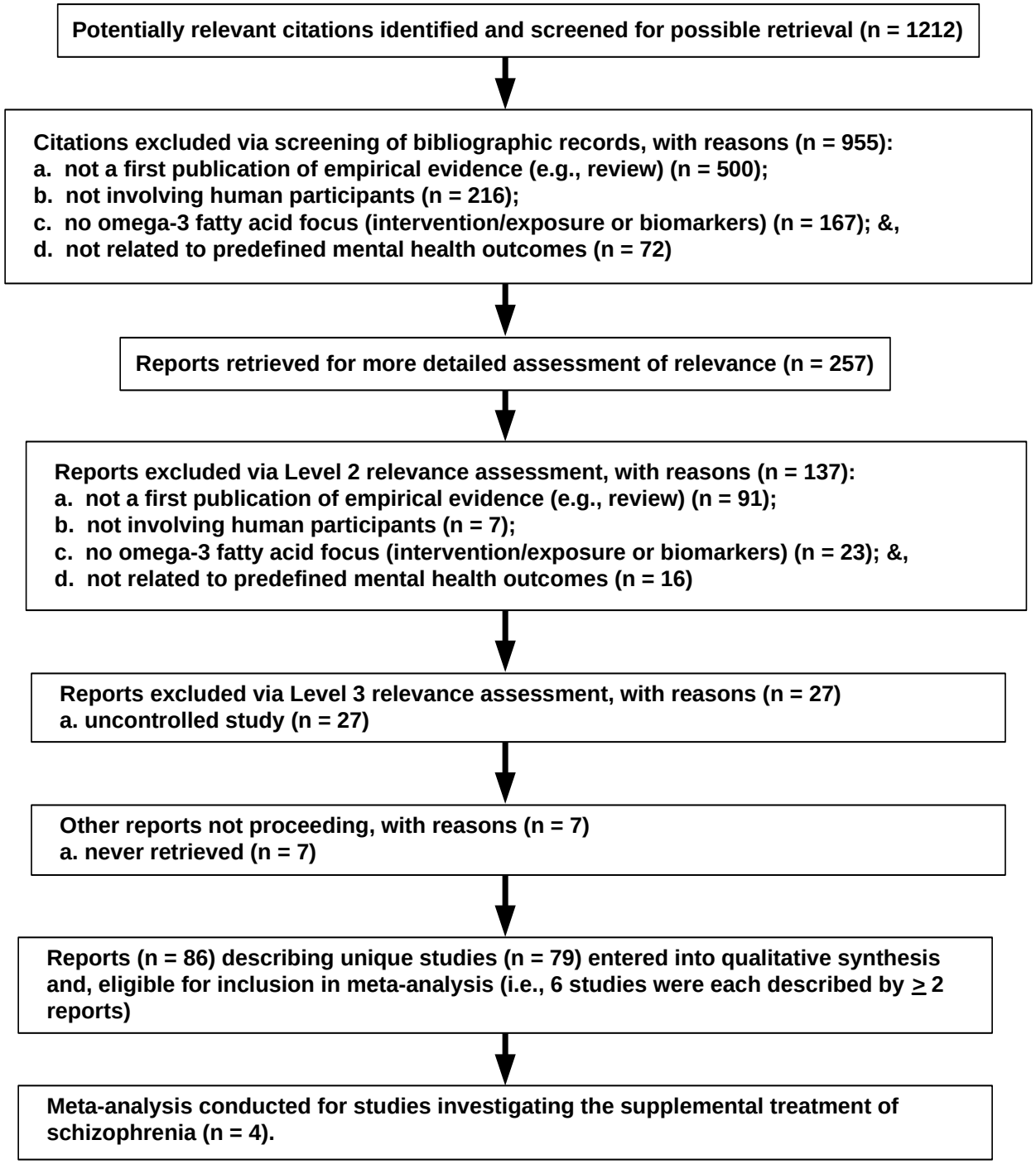
Assign 'II' to a target study population of otherwise "healthy" North American (or similar) individuals, with or without a known elevated risk for onset of a psychiatric disorder or problems, *yet* representing a more circumscribed socio-demographic picture (e.g., Asian-American/Canadian), and likely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

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

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

Appendix D. Modified QUOROM Flow Chart

Modified QUOROM Flow Chart



Appendix E. Evidence Tables

Evidence Table 1: Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Akkerhuis, 2003, NR [NR]: 4 wk "Controlled Study" {15}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=NR/NR • Age (M & range): NR • % Male: NR • Race: NR • Disease: bipolar disorder • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): NR	• Maximum 6g/d EPA ethyl ester • n=NR/NR	• placebo (undefined) • n=NR/NR	• Total quality: Could not evaluate • Applicability: X • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; NBD = not broken down; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (continued): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Brue, 2001, US [1]: 12 wk parallel RCT {1785}	• Inclusion: DSM-IV for AD/HD • Exclusion: serious & pre-existing medical or psychological conditions, stimulant meds besides Ritalin	• Enrolled/completed: n=60/51 • Age (M & range): 8.4 (4-12) y • % Male: 86% • Race: NR • Disease: AD/HD (DSM-IV) • Duration: NR • Interventions: non-Ritalin pts n-3: ginkgo biloba, melissa officinalis, grapine, dimethy-aminoethanol, L-glutamine; ritalin pts n-3: Ritalin + ginkgo biloba, melissa officinalis, grapine, dimethyaminoethanol, L-glutamine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Ritalin users: 1.0 g/d n-3, from NR (flaxseed) capsules 2/d, with breakfast & afternoon snack or dinner • Diet: NR • Cointerventions: NR • n=15/15	• non-Ritalin users: 1.0 g/d n-3, from NR (flaxseed) capsules 2/d, with breakfast & afternoon snack or dinner • Diet: NR • n=15/15 • non-Ritalin users: 0 g/d n-3, from NR (slippery elm) capsules 2/d, with breakfast & afternoon snack or dinner • n=15/15 • Ritalin users: 0 g/d n-3, from NR (slippery elm) capsules 2x/d, with breakfast & afternoon snack or dinner • n=15/15	• Jadad total score: 2/5 • Allocation concealment: Unclear • Applicability: I • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder; n-3 = omega-3

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Emsley, 2002, South Africa [1]: 12 wk parallel RCT {89}	• Inclusion: 18-55 y, DSM-IV criteria for schizophrenia, received fixed doses of antipsychotics >6 mo, PANSS total score >50 • Exclusion: substance abuse, significant medical conditions	• Enrolled/completed: n=40/39 • Age (M & SD): E-EPA: 46.2 (10.6) y; pb: 43.6 (13.9) y • % Male: NR • Race: NR • Disease: schizophrenia disorder (DSM-IV; anti-psychotics >6 mo; PANSS score >50) • Duration: E-EPA: 23.1 (8.5) y; pb: 22.2 (12.4) y • Interventions: chlorpromazine, clozapine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 3 g/d E-EPA, from 3x2 [0.5 g gelcap] capsules/d • Diet: unchanged; EPA: 0.56 g/wk to 1.13g/wk • n=20/19	• 3 g/d liquid paraffin oil, from 3x2 [0.5 g gelcap] capsules/d • Diet: unchanged; EPA: 0.56 g/wk to 1.13 g/wk • n=20/20	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: Medical Research Council of South Africa (Government), Laxdale Ltd. (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; EPA = eicosapentaenoic acid; PANSS = Positive and Negative Syndrome Scale

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Fenton, 2001, US [1]: 16 wk parallel RCT {84}	• Inclusion: 18-65 y, DSM-IV criteria for schizophrenia/schizo-affective disorder, no change of meds in prior 30 d, pharmacological tx that conforms to schizophrenia pt outcome research team, residual symptoms defined as ≥ 1 (+) &/or (-) symptom scores >4, total scores >45 with a score of >3 on ≥ 3 (+) or (-) items on the (+) & (-) PANSS scale • Exclusion: substance dependence/mental retardation, bleeding disorder, fish oil supplements, anticoagulants, cholestyramine, or clofibrate antilipemic agents	• Enrolled/completed: n=90/75 • Age (M & SD): 40 (10) y • % Male: 61% • Race: White 84% • Disease: schizophrenia disorder, schizoaffective disorder (DSM-IV) • Duration: NR • Interventions: neuroleptic, risperidone, olanzapine, quetiapine, clozapine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): NS	• 3 g/d EPA, from 6 [gelcap] E-EPA capsules/d; 4mg vitamin E per capsule • Diet: maintain background diet; 0.367 (0.378) g/d, likely EPA or DHA, from fish in diet • n=45/37	• 3 g/d mineral oil, from 6 [gelcap] capsules/d; 4mg vitamin E per capsule • Diet: maintain background diet; 0.367 (0.378) g/d, likely EPA or DHA, from fish in diet • n=45/38	• Jadad total score: 4/5 • Allocation concealment: Unclear • Applicability: I • Funding: Stanley Foundation/National Alliance for the Mentally Ill Research Institute (Government); N33: Laxdale Ltd. (Industry); National Institute on Alcohol Abuse & Alcoholism.

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; (+) = positive; (-) = negative; PANSS = Positive and Negative Syndrome Scale

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Fux, 2004, Israel [1]: 6 wk crossover RCT {3064}	• Inclusion: current OCD according to DSM-IV, 18-75 y, currently on stable maximally tolerated dose of SSRI, response to tx but no further improvement over the last 2 mo • Exclusion: unstable medical disease, alcohol/drug abuse, comorbid Axis II psychiatric diagnosis	• Enrolled/completed: n=11/10 • Age (M & SD): 33.5 (5) y • % Male: 27% • Race: NR • Disease: OCD (DSM-IV; YBOCS: 26.0 (5); HDRS: 11.3 (7); HAM-A: 14.3 (8) • Duration: 14.1 ± 8 y • Interventions: paroxetine, fluvoxamine, fluoxetine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 2 g/d E-EPA for 6 wk, from 4 [0.5 g gelcap] fish oil capsules/d, 0.2% vitamin E • capsules: 96% pure semi-synthetic ethyl-EPA, 4 % other fatty acids • Diet: NR • Cointerventions: NR • n=11/10	• 2 g/d liquid paraffin oil for 6 wk • Capsules/d: NR • Diet: NR • n=11/10	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; SSRI = selective serotonin reuptake inhibitors; OCD = obsessive compulsive disorder; tx = treatment; meds = medication/medicated; SD = standard deviation; HAM-A = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; YBOCS = Yale-Brown Obsessive Compulsive Scale; EPA = eicosapentaenoic acid; OCD = Obsessive compulsive disorder

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Gesch, 2002, UK [1]: ~142-d (mean) parallel RCT {1772}	• Inclusion: >18 y • Exclusion: NR	• Enrolled/completed: n=231/112 • Age (M & range): NR • % Male: NR • Race: NR • Disease: antisocial behaviour status • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 0.08 g/d EPA, 0.044 g/d DHA, from 4 capsules/d • Diet: permitted: 1.26 g/d LA, 0.16 g/d GLA • n=NR/57	• NR, likely trace g/d EPA, trace g/d DHA, from 4 capsules/d (vegetable, oil-based) • Diet: NR • n=NR/55	• Jadad total score: 5/5 • Allocation concealment: Adequate • Applicability: II • Funding: Research Charity, Natural Justice (Private), Scotia Pharmaceuticals Ltd (Industry), & Unigreg Ltd. (Industry - supplied nutritional supplements)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; n-6 = omega-6 fatty acids

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hamazaki, 2002, Thailand, [≥2]: 2 mo parallel RCT {97}	• Inclusion: elderly residents from farming village & employees of a university, no meds regularly • Exclusion: myocardial/cerebral infarction, cancer, other disease including alcoholism & severe hypertension	• Enrolled/completed: n=41/40 • Age (M & range): NR (50-60) y • % Male: 53.6% • Race: Thai 100% • Disease: healthy volunteers • Biomarkers (S between-grp differences): NS	• 1.5 g/d DHA, 0.2 g/d EPA, from 10 fish oil capsules/d (3 g/d), after each meal or after two of the three meals/d • Diet: maintain background diet • n=20/19	• 54.1% LA (n-6), 22.3% oleic acid (n-9), 10.8% palmitic acid (n-7), 6.8% ALA (18:3n-3), 3.7% stearic acid, 0.5% (probably trace) DHA, from 10 fish oil capsules/d (3 g/d mixed plant oil) after each meal or after 2 of 3 meals/d • Diet: maintain background diet • n=21/21	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: Science & Technology Agency of the Japanese Government, GoHo Life Sciences International Fund, Japan-US Cooperative Medical Science Program

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; LA = linoleic acid; ALA = alpha linolenic acid

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hamazaki, 1998, Japan [2]: 3 mo parallel RCT {236}	• Inclusion: nonsmoking students, good health determined by hx & physical exam, no chronic illness including alcoholism, no meds regularly • Exclusion: <70% capsule intake, > 3 kg changes in body weight, decrease in RBC DHA (DHA group only)	• Enrolled/completed: n=59/46 • Age (mean & range): Toyama: 22 (21-30) y; Kogakkan: NR (20-22) y • % Male: 50.8% • Race: likely Asian • Disease: healthy volunteers • Biomarkers (S between-grp differences): NS	• 1.5 g/d DHA, from 10 fish oil capsules/d, after each meal or after two of the three meals/d • Diet: maintain background diet • n=29/22	• 54.1% linoleic acid, 22.3% oleic acid, 10.8% palmitic acid, 6.8% alpha linolenic acid, 3.7% stearic acid, 0.5% (probably trace) DHA, from 10 fish oil capsules/d, after each meal or after two of the three meals/d; • Diet: maintain background diet • n=30/24	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: Shorai Foundation for Science & Technology; Special Coordination Funds for promoting science & technology of the Sciences & Technology Agency of the Japanese Government

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation;; RBC = red blood cells; DHA = docosahexaenoic acid

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hamazaki, 1996, Japan [2]: 3 mo parallel RCT {293}	• Inclusion: healthy, nonsmoking, volunteers from 2 universities, no meds regularly • Exclusion: NR	• Enrolled/completed: n=53/41 • Age (median & range): Toyama: 22 (21-30) y; Yokkaichi: NR (19-20) y • % Male: 35.8% • Race: Likely Asian • Disease: healthy volunteers • Biomarkers (S between-grp differences): NS	• 1.5 to 1.8 g/d DHA & some EPA, from 10 to 12 fish oil capsules/d (depending on pts weight), after each meal or after two of the three meals/d • Diet: maintain background diet • n=27/22	• 54.1% LA (n-6), 22.3% oleic acid (n-9), 10.8% palmitic acid (n-7), 6.8% alpha-linolenic acid (18:3n-3), 3.7% stearic acid, 0.5% (probably trace) DHA, from 10 to 12 (depending on pt's weight) capsules/d, from 97% soybean oil + 3% fish oil after each meal or after 2 of 3 meals/d • Diet: maintain background diet • n=26/20	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: Nissin Seifun Foundation (private) & the Japanese-US Cooperative Medical Science Program

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; DHA = docosahexaenoic acid; LA = linoleic acid

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Harding, 2003, US [1]: 4 wk comparative before-after study {1631}	• Inclusion: age 7-12 y • Exclusion: pts with comorbid disorders, meds use, street drugs, other nutritional or botanical supplements	• Enrolled/completed: 20/20 • Age (M & range): NR (7-12) y • % Male: NR • Race: NR • Disease: AD/HD (DSM-IV) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 0.18 g/d EPA, 0.12 g/d DHA, from NR capsules, vitamin E and other vitamins (B1, B2, B3, B5, B6, B12, C, A, D3, K) Folic acid, Biotin • n=10/10	• Ritalin • n=10/10	• Total quality: 4/11 • Applicability: I • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; NRCT = nonrandomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder; EPA = eicosapentaenoic acid

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hirayama, 2004, Japan [1]: 2 mo parallel RCT {3041}	• Inclusion: children 6-12 y, suspected or diagnosed AD/HD according to DSM-IV & diagnostic interviews including behavioral observations by psychiatrists • Exclusion: NR	• Enrolled/completed: n=40/40 • Age (M & range): n-3: 9 (6.8-11.3) y; pb: 9 (7-10.3) y • % Male: n-3: 80%; pb: 80% • Race: likely Asian • Disease: AD/HD (DSM-IV; N of symptoms, median scores – pts: 11 (7.5-4.5) • Duration: NR • Interventions: methylphenidate, risperidone, carbamazepine, fluvoxamine, sulpiride • Concurrent: Asperger's syndrome, conduct disorder, learning disorder, mood disorder • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 3.6g/wk DHA, 0.7g/wk EPA, from fish oil mixed with soybean milk, bread rolls & steamed bread 2/wk • n=20/20	• olive oil placebo • n=20/20	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: Japan Fisheries Association (Government) & Foundation for Total Health & Promotion (Private)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; AD/HD = attention deficit/hyperactivity disorder

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Llorente, 2003, US [1]: 4 mo parallel RCT {26}	• Inclusion: pregnant women, 18-42 y, planned to breastfeed their infants for ≥ 4 mo, not been pregnant >5 times • Exclusion: chronic medical conditions, taking dietary supplements other than vitamins, smoking	• Enrolled/completed: n=138/89 • Age (M & SD): DHA: 31.2 (4.28) y; pb: 31.7 (4.86) y • % Male: 0% • Race: White (82%), Black (NR), Hispanic (NR) • Disease: N/A (BDI M & (SD): pb: 6.5 (4.2); DHA: 7.1 (4.7)) • Biomarkers (S between-grp differences): NS	• 0.2 g/d DHA, from 1 [algae-derived TG] capsule/d • n=NR/44	• 0 g/d DHA, from 1 [algae-derived TG] capsule/d • n=NR/45	• Jadad total score: 5/5 • Allocation concealment: Adequate • Applicability: II • Funding: Martek Biosciences Corporation (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; DHA = docosahexaenoic acid ; TG = triglycerides

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Marangell, 2003, US [1]: 6 wk parallel RCT {27}	• Inclusion: 18-65 y, MADRS score ≥12, HDRS score ≥17, no psychotropic meds for at ≥ 2 wk, only 1 serving of fish/wk • Exclusion: comorbid psychiatric or medical illness, tx resistance (lifetime failure of ≥2 antidepressant trials)	• Enrolled/ completed: n=36/35 • Age (M & SD): n-3: 46.9 (11.6) y; pb: 47.9 (11.2) y • % Male: n-3: 22.2%; pb: 17.6% • Race: NR • Disease: major depressive disorder (DSM-IV) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): active = pb (no test reported)	• 2 g/d DHA • Diet: NR • Cointerventions: NR • n=18/18	• 0 g/d DHA (placebo: source undefined) • Capsules/d: NR • Diet: NR • n=18/17	• Jadad total score: 2/5 • Allocation concealment: Unclear • Applicability: X • Funding: Martek Biosciences Corporation (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; MADRS = Montgomery Asberg Depression Rating Scale; HDRS = Hamilton Depression Rating Scale; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Nemets, 2002, Israel [1]: 4 wk parallel RCT {101}	• Inclusion: major depressive disorder (DSM-IV); 18-75 y • Exclusion: alcohol/drug abuse, unstable medical disease, psychotic features, hypo-mania/mania, comorbid psychiatric diagnosis (except panic disorder, dysthymic disorder, OCD)	• Enrolled/completed: n=20/19 • Age (M & range): 53.4 (28-73) y • % Male: 15% • Race: Middle Eastern • Disease: major depressive disorder (DSM-IV; HDRS $\geq$18) • Duration: EPA: 7.6 (7.6) y; pb: 8.0 (6.5) y • Interventions: fluoxetine, mirtazapine, paroxetine, fluvoxamine, citalopram, moclobernide • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 2 g/d E-EPA from 2 [unclear whether 0.5g or 1 g gelatin capsules] fish oil capsules/d • E-EPA (ethyl ester of EPA) derived from 96 % pure fish oil, amount probably of EPA & DHA (fish oil, 4% of total dose), vitamin E corresponding to 0.2% of total dose • Diet: NR • Cointerventions: NR • n=10/10	• 0 g/d E-EPA, from 2g/d placebo, from 0.5g gelatin capsules • Capsules/d: NR • Diet: NR • n=10/9	• Jadad total score: 4/5 • Allocation concealment: Unclear • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; HDRS = Hamilton Depression Rating Scale; OCD = Obsessive compulsive disorder; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Ness, 2003, Wales [1]: 6 mo parallel RCT (one factor in factorial RCT) {1701}	• Inclusion: 37-70 y, males, tx for angina • Exclusion: denying ever having stress related chest pain, awaiting coronary artery bypass surgery, eat oily fish 2/wk, can't tolerate oily fish, serious illness, likelihood of moving from the area	• Enrolled/completed: n=452/377 • Age (M & SD): fish advice: 61.1 (6.7) y; no fish advice: 61.4 (6.2) y • % Male: 100% • Race: NR • Disease: angina pectoris • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Diet: advice to eat more fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon or trout), eat more fruit & vegetables, & stress management; 78% pts ate fatty fish wkly or took MaxEPA® capsules if could not tolerate taste of fish • Cointerventions: NR • n=229/226	• NR (no fish advice) • Capsules/d: NR • Diet: no fish, fruit & vegetable, or stress management advice; 14% of pts had fish in the diet • n=223/219	• Jadad total score: 2/5 • Allocation concealment: Unclear • Applicability: II • Funding: UK Medical Research Council (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 2002, England, Scotland [NR, likely 2]: 12 wk parallel RCT {87}	• Inclusion: 18-70 y, ≥15 on HDRS, on-going tx with antidepressants at adequate dose • Exclusion: NR	• Enrolled/completed: n=70/60 • Age (M & range): 44.8 y • % Male: 15.7% • Race: NR • Disease: depression (HRSD; score ≥15) • Duration: NR • Interventions: tricyclics, SSRIs, • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 4.0 g/d E-EPA (E-EPA), from 2x4 (500 mg gelcap) capsules/d, morning & evening • Diet: NR • Cointerventions: NR • n=17/15	• 2.0 g/d E-EPA, from 2x2 (500 mg gelcap) capsules/d, 0 g/d E-EPA from 2 x 2 (500 mg gelcap) liquid paraffin capsules/d, morning & evening • Diet: NR • n=18/16 • 1.0 g/d E-EPA, from 2x1 (500 mg gelcap) capsules/d, 0 g/d E-EPA from 2 x 3 (500 mg gelcap) liquid paraffin capsules/d, morning & evening • n=17/15 • 0 g/d E-EPA, from 2x4 (500 mg gelcap) liquid paraffin capsules/d, morning & evening • n=18/14	• Jadad total score: 4/5 • Allocation concealment: Adequate • Applicability: II • Funding: Laxdale Research Ltd (industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; SSRI = selective serotonin reuptake inhibitors; HDRS = Hamilton Depression Rating Scale; meds = medication/medicated; SD = standard deviation; tx = treatment

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 2002, England [9]: 12 wk parallel RCT {104}	• Inclusion: met DSM-IV criteria for schizophrenia, 18-70 y, time since 1st diagnosis ≤ 20 y, no important medical conditions • Exclusion: NR	• Enrolled/completed: n=122/109 • Age (M & range): pb: 39 (22-61) y; EPA 1g: 38 (20-60) y; EPA 2g: 34 (20-62) y; EPA 4g: 37 (20-56) y • % Male: pb: 65%: EPA 1g: 66%: EPA 2g: 71%; EPA 4g: 63% • Race: NR • Disease: schizophrenic disorder (DSM-IV; >50 on PANSS, >15 on Positive Symptoms subscale) • Duration: ≤20 y • Interventions: clozapine, olanzapine, risperidone, quetiapine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): NR	• 4 g/d E-EPA, from 4x2 [gelcap] E-EPA capsules/d, morning & evening • Diet: NR • Cointerventions: NR • n=27/25	• 2 g/d E-EPA, from 4 [gelcap] E-EPA capsules/d; 2 g/d liquid paraffin, from 4 [gelcap] capsules/d, morning & evening • Diet: NR • n=32/24 • 1 g/d E-EPA, from 2 [gelcap] E-EPA capsules/d; 3 g/d liquid paraffin, from 6 [gelcap] capsules/d, morning & evening • Diet: NR • n=32/29 • 0 g/d E-EPA, from 4 g/d liquid paraffin, from 4 x 2 [gelcap] capsules/d, morning & evening • Diet: NR • n=31/28	• Jadad total score: 4/5 • Allocation concealment: Adequate • Applicability: II • Funding: Laxdale Ltd. (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; PANSS = Positive and Negative Syndrome Scale

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 2001, India [1]: 3 mo parallel RCT {140}	• Inclusion: DSM-IV diagnosis of schizophrenia, symptomatic with PANSS score ≥40 • Exclusion: significant physical illness or other psychiatric disorders, antipsychotic meds	• Enrolled/completed: n=30/26 • Age (M & SD): EPA: 33.4 ± 8.5 y; pb: 36.7 ± 8.1 y • % Male: NR • Race: NR • Disease: schizophrenic disorder (DSM-IV; 100% symptomatic, PANSS score ≥ 40) • Duration: EPA: 5.7 (3.9) y; pb: 7.1 (4.1) y • Interventions: flupenthixol, haloperidol, clozapine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): EPA = ctrl (no test reported)	• 2 g/d EPA, from EPA enriched oil • Diet: NR • Cointerventions: NR • n=15/14	• 2 g/d corn oil (pb) • Diet: NR • n=15/12	• Jadad total score: 3/5 • Allocation concealment: Adequate • Applicability: III • Funding: Laxdale Ltd. (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation; PANSS = Positive and Negative Syndrome Scale

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 2001, England [1]: 3 mo parallel RCT {140}	• Inclusion: DSM-IV diagnosis of schizophrenia, symptomatic with a PANSS score ≥ 40, on stable anti-psychotic meds • Exclusion: physical illness/other psychiatric disorders	• Enrolled/completed: n=55/45 • Age (M & range): EPA: 44.2 (11.3) y; DHA: 42.0 (10.6) y; pb: 43.8 (10.8) y • % Male: EPA: 67%; DHA: 75%; pb: 57% • Race: NR • Disease: schizophrenic disorder (DSM-IV; PANSS ≥40) • Duration: NR • Interventions: antipsychotics, anti-cholinergic meds • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): EPA = DHA = ctrl (no test reported)	• 2 g/d DHA, from DHA enriched oil • Diet: NR • Cointerventions: NR • n=NR/16	• 2 g/d EPA, from EPA enriched fish oil • Capsules/d: NR • Diet: NR • n=NR/15 • 2 g/d corn oil (pb) • Capsules/d: NR • Diet: NR • n=NR/14	• Jadad total score: 4/5 • Allocation concealment: Adequate • Applicability: II • Funding: Laxdale Ltd (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation; PANSS = Positive and Negative Syndrome Scale

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Richardson, 2002, UK [1]: 12 wk parallel RCT {1819}	• Inclusion: ability normal range on BAS, reading (BAS) >2 SD below expected level, English as 1st language, endorsement from family physician, above avg. scores for age on parent rating scales (AD/HD) • Exclusion: use of fatty acid supplements in last 6 mo, eat oily fish >2/wk, hx of neurological/major psychiatric disorder or medical problem, receiving tx for AD/HD	• Enrolled/completed: n=41/29 • Age (M & range): 10.25 (8-12) y • % Male: HUFA: 82%; pb: 89% • Race: White 100% • Disease: learning difficulties, AD/HD (DSM-IV) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• 0.186 g/d EPA, 0.48 g/d DHA, from 8 capsules/d; 0.096 g/d GLA (18:3n-3), 0.864 g/d cis-linoleic acid (n-6), 0.042 g/d AA, vitamin E & 8 mg/d thyme • Diet: NR • Cointerventions: NR • n=22/15	• 0 g/d EPA, 0 g/d DHA, from 8 capsules/d; olive oil (n-9) • Diet: NR • n=19/14	• Jadad total score: 5/5 • Allocation concealment: Adequate • Applicability: II • Funding: Dyslexia Research Trust (Private)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation; BAS = British Ability Scales ; AD/HD = attention deficit/hyperactivity disorder; ALA = alpha linolenic acid; AA = arachidonic acid

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Stevens, 2003, US [1]: 4 mo parallel RCT {3107}	• Inclusion: 6-13 y, AD/HD diagnosed by clinical psychologist, psychiatrist or paediatrician, thirst/skin problems, with a thirst/skin score of >4 • Exclusion: age, distance from test site, inability to swallow capsules, lack of interest, chronic illness	• Enrolled/completed: n=50/33 • Age (M & SD): n-3: 9.5 (1.7) y; pb: 10.1 (2.0) y • % Male: n-3: 88.9%; pb: 86.7% • Race: NR • Disease: ADHD • Duration: NR • Interventions: methylphenidate • Concurrent: thirst/skin symptoms • Cointerventions: NR • Biomarkers (S between-grp differences): NS	• 0.48 g/d DHA, 0.08 g/d EPA, 0.04 g/d AA, 0.096 g/d GLA, 0.024 g/d vitamin E, from 8 [PUFA] capsules/d • Diet: NR • Cointerventions: NR • n=25/18	• 6.4 g/d olive oil, from 8 capsules/d • Diet: NR • n=25/15	• Jadad total score: 3/5 • Allocation concealment: Adequate • Applicability: I • Funding: National Institute of Mental Health (Government), Scotia Pharmaceuticals (Industry), National Fisheries Institute (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Stoll, 1999, US [2] 4 mo parallel RCT {213}	• Inclusion: male or female, 18-65 y, met DSM-IV criteria for bipolar disorder (types I or II), free medical & psychiatric comorbidity, ≥ 1 manic or hypomanic episode within last y • Exclusion: no new psychotherapy tx	• Enrolled/completed: n=44/30 • Age (M & SD): n-3: 14.4 (6.8) y; pb: 44.6 (10.4) y • % Male: n-3: 35.7%; pb: 31.25% • Race: NR • Disease: bipolar disorder (types I or II) (DSM-IV; ≥ 1 manic or hypomanic episode within past y, major depression, euthymic, mania phase) • Duration: NR • Interventions: carbamazepine, gabapentin, sertraline, lithium, bupropion, alprazolam, divalproex, sertraline, trazodone, lamotrigine, bupropion, paroxetine, clonazepam • Concurrent: NR • Cointerventions: psychiatrist or psychotherapist • Biomarkers (S between-grp differences): N/A	• 6.2 g/d EPA, 3.4 g/d DHA, from 2x7 [1g gelatin outer] menhaden fish oil capsules/d; 0.2mg t-butylhydroquinone & 2mg tocopherols per capsule • Diet: NR • Cointerventions: NR • n=~22/14	• 9.6 g/d olive oil ethyl ester, from 2x7 [1g gelatin outer] olive oil capsules/d; 0.2mg t-butylhydroquinone & 2mg tocopherols per capsule • Diet: NR • n=~22/16	• Jadad total score: 4/5 • Allocation concealment: Adequate • Applicability: I • Funding: NARSAD (Government), capsules & placebo provided by the Fish Oil Test Materials Program (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; NARSAD = National Alliance for Research on Schizophrenia and Depression

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Su, 2003, China [1]: 8 wk parallel RCT {5}	• Inclusion: major depressive disorder pts (DSM-IV); no other comorbid Axis I or Axis II conditions, Rated >18 on HDRS, no change in meds or psychotherapy 4 wks prior to study, physically healthy, competent to understand study • Exclusion: NR	• Enrolled/completed: n=28/22 • Age (M & SD): n-3: 35.2 (11.6) y; pb: 42.3 (10.7) y • % Male: pb: 20%; n-3: 16% • Race: likely Asian • Disease: major depressive disorder (DSM-IV; >18 HRSD) • Duration: NR • Interventions: fluoxetine equivalent • Concurrent: NR • Cointerventions: psychotherapy • Biomarkers (S between-grp differences): NR	• 0.44 g/d EPA, 0.22 g/d DHA, from 2 x 5 (gelcap) fish oil (menhaden) capsules/d; 0.2mg/g t-butylhydroquinone & 0.2mg/g tocopherols (antioxidants); orange flavor • Diet: NR • Cointerventions: NR • n=14/12	• NR, (probably trace) amount EPA & DHA, from 2 x NR (gelcap) capsules/d, olive oil ester, same antioxidants as n-3 grp • Diet: NR • n=14/10	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: III • Funding: National Science Council (Government), China Chemical & Pharmaceutical Co. (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; HDRS = Hamilton Depression Rating Scale; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Voigt, 2001, US [1]: 4 mo parallel RCT {132}	• Inclusion: diagnosis of AD/HD by physician, met DSM-IV criteria for AD/HD, tx successfully with stimulant meds, clinical impairment in social/academic functioning • Exclusion: ineffective tx with stimulant meds, other psychotropics, other childhood psychiatric disorders, dietary supplements other than vitamins, significant life event in last 6 mo, hx of head injuries/seizures, mental retardation/ pervasive developmental disorder, premature birth, exposure to alcohol, tobacco/other drugs in utero, disorder of lipid metabolism/other chronic medical condition	• Enrolled/completed: n=63/54 • Age (M & SD): n-3: 9.1 (2.1) y; pb: 9.5 (1.7) y • % Male: n-3: 78%; pb: 78% • Race: n-3: 100% white; pb: 85% • Disease: AD/HD (DSM-IV) • Duration: NR • Interventions: methylphenidate, dextroamphetamine, amphetamine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): active = pb (no test reported)	• 0.345 g/d DHA, from 1 algae-derived triglyceride capsule/d • Diet: NR • Cointerventions: NR • n=32/27	• NR • Capsules/d: NR • Diet: NR • n=31/27	• Jadad total score: 4/5 • Allocation concealment: Adequate • Applicability: I • Funding: US Department of Agriculture (Government); Martek Biosciences Corporation (Industry): DHA & pb capsules

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder; tx = treatment

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Wardle, 2000, England [1]: 12 wk parallel RCT {1522}	• Inclusion: serum cholesterol level >5.2 mM, no serious illness, no current/previous (within 3 mo) use of lipid-lowering meds, physician's permission to participate, signed informed consent • Exclusion: pregnancy, lactation, planning to become pregnant, serum cholesterol level >7.8 mM, use of lipid lowering meds in last 3 mo	• Enrolled/completed: n=176/155 • Age (M & SD): Low fat: 52 (11) y; Mediterranean: 54 (11) y; ctrl: 53 (8) y • % Male: Low fat: 58%; Mediterranean: 44%; ctrl: 43% • Race: NR • Disease: hypercholesterolemia • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Mediterranean diet, rich in oily fish, monounsaturated fatty acid, fruit & vegetables • Diet: increase in fruit & vegetables & oily fish; reduction in fat to 30% of energy, with substitution of predominantly monounsaturated fats for saturated fats • Cointerventions: NR • n=61/53	• Low fat diet, rich in polyunsaturated fats, low in saturated fats • Capsules/d: NR • Diet: increase polyunsaturated fats & decrease saturated fats in the diet • n=59/52 • controls not given specific advice in diet • Capsules/d: NR • Diet: maintain background diet • n=56/50	• Jadad total score: 2/5 • Allocation concealment: Adequate • Applicability: II • Funding: Biotechnology & Biosciences Research Council (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 1 (cont'd): Experimental study evidence for the effects of omega-3 fatty acids on mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Zanarini, 2003, US [1]: 8 wk parallel RCT {64}	• Inclusion: women, age 18-40 y, met DSM-IV criteria for borderline personality disorder • Exclusion: medically ill, currently on psychotropic drugs, taking E-EPA supplements or had >1-2 servings of fatty fish/wk, abusing alcohol/actively suicidal, met criteria for schizophrenia, schizoaffective disorder, bipolar I or II disorder, currently in a major depressive episode	• Enrolled/completed: n=30/27 • Age (M & SD): 26.3 (6.2) y • % Male: 0% • Race: White 76.7% • Disease: borderline personality disorder (DSM-IV) • Duration: NR • Interventions: psychotropic medications • Concurrent: NR • Cointerventions: psychotherapy • Biomarkers (S between-grp differences): N/A	• 1.0 g/d E-EPA, from 2 [0.5 g] capsules/d • Diet: NR • Cointerventions: NR • n=20/18	• 0 g/d E-EPA, from 2 (mineral oil) capsules/d • Diet: NR • n=10/9	• Jadad total score: 3/5 • Allocation concealment: Unclear • Applicability: I • Funding: NARSAD

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 2: Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Alling, 1984, Sweden [1]: N/A (i.e., no followup in cross-sectional studies), Multiple-group cross-sectional study {429}	• Inclusion: pts: chronic alcoholics; ctrl: meds free, no somatic or mental illness • Exclusion: NR	• Enrolled/completed: n=34/34 • Age (M & range): pts: 54 (41-68) y; ctrl: 39 (22-58) y • % Male: 100% • Race: NR • Disease: chronic alcoholism • Duration: 19 (10-37) y • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A (i.e., no followup in cross-sectional designs)	• Chronic alcoholics • n=13	• Healthy controls • n=21	• Total quality: 2/9 • Applicability: III • Funding: Swedish Medical Research Council, Merck, Darmastadt (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Amore, 2003, Italy [2]: N/A, Case-control study {7}	• Inclusion: schizophrenic pts, living mother • Exclusion: refusal either by pt or mother to participate	• Enrolled/completed: n=366 • Age (M & range): schizophrenic pts: 28 (20-62) y, siblings: 37 (10-67) y, ctrl: 36 (21-60) y • % Male: schizophrenic pts: 67.3%, siblings: 46.4%, ctrl: 67.3% • Race: NR • Disease: schizophrenia disorder (DSM-IV; Axis I disorders SCID-P) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Medicated schizophrenic pts • n=113	• Siblings • n=140 • Healthy controls • n=113	• Total quality: 6/10 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Arvindakshan, 2003, India [1]: N/A, Multiple-group cross-sectional study at baseline of before-after study {1657}	• Inclusion: NR • Exclusion: pts: WAIS-R full-scale IQ <80, high levels of dietary supplements, severe malnourishment, seizure disorder, head injury with loss of consciousness, alcohol & substance abuse & dependence, excessive smoking, type II diabetes, lipid disorders, cardiovascular disease, hypertension, obesity; ctrl: psychosis & major mood disorder, use of meds	• Enrolled/completed: n=73 • Age (mean & SD): schizophrenics: 29.57 (7.03) y; ctrl: 31.29 (9.86) y • % Male: schizophrenic pts: 64.3%; ctrl: 66.7% • Race: NR • Disease: schizophrenic disorder (DSM-IV) • Duration: 10.14 (6.04) y • Interventions: haloperidol, risperidone, olanzapine, clozapine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=28	• Healthy controls • n=45	• Total quality: 4/9 • Applicability: III • Funding: Council of Scientific & Industrial Research, M.L. Vasa, Laxmichand Dayabhai NIH/Fogarty International Center, Interactive Research School for Health Affairs, Vasa Heart Foundation, Bombay, India

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; tx = treatment; meds = medication/medicated; SD = standard deviation; WAIS-R = Wechsler Adult Intelligence Scale-Revised; IQ = Intelligence Quotient; NIH = National Institutes of Health; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Arvindakshan, 2003, India, [2]: N/A, Multiple-group cross-sectional study {47}	• Inclusion: 18-45 y, drug-free FEP pts with schizophrenia or schizoaffective or schizo-phreniform disorder, chronic schizophrenics • Exclusion: full scale IQ, dietary supplements, mal-nourishment, seizure disorder, head injury with loss of consciousness, alcohol/substance abuse/dependence, type II diabetes, lipid disorders, CV disease, hyperten-sion, obesity; ctrl: psychosis or major mood disorder; use of meds	• Enrolled/completed: n=97/97 • Age (M & SD): ctrl: 29.24 (8.87) y; never-med schizophrenic pts: 29.40 (9.73) y; med schizophrenic pts: 31.31 (SD 10.31) y • % Male: ctrl: 55.6%; never-med pts: 60%; med pts: 65.6% • Race: NR • Disease: schizophrenia, schizoaffective or schizophreniform disorder (DSM-IV) • Duration: non-medicated schizophrenic/schizoaffective/ schizophreniform: 2.47 (4.89) y; medicated schizophrenics: 10.12 (6.92) y • Interventions: risperidone, clozapine, olanzapine, typical antipsychotics • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Non-medicated schizophrenic pts • n=20	• Medicated schizophrenic pts • n=32 • Healthy controls • n=45	• Total quality: 2/9 • Applicability: III • Funding: Stanley Research Foundation, Washington DC, NIH/Fogarty International, Council of Scientific & Industrial Research, India, Interactive Research School for Health Affairs, Bharati Vidhyapeeth, Pune, India

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; FEP = first episode psychosis; tx = treatment; meds = medication/medicated; SD = standard deviation; CV = cardiovascular; IQ = Intelligence Quotient; NIH = National Institutes of Health

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Assies, 2001, Holland [1]: N/A, Multiple-group cross-sectional study {149}	• Inclusion: NR • Exclusion: major medical illness, mental retardation, endocrine disorders, & cholesterol-lowering diet or meds	• Enrolled/completed: n=33/33 • Age (M & SD): pts: 21.2 (2.39) y; ctrl: 20.9 (2.23) y • % Male: pts: 89.5%; ctrl: 85.7% • Race: NR • Disease: schizophrenia disorder (paranoid, disorganized, undifferentiated), schizoaffective disorder, bipolar disorder, psychotic disorder (DSM-IV) • Duration: schizophrenia pts: 11.2 (10.4) mo • Interventions: olanzapine, pimozide, risperidone, clozapine, paroxetine, fluvoxamine, oxazepam, temazepam, alprazolam, biperideen, trihexyfenidyl, dexetimide, lithium carbonate • Concurrent: cannabis abuse • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts & other diagnoses • n=19	• Matched controls • n=14	• Total quality: 2/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Buydens-Branchey, 2003, US [1]: N/A, Multiple-group cross-sectional study {3018}	• Inclusion: DSM-IV criteria cocaine dependence • Exclusion: intravenous substance use, used opiates during y before study, used >0.8g/kg of pure ethanol during y before study	• Enrolled/completed: n=24/24 • Age (M & SD): 39.0 (6.1) y (aggressive: 38 y; non-aggressive: 39.6 y) • % Male: 100% • Race: NR • Disease: cocaine addicts (DSM-IV) • Duration: NR • Interventions: NR • Concurrent: aggression • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Aggressive cocaine addicts • Diet: standard diet • n=6	• Non-aggressive cocaine addicts • Diet: standard diet • n=18	• Total quality: 4/9 • Applicability: I • Funding: Veterans Administration (Private), NIDA (Government), & NIAAA (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; FEP = first episode psychotic; meds = medication/medicated; SD = standard deviation; NIDA = National Institute of Drug Abuse; NIAAA = National Institute of Alcohol Abuse and Alcoholism

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Chiu, 2003, Taiwan [1]: N/A, Multiple-group cross-sectional study {39}	• Inclusion: pts: no medical illness, 18-65 y; ctrl: hx of mental disorder & use of psychotropic agents • Exclusion: bipolar pts with mixed episode of mood symptoms or other comorbid Axis I disorders, low fat diet or vegetarian	• Enrolled/completed: n=40/40 • Age (M & SD): pts: 39 (10.5) y; ctrl: 38.7 (12.8) y • % Male: pts: 50%; ctrl: 45% • Race: 100% Han • Disease: bipolar I disorder (DSM-IV; manic phase) • Duration: 11.1 (9.6) y • Interventions: benzodiazepine, lithium, valproate, carbamazepine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Bipolar disorder pts, acute manic phase • n=20	• Healthy volunteers • n=20	• Total quality: 5/9 • Applicability: III • Funding: National Science Council, China Chemical & Pharmaceutical Company, Taipei, Taiwan

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Edwards, 1998, UK [1]: N/A, Multiple-group cross-sectional study {249}	• Inclusion: NR • Exclusion: physical illness of a nature/ severity suggestive of low omega-3 fatty acid levels	• Enrolled/completed: n=24/24 • Age (M & SD): pts: 38.7 (10.2) y; ctrl: 39.4 (10.9) y • % Male: pts: 20%; ctrl: 14.3% • Race: NR • Disease: major depressive episode (DSM-IV; BDI: 26.9 [4.7]) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: antidepressants • Biomarkers (S between-grp differences): N/A	• Major depressive episode pts • n=10	• Matched healthy controls • n=14	• Total quality: 6/10 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Ellis, 1977, UK [1]: N/A, Multiple-group cross-sectional study {1590}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=16/16 • Age (M & range): NR • % Male: NR • Race: NR • Disease: endogenous depression, non-depressive psychiatric disorders • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Depressive disorder pts • n=6	• Non-depressive psychiatric disorder pts • n=4 • Age- & sex-matched healthy controls • n=6	• Total quality: 2/9 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Evans, 2003, US [2]: Multiple-group cross-sectional study at baseline of single prospective cohort study {3101}	• Inclusion: DSM-IV diagnosis of schizophrenia > 6 mo followup; medically healthy • Exclusion: seizures or severe head injury with loss of consciousness, hx of substance abuse < 6 mo	• Enrolled/completed: n=41/41 • Age (M & SD): FEP: 19.28 (5.1) y; ctrl: 25 (4.2) y • % Male: FEP: 87.5% • Race: NR • Disease: FEP & schizophreniform disorder (DSM-IV) • Duration: < 1 mo • Interventions: risperidone, olanzepine, • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• FEP pts • n=16	• Healthy controls • n=25	• Total quality: 1/9 • Applicability: I • Funding: NIH/NCCAM (Government) & Stanley Foundation (Private)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation; NIH = National Institutes of Health; FEP = first episode psychosis

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Fehily, 1981, UK [1]: N/A, Multiple-group cross-sectional study {2241}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=NR/60 • Age (M & range): endogenous depression: 52 (21-74) y, reactive depression: 38 (22-65) y, other psychiatric disorders: 35 (19-59) y • % Male: NR • Race: NR • Disease: endogenous depression, reactive depression, schizophrenia, personality disorders • Duration: NR • Interventions: hypnotic, tranquilliser, neuroleptic • Concurrent: bipolar disorder • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Endogenous depression pts • n=26	• Reactive depression pts • n=23 • Other psychiatric disorder pts • n=11 • Controls • n=NR	• Total quality: 3/9 • Applicability: II • Funding: South Thames Regional Health Authority

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Fischer, 1992, Germany [1]: N/A, Multiple-group cross-sectional study {346}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=24/24 • Age (range): high dose: NR (24-42) y; low dose: NR (35-53) y; untreated: NR (24-33) y; ctrl: NR (21-41) y • % Male: high dose: 78%; low dose: 29%; untreated: 50%; ctrl: 100% • Race: NR • Disease: schizophrenic disorder (high dose & low dose monotherapy (phenothiazine or thioxanthene) • Duration: NR • Interventions: perazine, flupentixol, levome-promazine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts, high dose • n=9	• Schizophrenic pts, low dose • n=7 • Schizophrenic pts, untreated • n=2 • Controls • n=6	• Total quality: 1/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hakkarainen, 2004, Finland [1]: 9 y single prospective cohort study from RCT {3001}	• Inclusion: males, 50-69 y, residing in south-western Finland 1985 • Exclusion: NR	• Enrolled/completed: n=29,133/27,111 • Age (M & range): NR • % Male: NR • Race: NR • Disease: depression/suicide • Duration: 5-8 y (median=6) • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=29,133/27,111	• N/A	• Total quality: 5/10 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hibbeln, 1998, US [1]: N/A, Multiple-group cross-sectional study {232}	• Inclusion: hx of >5 episodes of violent physical aggression, absence of major medical problems, completion of the DSM-III SCID, abstinent from alcohol, meds free • Exclusion: violent pts: major psychotic or a major affective disorder, head trauma resulting in loss of consciousness for >1h, amphetamine, hallucinogen, or opiate dependence, & current dependence on cocaine/ other illicit drugs; ctrl: 1 episode of violent physical aggression	• Enrolled/completed: n=58/58 • Age (M & SD): pts: 38.5 (6.4) y; ctrl: 39.9 (8.0) y • % Male: pts: 78%; ctrl: 71% • Race: NR • Disease: violent (DSM-III-R & RDC; >5 episodes of violent, physical aggression) • Duration: NR • Interventions: NR • Concurrent: alcohol dependent • Cointerventions: no pts on MAOI's or SSRI's in < 3 mo • Biomarkers (S between-grp differences): N/A	• Violent pts • n=27	• Non-violent controls • n=31	• Total quality: 2/9 • Applicability: I • Funding: NARSAD

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitors; tx = treatment; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hibbeln, 1998, US [1]: N/A, Multiple-group cross-sectional study {233}	• Inclusion: ctrl: negative alcohol breath tests & urine drug testing, no major medical disorders, did not meet criteria for current or lifetime psychiatric or substance use disorder; pts: abstinent for 21-63 d at time of study • Exclusion: lifetime hx of major psychotic illness or bipolar affective disorder	• Enrolled/completed: n=176/176 • Age (M & SD): late-onset alcoholics: 45.5 (8.8) y; early-onset alcoholics: 36.5 (8.7) y; ctrl: 37 (15.7) y • % Male: late-onset: 85%; early-onset: 96%; ctrl: 77.5% • Race: White, Black • Disease: alcoholics (DSM-III-R; early onset: excessive alcohol use < 25 y age) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Early onset alcoholic pts • n=88	• Late onset alcoholic pts • n=39 • Healthy controls • n=49	• Total quality: 3/9 • Applicability: I • Funding: NARSAD

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Holman, 1995, US [1]: N/A, Multiple-group cross-sectional study {314}	• Inclusion: pts: females, diagnosed as anorexia nervosa by staff psychiatrist; ctrl: healthy females <19 y • Exclusion: NR	• Enrolled/completed: n=27/27 • Age (M & range): pts: 18.4 (15-24) y, ctrl: 23.5 (1.7) y • % Male: 0% • Race: NR • Disease: anorexia nervosa • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Anorexic pts • n=8	• Healthy controls • n=19	• Total quality: 1/9 • Applicability: I • Funding: Carle Foundation (Private), NIH, Harmel Foundation (Private), & by Scotia Pharmaceuticals (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation; NIH = National Institutes of Health

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Horrobin, 1989, England, Scotland, Ireland [3]: N/A, Multiple-group cross-sectional study {389}	• Inclusion: schizophrenia disorder according to DSM-III criteria • Exclusion: NR	• Enrolled/completed: n=203/203 • Age (M & range): pts: 40.8 (20-71) y; ctrl: 35.7 (19-66) y • % Male: pts: 72.6%, ctrl: 51.3% • Race: NR • Disease: schizophrenic disorder (DSM-III-R & Research Diagnostic Criteria) • Duration: NR • Interventions: neuroleptic drugs • Concurrent: tardive dyskinesia (AIMS score > 2) • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=84	• Controls • n=119	• Total quality: 2/9 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; TD = tardive dyskinesia; NBD = not broken down; tx = treatment; AIMS = Abnormal Involuntary Movement Scale

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Iribarren, 2004, US [3]: N/A, Single population cross-sectional survey {3076}	• Inclusion: Black or White, males or females, age 18-30 y • Exclusion: NR	• Enrolled/completed: n=5,115/3,581 • Age (M & SD): Black men 29.4 (3.7) y; White men 30.5 (3.3) y; Black women 29.6 (3.8) y; White women 30.6 (3.4) y • % Male: 44.5% • Race: Black: 45.7%, White: 54.2% • Disease: Hostility • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=5,115/3,581	• N/A	• Total quality: 5/9 • Applicability: II • Funding: National Heart Lung & Blood Institute (Government) & the National Institutes of Health (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Kaiya, 1991, Japan [1]: N/A, Multiple-group cross-sectional study {363}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=107/107 • Age (M & SD): ctrl: 36.3 (12.6) y; schizophrenia: 35.7 (9.9) y; other disorders: 36.3 (12.6) y • % Male: ctrl: 37.5%; schizophrenia: 61%; other disorders: 37.5% • Race: NR • Disease: schizophrenia, affective, & paranoid disorder (DSM-III, DSM-III-R; platelets hyposensitive to prostaglan-din) • Duration: NR • Interventions: neuroleptics, haloperidol equivalents, antidepressants • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • Diet: maintain Japanese diet rich in rice & seafood • n=59	• Other psychiatric disorder pts • Diet: maintain Japanese diet rich in rice & seafood • n=24 • Controls • Diet: maintain Japanese diet rich in rice & seafood • n=24	• Total quality: 3/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Khan, 2002, US, [3]: N/A, Multiple-group cross-sectional study {71}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=68/68 • Age (M & SD): FEP: 22.40 (4.08) y; chronic medicated-schizophrenics: 45.89 (6.32) y; ctrl: 24 (5.6) y • % Male: FEP: 81.8%; chronic med-schizophrenics: 100%; ctrl: 87.5% • Race: NR • Disease: schizophrenia or schizophreniform disorder (DSM-IV) • Duration: FEP: ± 4.5 d; chronic med schizophrenics: 23.55 (7.38) y • Interventions: clozapine, haloperidol, olanzapine, risperidone • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Medicated schizophrenic pts • n=30	• Non-medicated FEP pts • n=22 • Healthy controls • n=16	• Total quality: 3/9 • Applicability: I • Funding: NIH/NCCAM (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; FEP = first episode psychosis; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Langan, 1985, US [1]: N/A, Multiple-group cross-sectional study {419}	• Inclusion: admission to the young adult psychosomatic ward (University of Wisconsin Clinical Sciences Center for anorexia nervosa), availability of plasma leftover after laboratory studies upon admission • Exclusion: NR	• Enrolled/completed: n=28/26 • Age (M & SD): pts: 16.8 (2.3) y; ctrl: 20.7 (1.0) y • % Male: pts: 6% ctrl: 0% • Race: NR • Disease: anorexia nervosa • Duration: 17.2 (1-39) mo • Interventions: NR • Concurrent: 10/15 pts secondary amenorrhea • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Anorexic pts • n=17	• Healthy controls • n=11	• Total quality: 2/9 • Applicability: I • Funding: NIH

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation; NIH = National Institutes of Health

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Leask, 2000, UK [2]: N/A, Case-control study {3142}	• Inclusion: national birth cohort 1946; national birth cohort 1958 • Exclusion: NR	• Enrolled/completed: n=24,218 • Age (M & range): 1946: pts: 43 (NR) y; ctrl: 43 (NR) y; 1958: 16-28 y • % Male: 1946: 52%; 1958: 51% • Race: NR • Disease: 1946: schizophrenia (DSM-III-R); 1958: schizophrenia (CATEGO) • Duration: N/A • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp diff): N/A	• National birth cohort, 1946 • n=5,362	• National birth cohort, 1958 • n=18,856	• Total quality: 5/10 • Applicability: II • Funding: Stanley Foundation Grant

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Maes, 1999, Belgium [1]: N/A, Multiple-group cross-sectional study {209}	• Inclusion: NR • Exclusion: pts: Axis I dx, unipolar major depression, Axis II, borderline & anti-social personality disorder, abnormal heart & lungs XR tx fluoxetine, trazodone, MAOIs, antipsychotic drugs, anticonvulsants, lithium, ECT 1 y before study; ctrl: abnormal lab tests, acute or chronic medical illness, acute infectious/allergic reactions < 2 study, low fat diet/cholesterol lowering drugs, meds affecting fatty acid metabolism/endocrine/ immune functions, BMI >normal, smokers, not on normal Belgium diet	• Enrolled/completed: n=48/48 • Age (M & SD): pts: 52.2 (13.6) y; ctrl: 48.3 (15.2) y • % Male: pts: 53%; ctrl: 64% • Race: White 100% • Disease: major depression (DSM-III-R) • Duration: NR • Interventions: antidepressants • Concurrent: NR • Cointerventions: benzodiazepines permitted • Biomarkers (S between-grp differences): N/A	• Major depression pts • n=34	• Controls • n=14	• Total quality: 6/9 • Applicability: III • Funding: Funds for Scientific Research, Vlaanderen, Belgium, the Clinical Research Center Mental Health, Antwerp, Belgium, Staglin Investigator Award.

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; MAO = monoamine oxidase; tx = treatment; meds = medication/medicated; SD = standard deviation; XR = radiograph

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Maes, 1996, Belgium [1]: N/A, Multiple-group cross-sectional study {285}	• Inclusion: no medical illness • Exclusion: ethnic minority, mental disorders, low fat diet, Axis I diagnosis beside unipolar depression, substance use/abuse disorder, borderline or antisocial personality disorder, MAOIs, anticonvulsants, lithium or ECT 1 y prior to study, abnormal heart & lungs XR	• Enrolled/completed: n=74/74 • Age (M & SD): ctrl: 42.0 (13.6) y; minor depression: 44.5 (14.3) y; major depression: 47.4 (17.0) y • % Male: ctrl: 50%; minor: 36%; major: 31% • Race: 100% Flemish • Disease: major & minor depression (DSM-III-R) • Duration: NR • Interventions: antidepressants, benzodiazepines, haloperidol, chlorazepate • Concurrent: melancholia, adjustment disorder, depressed mood, dysthymia • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Major depression pts • n=36	• Minor depression pts • n=14 • Healthy volunteers • n=24	• Total quality: 6/9 • Applicability: III • Funding: Elisabeth Severance Prentiss & John Pascal Sawyer Foundations; National Funds for Scientific Research, IUAP Program, Antwerp, Belgium; USPHS Research Career Scientist Award

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; MAO = monoamine oxidase; meds = medication/medicated; SD = standard deviation; EEG = electroencephalogram; EKG = electrocardiogram; XR = radiograph

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Mahadik, 1996, US [2]: N/A, Multiple-group cross-sectional study {278}	• Inclusion: DSM-III-R diagnosis of schizophrenia, BMD, monitoring of FEP pts for 1st 6 mo of illness, healthy; ctrl: no hx of psychosis, major mood disorder, type II diabetes • Exclusion: substance abuse/dependence, seizure disorder, head injury/loss of consciousness, family hx Huntington's disease, dementia, mental retardation	• Enrolled/completed: n=26/26 • Age (M & SD): schizophrenic: 26.75 (10) y; BMD: 33.00 (6.8) y; ctrl: 33.63 (5.5) y • % Male: schizophrenic: 100%; BMD: 91.7%; ctrl: 75% • Race: NR • Disease: schizophrenia, bipolar mood disorder (DSM-III-R) • Duration: FEP pts: 4.6 (2.8) d • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=12	• Bipolar disorder pts • n=6 • Controls • n=8	• Total quality: 5/9 • Applicability: I • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = pb = placebo; MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitors; FEP = first episode psychosis; BMD = bipolar disorder; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
McCreadie, 1997, UK [1]: N/A, Case-control study {3143}	• Inclusion: schizophrenic pts • Exclusion: NR	• Enrolled/completed: n=137/137 • Age (M & range): NR • % Male: pts: 64%; ctrl: NR • Race: NR • Disease: schizophrenia (ICD-9) • Duration: N/A • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp diff): N/A	• Schizophrenic pts • n=45	• Siblings • n=92 • National surveys: • Great Britain 1946, n=13,687 • Scotland 1958, n=1,648 • Scotland 1980, n=1,718	• Total quality: 4/10 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Mellor, 1996, England [1]: 1 wk single prospective cohort study at baseline of a non-comparative before-after study {2101}	• Inclusion: currently long-term inpatients, receiving neuroleptic meds • Exclusion: NR	• Enrolled/completed: n=20/20 • Age (M & range): 56.1 (NR) y • % Male: 65% • Race: NR • Disease: chronic schizophrenia (DSM-III-R) • Duration: NR • Interventions: N/A • Concurrent: NR • Cointerventions: N/A • Biomarkers (S between-grp diff): N/A	• Chronic schizophrenia pts • n=20	• N/A	• Total quality: 4/10 • Applicability: II • Funding: Seven Seas Healthcare Ltd., Hull, for MaxEPA® capsules

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Mitchell, 1987, New Zealand [1]: N/A, Multiple-group cross-sectional study {401}	• Inclusion: diagnosed with AD/HD by parents on RBPC & by teachers on CTQ; ctrl: score < P 65 on 4 subscales of hyperactivity • Exclusion: NR	• Enrolled/completed: n=97/97 • Age (M & SD): hyperactive: 9.1 (2.3) y; ctrl: 8.7 (2.3) y • % Male: hyperactive: 85.5%; ctrl: 81.8% • Race: European: hyperactive: 92%; ctrl: 92% • Disease: hyperactive (DSM-III, RBPC, CTQ; >P 90 on subscales of RBPC) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Hyperactive children • n=48	• Controls • n=49	• Total quality: 4/8 • Applicability: III • Funding: Efamol Research Ltd (Industry), Medical Research Council of New Zealand

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; RBPC = Revised Behavior Problem Checklist; CTQ = Conners Teacher Questionnaire; meds = medication/medicated; SD = standard deviation; P = percentile

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Mitchell, 1983, New Zealand [1]: N/A, Multiple-group cross-sectional study {439}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=43/43 • Age (M & range): maladjusted: (7.5-13) y; ctrl: (10-13) y • % Male: maladjusted: 91%; ctrl: 50% • Race: NR • Disease: maladjusted children (Handicapped Pupils & School Health Service Regulations) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Maladjusted (hyperactive) children • n=23	• Normal children • n=20	• Total quality: 1/8 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Obi, 1979, Nigeria [1]: N/A, Multiple-group cross-sectional study {458}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=12/12 • Age (M & range): schizophrenia: NR (30-50) y; ctrl: NR (22-45) y • % Male: NR • Race: NR • Disease: schizophrenic disorder • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=6	• Healthy controls • n=6	• Total quality: 1/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 1998, England [1]: N/A, Multiple-group cross-sectional study {251}	• Inclusion: suffering from a major depressive episode, unipolar illness, 18-65 y • Exclusion: NR	• Enrolled/completed: n=30/30 • Age (M & SD): pts: 47.4 (11.0) y; ctrl: 47.0 (10.3) y • % Male: pts: 53%; ctrl: 53% • Race: NR • Disease: major depressive episode, unipolar illness (DSM-IV) • Duration: NR • Interventions: dothiepin, paroxetine, fluoxetine, trazodone, lofepramine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Major depressed pts, unipolar • n=15	• Healthy controls • n=15	• Total quality: 4/9 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 1997, UK [1]: N/A, Case-control study {3145}	• Inclusion: schizophrenic pts; ctrl: non-psychiatric pts • Exclusion: NR	• Enrolled/completed: n=110/110 • Age (M & range): pts: 34 (NR) y; ctrl: NR • % Male: pts: 85% ctrl: (NR) • Race: NR • Disease: schizophrenia (DSM-IV) • Duration: NR • Interventions: N/A • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=55	• Non-psychiatric controls • n=55	• Total quality: 3/10 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 1995, UK [1]: N/A, Multiple-group cross-sectional study {303}	• Inclusion: pts: neuroleptic-treated, physically healthy, schizophrenia (DSM-III criteria); ctrl: hospital staff, no hx of mental disorder, on no meds • Exclusion: NR	• Enrolled/completed: n=39/39 • Age (M & range): pts: 55 (28-75) y • % Male: pts: 69.5% • Race: NR • Disease: schizophrenia disorder (DSM-III-R) • Duration: >5 y • Interventions: chlorpromazine • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts with tardive dyskinesia • n=23	• Healthy controls • n=16	• Total quality: 3/9 • Applicability: II • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Ranjekar, 2003, India [2]: N/A, Multiple-group cross-sectional study {3094}	• Inclusion: schizophrenics or BMD • Exclusion: WAIS-R full scale IQ<80, high use of diet supplements, undernourishment or malnourishment, seizure disorder, head injury, substance abuse/dependence, type II diabetes, lipid disorders, CV disease, hypertension, family hx of same, obesity; ctrl: medications/substance abuse	• Enrolled/completed: n=72/72 • Age (M & SD): ctrl: 39.72 (8.87) y; schizophrenics: 37.32 (7.18) y; BMD: 40.8 (8.29) y • % Male: 100% • Race: NR • Disease: schizophrenic disorder & BMD (DSM-IV) • Duration: NR • Interventions: atypical antipsychotics, antidepressants • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts • n=31	• Bipolar disorder pts • n=10 • Healthy controls • n=31	• Total quality: 4/9 • Applicability: III • Funding: Mr. M.L. Vasa, Laxmichand Dayabhai (Export) Co. (Private)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; tx = treatment; meds = medication/medicated; SD = standard deviation; WAIS-R = Wechsler Adult Intelligence Scale - Revised; CV = cardiovascular

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Sasaki, 2000, Japan [2]: N/A, Case-control study {3144}	• Inclusion: schizophrenic pts • Exclusion: NR	• Enrolled/completed: n=337/337 • Age (M & range): pts: 32 ± 9 y; healthy siblings: 34.6 ± 8.4; ctrl: 31 ± 10 y • % Male: pts: 60%; healthy siblings: 59.5%; ctrl: 46% • Race: Asian • Disease: schizophrenia (DSM-IV) • Duration: N/A • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp diff): N/A	• Schizophrenic pts • n=100	• Healthy siblings • n=37 • Healthy controls • n=200	• Total quality: 5/10 • Applicability: III • Funding: Ministry of Welfare of Japan (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; pb = placebo; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Silvers, 2002, New Zealand [122 geographic areas; 11,921 households]: N/A, Single population cross-sectional survey {1483}	• Inclusion: resident of New Zealand in 1996 & 1997 • Exclusion: NR	• Enrolled/completed: n=12,506/4,644 • Age (M & range): grp 1: NR (15-24) y; grp 2: NR (25-44) y; grp 3: NR (45-64) y; grp 4: >65 y • % Male: NR • Race: NR • Disease: adults age >15 y • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=12,506/4,644 (adults age > 15 y)	• N/A	• Total quality: 5/9 • Applicability: III • Funding: New Zealand Ministry of Health (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Stevens, 1995, US [1]: N/A, Multiple-group cross-sectional study {301}	• Inclusion: males, 6-12 y, healthy with diagnosis of or suspected AD/HD, PTCRS score >15; ctrl: PTCRS <15 • Exclusion: NR	• Enrolled/completed: n=96/96 • Age (M & SD): AD/HD: 9.1 (2.0) y; ctrl: 9.1 (2.3) y • % Male: 100% • Race: NR • Disease: AD/HD (≥15 PTCRS) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Hyperactive (AD/HD) boys • n=53	• Normal boys • n=43	• Total quality: 3/8 • Applicability: I • Funding: State of Indiana (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; PTCRS = Parent/Teacher Conners Rating Scale; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Suzuki, 2004, Japan [1]: N/A, Single population cross-sectional survey {3038}	• Inclusion: lung cancer, diagnosis confirmed by histological examination, physically capable of completing questionnaires, no cognitive impairment, ability to provide written consent, problem with pts participation judged by physician • Exclusion: NR	• Enrolled/completed: n=902/771 • Age (M & SD): HADS-D ≤4: 64.0 (9.5) y; HADS-D ≥5: 64.3 (9.1) y • % Male: HADS-D ≤4: 72.2%; HADS-D ≥5: 72% • Race: likely Asian • Disease: lung cancer • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=902/771	• N/A	• Total quality: 7/9 • Applicability: III • Funding: Japanese Ministry of Health, Labor, & Welfare (Government)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention* (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s)* (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Tanskanen, 2001, Finland [1]: N/A, Single population cross-sectional survey {142}	• Inclusion: 25-64 y • Exclusion: NR	• Enrolled/completed: n=3,004/1,767 • Age (M & range): 25-64 y • % Male: NR • Race: NR • Disease: N/A • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=3,004/1,767	• N/A	• Total quality: 4/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Tanskanen, 2001, Finland [1]: N/A, Single population cross-sectional survey {1874}	• Inclusion: 25-64 y, Finnish adults • Exclusion: NR	• Enrolled/completed: n=5,105/3,204 • Age (M & range): 48.8 (NR) y • % Male: NR • Race: NR • Disease: N/A (20% mild depressive symptoms, 6.3% moderate, 1.5% severe) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=5,105/3,204	• N/A	• Total quality: 3/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Tiemeier, 2003, Holland [1]: N/A, Multiple-group cross-sectional study {1457}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: n=682/682 • Age (M & range): subthreshold depressive pts: 73.9 (61-93) y; depressive disorder pts: 73.7 (61-97) y; ctrl: 72.5 (61-101) y • % Male: subthreshold depressive pts: 22.7%; depressive disorder pts: 27.4%; ctrl: 41.4% • Race: NR • Disease: depressive disorders (major depression, dysthymia, minor depression) (DSM-IV; >16 on CES-D) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Depressive disorders • n=106	• Depressive symptoms • n=115 • Controls • n=461	• Total quality: 5/9 • Applicability: III • Funding: Ministry of Education & Science; Ministry of Health, Welfare, & Sports; Grant from Numico research

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Vaddadi, 1996, Australia [3]: N/A, Multiple-group cross-sectional study at baseline of multiple prospective cohort study {282}	• Inclusion: NR • Exclusion: hx of established neurological illness, developmental handicap or currently receiving nonsteroidal anti-inflammatory drugs	• Enrolled/completed: n=114/52 • Age (M & range): pts: 35.4 (18-64) y • % Male: pts: 75% • Race: NR • Disease: schizophrenia & schizoaffective disorder (DSM-III-R) • Duration: 12.3 (8.9) y • Interventions: neuroleptics • Concurrent: tardive dyskinesia (TD) • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Schizophrenic pts without TD • n=40	• Schizophrenic pts with TD • n=32 • Normal controls • n=39	• Total quality: 1/9 • Applicability: III • Funding: Scotia Pharmaceuticals Ltd. Guildford, UK (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; TD = tardive dyskinesia; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Vancassel, 2001, France [1]: N/A, Multiple-group cross-sectional study {131}	• Inclusion: no hx of endocrine or systemic disease • Exclusion: NR	• Enrolled/completed: n=33/33 • Age (M & range): autism: 8.3 (3-17) y; mentally retarded: 8.7 (1-19) y • % Male: autism: 73.3%; mentally retarded: 72.2% • Race: NR • Disease: autism, mentally retarded (DSM-III-R & DSM-IV) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Autistic children • n=15	• Mentally retarded children • n=18	• Total quality: 4/9 • Applicability: III • Funding: INRA, INSERM U316, INSERM Network 4R002B, Foundation France Telecom

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Virkkunen, 1987, Finland [1]: N/A, Multiple-group cross-sectional study {397}	• Inclusion: committed ≥1 violent crime, ≥2 episodes of loss of control of aggressive impulses resulting in serious assault/bodily harm, DSM-III criteria for antisocial personality/intermittent explosive disorder/ alcohol abuse • Exclusion: mentally retarded (IQ < 68), chromosome abnormality, antisocial personality, no violent tendency, schizophrenia	• Enrolled/completed: n=50/50 • Age (M & range): antisocial: 28.5 (12.9) y; explosive: 36.8 (16.4) y; ctrl: 33 (11.1) y • % Male: 100% • Race: NR • Disease: violent, alcohol abuse, epilepsy, borderline personality disorder, paranoid personality disorder, antisocial personality disorder (DSM-III; committed ≥1 violent crime, ≥2 episodes of loss of control) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Violent antisocial personality disorder pts • n=15	• Intermittent explosive disorder pts • n=19 • Healthy controls • n=16	• Total quality: 4/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Woo, 2002, China [NR]: 36 mo single prospective cohort study {1777}	• Inclusion: age >70 y • Exclusion: NR	• Enrolled/completed: n=2,032/1,171 • Age (M & SD): 80 (7.1) y • % Male: 49.2% • Race: Asian 100% • Disease: N/A • Duration: N/A • Interventions: N/A • Concurrent: N/A • Cointerventions: N/A • Biomarkers (S between-grp differences): N/A	• n=2,032/1,171	• N/A	• Total quality: 4/10 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Yang, 1999, Taiwan [1]: N/A, Multiple-group cross-sectional study {1962}	• Inclusion: pts: met DSM-IV AD/HD diagnosis, >80% on standard, Child Activity Level Form ctrl: 4-8 y, verified in good health • Exclusion: ctrl: children with suspected case of AD/HD	• Enrolled/completed: n=52/52 • Age (M & SD): ctrl: 5.2 (1.1) y; pts: 5.7 (0.9) y • % Male: ctrl: 91%; pts: 90% • Race: likely Asian • Disease: AD/HD (DSM-IV; >80% on Standard, Child Activity Level Form) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• AD/HD children • n=20	• Healthy control children • n=32	• Total quality: 5/8 • Applicability: III • Funding: Chun Qing Infant & Child Nutritional Research Foundation

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation; AD/HD = attention deficit/hyperactivity disorder

Evidence Table 2 (cont'd): Observational study evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Yao, 2002, US [1]: N/A, Multiple-group cross-sectional study {1459}	• Inclusion: pts: IQ ≥75, 12-45 y, no hx of neuroleptic tx, DSM-IV criteria for schizophrenia, schizophreniform, schizoaffective disorder; ctrl: 12-45 y, no hx or current psychiatric/neurologic disorder • Exclusion: pts: substance use within 4 wk of study, medical illness, hyperlipidemia, starvation < 2 wk, neurologic disorders, head injury with loss of consciousness, psychosis >2 y, comorbidity for DSM-IV Axis I diagnosis; ctrl: hx of psychosis or major mood disorder, family hx of psychosis/major mood disorder	• Enrolled/completed: n=22/22 • Age (M & range): pts: 26 (17-44) y; ctrl: 26 (19-39) y • % Male: pts: 54.5%; ctrl: 54.5% • Race: NR • Disease: schizophrenia, schizophreniform, schizoaffective disorder (DSM-IV) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Drug-naïve, FEP schizophrenic pts • n=11	• Normal controls • n=11	• Total quality: 3/9 • Applicability: I • Funding: National Institute of Mental Health, NARSAD Young Investigator Award, Office of Research & Development, Department of Veteran Affairs, Highland Drive VA Pittsburgh Healthcare System

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation; tx = treatment; FEP first episode psychosis

Evidence Table 3: Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Christensen 1988, [8 countries]: N/A, Cross-national ecological analysis {3125}	• Inclusion: NR • Exclusion: NR	• Enrolled/completed: NR • Age (M & range): NR • % Male: NR • Race: NR • Disease: schizophrenia • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• Diet: saturated fatty acids, n-3 and n-6 fatty acids: fat from land animals & birds; 1.7 - 32.1% of energy derived from fat from land animals & birds; EPA, DHA & ALA: fat from vegetables, fish & seafood; 7.5 - 14.5% of energy derived from fat from vegetables, fish & seafood • n=8 countries	• N/A	• Total quality: 3/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = historymeds = medication/medicated; SD = standard deviation; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ALA = alpha linolenic acid

Evidence Table 3 (cont'd): Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hibbeln, 2002, US [23 countries]: N/A, Cross-national ecological analysis {59}	• Inclusion: major postpartum depressive symptoms • Exclusion: NR	• Enrolled/completed: n=14,532/14,532 • Age (M & SD): 28.4 (1.3) y • % Male: 0% • Race: NR • Disease: major postpartum depressive symptoms (EPDS; EPDS score >12/13) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=23 countries (total)	• N/A	• Total quality: 7/9 • Applicability: III • Funding: NARSAD

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; EPDS= Edinburgh Postpartum Depression Scale; meds = medication/medicated; SD = standard deviation

Evidence Table 3 (cont'd): Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hibbeln, 2001, [26 countries]: N/A, Cross-national ecological analysis {1503}	• Inclusion: countries with data on seafood consumption & deaths due to homicide (WHO) • Exclusion: US (rate of death due to homicide too high)	• Enrolled/completed: NR • Age (M & range): NR • % Male: NR • Race: NR • Disease: homicide deaths • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=26 countries (total)	• N/A	• Total quality: 4/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; WHO = World Health Organization

Evidence Table 3 (cont'd): Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Hibbeln, 1998, US [9 countries]: N/A, Cross-national ecological analysis {239}	• Inclusion: ≥ 1 depressive episode, including grief lasting > 1 y • Exclusion: criteria for a manic episode	• Enrolled/completed: NR • Age (M & range): NR (18-65) y • % Male: US: 41%, Alberta: 41%, Puerto Rico: 43%, France: 38%, Germany: 48%, Italy: 47%, Lebanon: 43%, Taiwan: 52%, Korea: 48%, New Zealand: 34% • Race: NR • Disease: major depression (DSM-III) • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=9 countries	• N/A	• Total quality: 2/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean

Evidence Table 3 (cont'd): Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Noaghiul, 2003, [11 countries (bipolar disorder), 14 countries (schizo-phrenia disorder]: N/A, Cross-national ecological analysis {3020}	• Inclusion: community samples with clearly defined sample population, large sample size, age 18-64 y, appropriate sampling methods, structured diagnostic instruments • Exclusion: NR	• Enrolled/completed: NR • Age (M & range): NR (18-64) y • % Male: NR • Race: NR • Disease: Bipolar Disorder/Schizophrenia • Duration: NR • Interventions: NR • Concurrent: NR • Cointerventions: NR • Biomarkers (S between-grp differences): N/A	• n=11 countries (bipolar disorder), 14 countries (schizophrenia)	• N/A	• Total quality: 4/9 • Applicability: III • Funding: NR

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; hx = history; meds = medication/medicated; SD = standard deviation

Evidence Table 3 (cont'd): Cross-national ecological analytic evidence for the association between omega-3 fatty acids and mental health

Author, Year, Location [N sites]: Length & Design	Eligibility Criteria	Prestudy/ Baseline Population Characteristics	Intervention (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Comparator(s) (Dose/Type/Source/ Delivery) & N Enrolled/Completed	Study Quality (internal validity)/ Applicability (external validity)/ Funding Source
Peet, 2004, UK [8 countries] N/A, Cross-national ecological analysis {3128}	• Inclusion: data in data-bases on international variations in outcome of schizophrenia, prevalence of depression, patterns of food usage • Exclusion: NR	• Enrolled/completed: 8/8 (countries) • Age (M & range): NR • % Male: NR • Race: NR • Disease: Schizophrenia/Depression • Duration: NR • Biomarkers (S between-grp differences): N/A	• n=8 countries	• N/A	• Total quality: 3/9 • Applicability: III • Funding: Laxdale Ltd (Industry)

length = intervention/exposure length; design = research design; intervention = intervention/exposure; disease = diagnosis & severity; duration = time since diagnosis; concurrent = concurrent conditions; pts = participants; n = number of participants; enrolled = n qualified; completed = n completing the study; RCT = randomized controlled trial; wk = week; y = year; g = gram; mo = month; d = day; grp = group; S = significant; NS = nonsignificant; N/A = not applicable; NR = not reported; ctrl = control(s); M = mean; meds = medication/medicated; SD = standard deviation

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Additional Acknowledgements

The UO-EPC gratefully acknowledges the following individuals who served on our Technical Expert Panel (TEP). Acknowledgement does not reflect endorsement of this report.

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The UO-EPC gratefully acknowledges the following individuals who reviewed the initial draft of this evidence report, and provided constructive feedback. Acknowledgement does not reflect endorsement of this report.

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