Health Effects of Omega-3 Fatty Acids on Asthma

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Preface

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

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

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

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Acknowledgments

Structured Abstract

Context. Considerable interest in the possible value of omega-3 fatty acid supplementation in asthma was sparked by Horrobin's hypothesis that the low incidence of asthma in Eskimos stems from their consumption of large quantities of oily fish, rich in omega-3 fatty acids. Additional impetus for research came from observations that omega-3 fatty acids' possible protective, or even therapeutic, effect might be afforded by their impact on mediators of inflammation thought to be related to the pathogenesis of asthma.

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 health effects of omega-3 fatty acids in asthma. Questions addressed the: efficacy of omega-3 fatty acids to improve respiratory outcomes; impact of covariates (e.g., omega-3 fatty acid source, type, and dose) on efficacy; influence of omega-3 fatty acids on mediators of inflammation thought to be related to the pathogenesis of asthma; value of omega-3 fatty acids as primary prevention as well as secondary prevention; and, safety profile in asthma populations, or subpopulations, and those at risk. The results may be used to inform a research agenda as well as to assist clinicians in advising patients who may wish to take this supplementation to treat or prevent asthma.

Data Sources. A comprehensive search for citations was conducted using six databases (Medline, Premedline, Embase, Cochrane Central Register of Controlled Trials, CAB Health, and, Dissertation Abstracts). Searches were not restricted by language of publication, publication type, or study design except with the MeSH term "dietary fats," which was limited by study design to increase its specificity. Search 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®; fish oil); and, relevant population terms (e.g., asthma; inflammation). Additional published or unpublished literature was sought through manual searches of reference lists of included studies and key review articles, and from the files of content experts.

Study Selection. Studies were considered relevant if they described human populations of any age, involved any type of study design, and investigated the use of any foods or extracts known to contain omega-3 fatty acids as a treatment, primary or secondary prevention. Populations in treatment or secondary prevention studies had to have received a diagnosis of asthma, whereas those in primary prevention studies could be either at elevated risk for asthma or healthy (i.e., without asthma). A treatment study could assess a respiratory outcome, mediators of inflammation, or safety. A primary prevention study needed, at the very least, to estimate asthma prevalence or incidence. A secondary prevention study required a longterm assessment of respiratory function. Two 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 checked by another one. Data pertained to the characteristics of the report, study, population, intervention/exposure and comparator(s), cointerventions, withdrawals and dropouts, and outcomes (including safety).

Study quality (internal validity) and study applicability (external validity) were each rated independently by two assessors, with disagreements resolved by forced consensus and, if necessary, third party intervention.

Data Synthesis. Question-specific qualitative syntheses of the evidence were derived. Problems and limitations of available studies made it inappropriate to conduct meta-analysis of randomized controlled trial (RCT) evidence for any question: e.g., missing data, flawed designs, non-comparable study parameters. In interpreting results, greater emphasis was placed on RCT evidence given its status as the gold standard by which an intervention/exposure's efficacy or effectiveness is investigated. Forced expiratory volume in one second (FEV_1) was selected as the primary outcome given its status as a gold standard index of pulmonary function. Thirty-one reports, describing 26 unique studies, were deemed relevant for the systematic review, with five studies each described by two reports.

Conclusions. Aside from an acceptable safety profile, it is impossible to definitively conclude anything with respect to the value of using omega-3 fatty acid supplementation in asthma for adults or children either in or beyond North America. The lack of sufficiently consistent evidence, as well as a paucity of evidence from well-designed, well-conducted and adequately powered studies suggests that no definitive conclusion can yet be drawn regarding the efficacy of omega-3 fatty acid supplementation as a treatment. The influence on efficacy of key intervention, population or cointervention factors (e.g., sources, types or doses of omega-3 fatty acid content) cannot yet be determined. The picture of the impact of the exposure on mediators of inflammation thought to be related to the pathogenesis of asthma is largely unclear. There are too few studies from which to conclude anything definitive with respect to primary prevention. Some data suggest that dietary fish consumption, including oily fish, may serve a protective role for children, yet this association was neither observed for adolescent (positive association) or adult populations (no association). Final follow-up data when children reach five years of age in a large randomized controlled trial should provide a clearer picture of the value of omega-3 fatty acids as early primary prevention. No safety profile relating to omega-3 fatty acid intake was reported for primary prevention studies, and little probability of harm beyond occasional mild discomfort was observed in treatment studies. The questions of secondary prevention and of safety related to omega-3 fatty acid use in subpopulations of asthmatics could not be addressed due to a lack of studies. Overall, the present collection of evidence likely does not constitute the best test of the overarching hypothesis that omega-3 fatty acid supplementation alone can foster asthma-related benefits. Future research investigating North American samples is likely needed to establish or refute the value of omega-3 fatty acids to treat or prevent asthma in North American adults and children.

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http://www.ahrq.goc/clinic/epcindex.htm

Health Effects of Omega-3 Fatty Acids on Asthma

Summary

Introduction

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 health effects of omega-3 fatty acids on asthma. 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) currently investigating 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 (UO) EPC. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

Asthma is a chronic inflammatory disorder of the airways leading to airways hyper-responsiveness and associated symptoms such as wheezing and coughing, and is also typically associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[1] The inflammatory process is a complex one, involving a multitude of cell types and activities marking the early and late phase asthmatic responses.[2] There are important issues requiring careful consideration in diagnosing asthma, including the need to distinguish it from transient wheezing disorders in children, especially under the age of 5 years, and also from chronic obstructive pulmonary disorder, especially in older adults who are current or ex-smokers.[3,4]

Various strategies have been developed to manage asthma. Since airway inflammation is multifactorial, involving various cell types and mediators, the drugs used to decrease inflammation may act at several different steps in the inflammatory process.[1,3] Agents that modify the asthma process, with some influencing inflammation, include: beta-2 adrenergic agonists, corticosteroids, leukotriene modifiers, mast-cell stabilizing agents, and theophylline.

Considerable interest in the possible value of omega-3 fatty acid supplementation in asthma was sparked by Horrobin's hypothesis that the low incidence of asthma in Eskimos stems from their consumption of large quantities of oily fish, rich in omega-3 fatty acids.[5] Additional impetus for research came from observations that omega-3 fatty acids' possible protective, or even therapeutic, effect might be afforded by their impact on mediators of inflammation thought to be related to the pathogenesis of asthma.[6]

Key Questions

It is from this vantage point that seven questions were investigated in the present systematic review:

1. What is the evidence for the efficacy of omega-3 fatty acids to improve respiratory outcomes among individuals with asthma?

2. What is the evidence that the possible value (efficacy/association) of omega-3 fatty acids in improving respiratory outcomes is dependent on the:

   - Specific type of fatty acid (docosahexaenoic acid [DHA, 22:6 n-3], eicosapentaenoic acid [EPA, 20:5 n-3], docosapentaenoic acid [DPA, 22:5 n-3], alpha linolenic acid [ALA, 18:3 n-3], fish, fish oil)?

   - Specific source (fish, plant, food, dietary supplement [fish oil, plant oil])?

- Its serving size or dose (fish or dietary supplement)?
- Amount/dose of omega-6 fatty acids given as a cointervention?
- Ratio of omega-6/omega-3 fatty acids used?
- Fatty acid content of blood lipid biomarkers?
- Absolute fatty acid content of the baseline diet?
- Relative fatty acid content of the baseline diet?
- Tissue ratios of fatty acid (omega-6/omega-3) during the investigative period?
- Intervention length?
- Anti-oxidant use?
- The manufacturer and its product(s) purity or presence of other potentially active agents?

3. What is the evidence that, in individuals with asthma, omega-3 fatty acids influence mediators of inflammation which are thought to be related to the pathogenesis of asthma?
4. Are omega-3 fatty acids effective in the primary prevention of asthma?
5. Among individuals with asthma, do omega-3 fatty acids alter the progression of asthma (i.e., secondary prevention)?
6. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acid use to treat or prevent asthma (DHA, EPA, DPA, ALA, fish oil, fish)?
7. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations of asthmatic individual such as diabetics?

Methods

A Technical Expert Panel (TEP) consisting of six 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

A comprehensive search for citations was conducted using six databases (MEDLINE®, PreMEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Commonwealth Agricultural Bureau Health, and Dissertation Abstracts). Searches were not restricted by language of publication, publication type, or study design except with the MeSH® term "dietary fats," which was limited by study design to increase its specificity. Search 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®; fish oil); and, relevant population terms (e.g., asthma; inflammation). 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 1,010 unique references was identified and posted to the UO EPC's Internet-based software system for review.

Studies were considered relevant if they described human populations of any age, involved any type of study design, and investigated the use of any foods or extracts known to contain omega-3 fatty acids as a treatment, primary, or secondary prevention. Populations in treatment or secondary prevention studies had to have received a diagnosis of asthma, whereas those in primary prevention studies could be either at elevated risk for asthma or healthy (i.e., without asthma). Ineligible for treatment studies or secondary prevention studies were populations exclusively exhibiting a subset of the symptoms or signs of asthma (e.g., wheeze), that is, without a clearly stated diagnosis of asthma. In primary prevention studies, methods had to have been employed to identify asthma as well as the omega-3 fatty acids exposure. Studies investigating polyunsaturated fatty acids were included if an explicit evaluation was also made of their omega-3 fatty acid content. Studies where an asthmatic response was experimentally induced in nonasthmatic populations were excluded. A treatment study could assess a respiratory outcome, mediators of inflammation, or safety. A primary prevention study needed to estimate asthma prevalence or incidence, although case-control studies employing outcomes pertinent to this question were also acceptable. A secondary prevention study required a long-term assessment of respiratory function to permit, for example, the observation of a maintained decrement in the need for medication in response to asthma exacerbations.

Two levels of screening for relevance, and two reviewers per level, were employed (bibliographic records, then full articles). Calibration exercises preceded each step of the screening process. Excluded studies were noted as to the reason for their ineligibility using a modified QUOROM format.[7] Disagreements were resolved by forced consensus and, if necessary, third party intervention.

Data Abstraction

Following a calibration exercise, three reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form. A second reviewer checked all abstracted data. Data included the characteristics of the report (e.g., publication status), study (e.g., research design), population (e.g., diagnosis description), intervention/exposure (e.g., omega-3 fatty acid type) and comparator(s) (i.e., comparison group[s]), cointerventions (e.g., asthma medications), withdrawals and dropouts, and outcomes (i.e., respiratory, mediators of inflammation, safety).

After calibration exercises, each study's quality (internal validity) and applicability (external validity) were rated independently by two assessors. Disagreements were resolved by forced consensus and, if necessary, third party intervention. Randomized controlled trials' (RCTs') reporting of

randomization, double blinding, withdrawals and dropouts, and the concealment of allocation, were evaluated using Jadad's[8] and Schulz's validated instruments.[9] Five items selected from Downs and Black's 27-item validated instrument were used to rate the study quality of all other study designs, including a clear description of the study hypothesis or objective, study participants, characteristics of participants lost to followup, the interventions/exposures of interest, and, whether the outcome measures were valid and reliable.[10] One applicability index for treatment and secondary prevention studies, and another for primary prevention studies, were constructed without rigorous validation. Applicability for treatment or secondary prevention studies was defined as the degree to which a given study's sample population was representative of a "typical" North American population of asthmatics. The reference standard for primary prevention studies was the "typical" healthy North American or one at risk for asthma.

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. In consultation with our TEP, forced expiratory volume in one second (FEV_1) was selected as the primary outcome, given its status as a gold standard index of pulmonary function. Problems and limitations of available studies made it inappropriate to conduct meta-analysis of RCT evidence for any question (see Discussion). For the purposes of interpreting the results, a greater emphasis was placed on RCT evidence given its status as the gold standard by which an intervention/exposure's efficacy or effectiveness is investigated.[11]

Results

Literature Search

Of 1,010 records entered into the initial screening for relevance, 851 were excluded. All but five of the remaining 159 reports were then retrieved, and subjected to a more detailed relevance assessment.[12-16] The second relevance screening then excluded 122 reports. In total, 31 reports, describing 26 unique studies, were deemed relevant for the systematic review, with five studies each described by two reports. To simplify matters, only one report per study is referred to in this summary. Yet, data from all of the study documents were included in the qualitative synthesis. Some information regarding the study parameters of an RCT exclusively described by an abstract[17] were taken from a Cochrane review,[18] which had obtained additional details from a source unavailable to the present review team.

Of the included studies, two were abstracts and the rest were published articles in scientific journals. One relevant, published report was identified by manual search. Five reports required

translation,[19-23] although one was not translated in time to include its data in the synthesis.[23] Question-specific synopses follow.

Question 1 (Impact on Respiratory Outcomes)

Ten RCTs and nine studies employing other designs (i.e., non-randomized controlled trials [non-RCTs]; noncomparative case series) addressed Question 1. Of the RCTs, two exclusively randomized children,[24,25] one included both older adolescents and adults,[26] one did not report any age data,[27] and six focused on adults.[17,28-32] Two non-RCTs focused on children[22,33] and seven other studies enrolled adults.[19,21,34-38] Of the latter, one was a non-RCT[21] and six involved noncomparative case series.[19,34-38] Given the largely inconsistent picture of efficacy within and across respiratory outcomes, it is impossible to conclude one way or the other whether omega-3 fatty acids are an efficacious adjuvant or monotherapy in improving respiratory outcomes in adults or children. This view is perhaps best illustrated by what was observed with respect to the primary outcome, FEV_1.

Adult RCTs revealed a somewhat contradictory picture of efficacy with respect to FEV_1. One very small adult study (n = 14) that employed uncontrolled dosing of perilla seed oil and corn oil (control) over a short intervention period (n = 4 wk) reported a significant effect. However, two RCTs each observed no benefit relating to an omega-3 fatty acid intervention. One compared high and low doses of EPA ethyl ester[31] over 16 weeks in a small study (n = 12), whereas the second investigated the benefit of low-dose EPA/DHA (versus olive oil) over 10 weeks in the systematic review's highest quality RCT.[32] The latter included one of the largest sample populations (n = 46) included in the evidence review. Emelyanov et al. also demonstrated good control of three confounding factors, while providing one of the most rigorous methods to select its asthma population.[32] No studies of adults using other research designs investigated this outcome. With regard to studies of children, one RCT[25] and a non-RCT[22] observed no benefit in terms of FEV_1. The fact that there were few studies to consider makes the most balanced understanding one that suggests more research is needed before anything definitive can be concluded about the impact of omega-3 fatty acids on FEV_1. A similar picture characterized the other respiratory outcomes.

The inconsistency among study results may be attributable to the heterogeneity in definitions of the:

- Settings (e.g., hospital versus outpatient; countries).
- Populations (e.g., age; gender; clinical picture of asthma, including its severity and concomitants, or triggers with the potential to impact asthma control).
- Interventions and their contrasts with comparators (e.g., different types and amounts of oil and omega-3 fatty acid contents; controlled versus uncontrolled dosing).
- Cointerventions (e.g., asthma medication with varying capacities to control asthma in the short term or long term).

This observation applies to all patterns of results relating to Questions 1, 2, 3, and 4.

Even though study quality, as operationally defined in the present review, was not an obvious shortcoming of the 20 included treatment studies, the very limited generalizability potential for all but two of them[31,36] can be taken to suggest that answering Question 1 requires more research conducted with North American samples. The prominent limitation for the RCTs was limited blinding, and the key limitation for the studies using designs other than an RCT was the poor description of study participants.

Question 2 (Impact of Effect Modifiers)

Given the inappropriateness of conducting meta-analysis, an informal assessment was undertaken looking at the possible consistent or exclusive relationship between significant clinical effects and specific definitions, or levels, of variables with the potential to account for these effects (e.g., high-dose supplementation). These variables are the predefined covariates, as well as any study-defined ones (e.g., type, source, or dose of omega-3 fatty acids). To be eligible, an outcome required results provided by at least two studies, with at least one of them noting a significant clinical effect in favor of the omega-3 fatty acids exposure. Question 2 involved data from 12 of the 19 studies addressing Question 1, including eight RCTs[17,26-32] and four noncomparative case series.[19,35,37,38] None of the studies included children, since the pediatric studies did not meet the criteria established with respect to this question. The assessment did highlight one exposure potentially worth exploring in future empirical investigations of the health effects of omega-3 fatty acids in asthma. It was noted that perilla seed oil supplementation, provided in an uncontrolled fashion to adults, was the only exposure that was exclusively associated with significant clinical effects (12/12) in favor of the omega-3 fatty acids exposure.[28,34,38] Yet, even this observation is likely unreliable. Without the option of meta-analysis, it is difficult to respond adequately to Question 2. It must be concluded that, at present, it is impossible to identify effect modifiers responsible for any significant asthma-related benefits accruing to omega-3 fatty acids supplementation. This exploration was complicated by the fact that few significant effects were found.

Question 3 (Impact on Mediators of Inflammation)

It is likewise unfeasible to conclude one way or the other that omega-3 fatty acids positively influence the lipid mediators of inflammation in adult studies in ways congruent with the biological model implicating the lipoxygenase and cyclooxygenase pathways in asthma. Moreover, virtually no other mediators of inflammation were investigated (e.g., TNF-α).[25] Question 3 was addressed by 11 studies, including five RCTs, one non-RCT, and four noncomparative case series. Of the RCTs, one involved children[25] and four included adults.[26,28,30,31] All of the studies using designs other than an RCT enrolled adults.[19,20,34,36-38]

The only consistent impacts of omega-3 fatty acids on mediators of inflammation involved the suppression of leukotriene C_4[28,34,38] and of polymorphonuclear leukocyte chemotaxis in response to various stimuli.[26,31] However, all of the results must be interpreted with caution given the small sample sizes, as well as the fact that the findings of significant effects for the same outcome involved different intervention-comparator contrasts and varying doses of omega-3 fatty acids. As with the evidence regarding Question 1, considerable clinical heterogeneity characterizes these studies. Their average study quality was good, and their applicability was restricted.

Question 4 (Impact on Primary Prevention)

Six studies investigated Question 4. Of these, one was an RCT looking at the impact of omega-3 fatty acids on neonates[39] and five were observational studies that focused on adults,[40] adolescents,[41] young children and adolescents,[42] and children.[43,44] Dietary fish consumption, including oily fish intake, assessed primarily through a retrospective food-frequency questionnaire, appeared to serve as primary prevention for asthma in two pediatric populations.[43,44] However, asthma prevalence and fish, or oily fish, intake were significantly and positively related in studies that included adolescents from Asia,[41,42] with one of these studies also including some children.[42] In a prospective study of nurses, no association was found between adult asthma onset and dietary fish intake.[40]

Mihrshahi et al.'s factorial RCT is, in large part, a study evaluating the impact of an omega-3 fatty acid regimen (versus placebo), initiated prebirth, on neonates at risk for asthma, given that at least one parent or sibling had received this diagnosis.[39] Their interim results indicated little benefit accruing to the omega-3 fatty acid exposure, yet 18 months is likely too early in life to reliably identify asthma. Final followup at 5 years of age should provide a clearer picture of the value of omega-3 fatty acids as primary prevention. Study quality was better, on average, for the observational studies than for the single RCT; and, as with treatment studies, almost no studies even remotely resembled the North American population standard established in this review.

Question 5 (Impact on Secondary Prevention)

Question 5 could not be addressed since this review failed to identify any secondary prevention studies.

Question 6 (Impact on Safety)

Eight RCTs and two studies employing other designs provided safety data addressing Question 6. No safety profile relating to omega-3 fatty acids as an exposure was observed for primary prevention studies and, on balance, the evidence suggests that the safety profile in the treatment studies was good. Most of the adverse events were related to the capsule delivery of oils, rather than to the oils per se.[17,24,26,29] On several occasions, an inability to swallow capsules led to a withdrawal.

Other participants may have had difficulties taking 18 capsules a day of oil in two specific RCTs, yet these difficulties were not reported.[26,29] The one moderately serious reaction was an undefined number of episodes of nausea and vomiting after ingesting fish oil capsules, and led to a withdrawal.[29] Unspecified numbers of children and adults experienced some (e.g., mild gastrointestinal) discomfort, but not all individuals had been receiving the omega-3 fatty acid exposure.[25] Fishy hiccups or burping were a rare complaint. By far the most serious event linked to a treatment study involved severe apnea associated with repeated allergen challenge.[21] The omega-3 fatty acid exposure had not yet begun.

Question 7 (Impact on Safety in Subpopulations)

Question 7 could not be evaluated since no study reported adverse events associated with a specific subpopulation (e.g., diabetics).

Discussion

Twenty-six studies, described by 31 reports, investigated five of the seven questions posed in this systematic review of the evidence concerning the health effects of omega-3 fatty acids in asthma. The questions of secondary prevention and of safety related to omega-3 fatty acid use in subpopulations of asthmatics could not be addressed due to a lack of studies. Eleven RCTs (ten treatment, one primary prevention) and 15 studies using other designs (ten treatment, five primary prevention) were included. Three of the former and six of the latter involved children or adolescents exclusively. It is likely that, other than Ashida et al.'s noncomparative case series lasting 2 weeks, [38] all treatment studies lasted long enough to demonstrate that a difference could be found in terms of respiratory outcomes and mediators of inflammation. Relevant studies could only be synthesized qualitatively according to the question(s) they addressed.

The present findings suggest that, with omega-3 fatty acid supplementation intended to influence asthma, there is little probability of harm beyond occasional mild discomfort. The most frequent troublesome events were produced by the delivery of the oils in large numbers and sizes of capsules. On the other hand, the lack of sufficiently consistent evidence, as well as a paucity of evidence from well-designed, well-conducted, and adequately powered studies, suggests that no definitive conclusion can yet be drawn regarding the efficacy of omega-3 fatty acid supplementation as a treatment for asthma in children and adults. Likewise, nothing specific can be concluded regarding the role of specific sources, types, or doses of omega-3 fatty acid content in producing significant clinical effects. One possible explanation for the inconsistent findings is the heterogeneity in definitions of settings, populations, interventions/exposures, and the types and doses of asthma medication.

Having too few well-designed studies with which to adequately address this question means that nothing definitive

can be said about the influence of omega-3 fatty acids on those mediators of inflammation thought to be implicated in the pathogenesis of asthma, or, about the actual role played by these mediators in asthma. More research is required.

No studies were identified which investigated the potential of omega-3 fatty acids as secondary prevention. Primary prevention attempts were found, yet they lacked unanimity in their findings. While two studies of children outside North America noted a protective effect of dietary fish intake for asthma,[43,44] one American survey, discovered after the present qualitative synthesis was completed, reported no benefit.[45] Moreover, studies outside North America, and primarily including adolescents, found that dietary fish intake actually increased the risk of asthma.[41,42] The only study involving adults found no relationship between these variables.[40] However, many of these studies employed different sampling methods and varying definitions of both the frequency of fish intake and fish types. Likely the most promising attempt to use omega-3 fatty acids as primary prevention involves a large, ongoing RCT of expectant mothers whose children at risk for asthma are being followed for 5 years.[39] To date, 18-month, interim analysis data are too unreliable given the difficulties in diagnosing asthma in children this young.

At this point in time, aside from an acceptable safety profile, it is impossible to definitively conclude anything with respect to the value of using omega-3 fatty acid supplementation in asthma for adults or children either in or beyond North America. Recommendations for future research follow directly from observations of the problems and limitations in the included studies. Flawed or problematic designs need to be avoided in any further attempts to assess the clinical utility of omega-3 fatty acids in asthma. These requirements include better control of factors with the potential to confound the interpretation of results. For example, failing to assure that the delivery of the supplementation is controlled, and hence definable as the "intervention," yields results difficult to interpret. Likewise, failing to assure that there is not an uneven distribution of corticosteroid users or doses across study arms/cohorts can restrict the ability to meaningfully attribute a significant or null effect to the actions of the omega-3 fatty acid supplementation. Asthma medications' capacity to improve asthma symptoms can mask the benefits linked to use of omega-3 fatty acid supplementation.

Poor reporting practices, which led to an inability to know whether, and how, these or other confounders might have influenced individual treatment RCT results, together with the lack of comparability in many of the RCTs' parameters (e.g., intervention-comparator contrasts), led to the decision to forego meta-analysis. Any pooled estimates would have been derived within a context instilling as little confidence in the appropriateness of the extrapolations of results as in the validity of the results themselves.

The present review highlighted some of the methodological issues worth considering in treatment RCTs. As carefully as it

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chooses a high quality design, future research likely needs to judiciously select the dose(s), while assuring the identity and purity of the exposure. It should also involve North American samples if there is any belief that omega-3 fatty acid supplementation may be helpful in asthma for North Americans. The need to study this population stems from a paucity of research investigations with this focus; and, possibly because North Americans' high omega-6/omega-3 fatty acid intake ratio may make it less likely that data obtained from populations (e.g., Japanese) with a substantially lower intake ratio (associated with a much higher consumption of omega-3 fatty acids) can be generalized to North Americans.

A potentially interesting hypothesis requiring investigation relates to the possible asthma-related benefits associated with actively and markedly decreasing levels of omega-6 fatty acid intake concurrent with increasing the intake of omega-3 fatty acids. At the same time, given that the present collection of evidence does not constitute the best test of the overarching hypothesis that omega-3 fatty acid supplementation alone can foster asthma-related benefits, more research is likely needed to adequately answer the questions posed in the present systematic review.

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, Ottawa, Canada, under Contract No. 290-02-0021. It is expected to be available in March 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 91, *Health Effects of Omega-3 Fatty Acids on Asthma*. 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

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Evidence Report

Chapter 1. Introduction

This evidence report by the University of Ottawa's Evidence-Based Practice Center (EPC) concerning the health effects of omega-3 fatty acids on asthma is one among several that address topics related to omega-3 fatty acids that were requested and funded by the Office of Dietary Supplements, National Institutes of Health (NIH), through the EPC program at the Agency for Healthcare Research and Quality (AHRQ). Three EPCs—the Tufts-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 asthma outcomes in humans. In this chapter, the metabolism, physiological functions, and sources of omega-3 fatty acids are briefly discussed. This constitutes background material, putting in context the data presented in the evidence report. As well, the description of the U.S. population intake of omega-3 fatty acids is provided in response to a general question posed within the task order. This introductory material is then complemented by a brief review of the epidemiology and natural history of asthma, in addition to its treatment. Subsequent chapters describe the methods used to identify and review studies related to omega-3 fatty acids and asthma, findings related to the effects of omega-3 fatty acids on asthma, and recommendations for future research in this area.

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, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. Unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Polyunsaturated fatty acids (or 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." The essential fatty acids can be converted in the liver to long-chain polyunsaturated fatty

acids (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% of the total PUFAs consumed, while ALA comprises 9%. 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, and 11-17 grams/day 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 1ß (IL-1ß), and tumor necrosis factor a (TNF-a)—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

Polyunsaturated Fatty Acids (PUFAs)

Omega-6
Large intake
(7-8% dietary energy)*

Omega-3
Minor intake
(0.3-0.4% dietary energy)*

*The dietary intake levels are based on approximate current levels in North American diets

Linoleic acid (LA)
18:2 n-6
(Sunflower, soy, cottonseed, safflower oils)

Alpha-Linolenic acid (ALA)
18:3 n-3
(Canola, Soybean, and Flaxseed oils, grains, green vegetables)

Delta-6 Desaturase (D6D)

Gamma-linolenic acid (GLA)
18:3 n-6
(Evening primrose, borage, black currant oils)

Delta-6 Desaturase (D6D)

Octadecatetranenoic acid
18:4 n-3

Elongase

Elongase

Dihomo-gamma-linolenic acid (DGLA)
20:3 n-6
(Liver & other organ meats)

Eicosatetraenoic acid
20:4 n-3

TNF-alpha
IL-1 beta

amino acids

Delta-5 desaturase (D5D)

Arachidonic acid (AA)
20:4 n-6
(Animal fats, brain, organ meats, egg yolk)

Eicosapentaenoic acid (EPA)
20:5 n-3
(Fish liver oils, fish eggs)

suppress

DNA

Lower VLDL, Apo B-100, Tg

Elongase

Adrenic acid
22:4 n-6

Docosapentaenoic acid (DPA)
22:5 n-3

Extracellular Ca^{2+}

Endothelial and smooth muscle cells

Elongase

24:4 n-6

24:5 n-3

Cell membrane

Adrenoceptors

D6D

24:5 n-6

24:6 n-3

Intracellular Ca^{2+}

Beta-oxidation

Docosapentaenoic acid (DPA)
22:5 n-6

Docosahexaenoic acid (DHA)
22:6 n-3
(Human milk, egg yolks, fish liver oils, fish eggs, liver, brain, other organ meats)

endoplasmic reticulum

Beta-oxidation

Energy metabolic pathway

Beta-oxidation

Eicosanoids

Series-1
Prostaglandins:
TXA_1 PGE_1 PGF_{1a}
PGD_1

Series-2
Prostaglandins:
TXA_2 PGE_2 PGF_{2a}
PGD_2 PGH_2 PGL_2

Series-4 Leukotrienes

Series-3
Prostaglandins:
PGE_3 PGH_3 PGI_3 TXA_3

Series-5 Leukotrienes

Thromboxanes (TX) are important for:
- blood clotting
- constricting blood vessels
- inflammatory function of white blood cells

Leukotrienes are important for:
- inflammation
- lung function

Prostaglandins (PG) are important for:
- pregnancy, birth
- stomach function
- kidney function
- maintaining blood vessel patency
- preventing blood clots
- inflammation, response to infection

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 2 nonconsecutive days via two 1-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, selected from the USDA website.[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	Food item	EPA	DHA	ALA
Fish (Raw [a])				**Fish, continued**			
Anchovy, European	0.6	0.9	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.2	0.4	0.1	Tuna, Light, Canned in Oil [e]	trace	0.1	trace
Bass, Striped	0.2	0.6	trace	Tuna, Light, Canned in Water [e]	trace	0.2	trace
Bluefish	0.2	0.5	-	Tuna, White, Canned in Oil [e]	trace	0.2	0.2
Carp	0.2	0.1	0.3	Tuna, White, Canned in Water [e]	0.2	0.6	trace
Catfish, Channel	trace	0.2	0.1	Whitefish, Mixed Sp.	0.3	0.9	0.2
Cod, Atlantic	trace	0.1	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	trace	0.1	trace	Wolffish, Atlantic	0.4	0.3	trace
Eel, Mixed Sp.	trace	trace	0.4				
Flounder & Sole Sp.	trace	0.1	trace				
Grouper, Mixed Sp.	trace	0.2	trace	**Shellfish (Raw)**			
Haddock	trace	0.1	trace	Abalone, Mixed Sp.	trace	-	-
Halibut, Atlantic and Pacific	trace	0.3	trace	Clam, Mixed Sp.	trace	trace	trace
Halibut, Greenland	0.5	0.4	trace	Crab, Blue	0.2	0.2	-
Herring, Atlantic	0.7	0.9	0.1	Crayfish, Mixed Sp., Farmed	trace	0.1	trace
Herring, Pacific	1.0	0.7	trace	Lobster, Northern	-	-	-
Mackerel, Atlantic	0.9	1.4	0.2	Mussel, Blue	0.2	0.3	trace
Mackerel, Pacific and Jack	0.6	0.9	trace	Oyster, Eastern, Farmed	0.2	0.2	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Wild	0.3	0.3	trace
Ocean Perch, Atlantic	trace	0.2	trace	Oyster, Pacific	0.4	0.3	trace
Pike, Northern	trace	trace	trace	Scallop, Mixed Sp.	trace	0.1	-
Pike, Walleye	trace	0.2	trace	Shrimp, Mixed Sp.	0.3	0.2	trace
Pollock, Atlantic	trace	0.4	-	Squid, Mixed Sp.	0.1	0.3	trace
Pompano, Florida	0.2	0.4	-				
Roughy, Orange	trace	-	trace				
Salmon, Atlantic, Farmed	0.6	1.3	trace	**Fish Oils**			
Salmon, Atlantic, Wild	0.3	1.1	0.3	Cod Liver Oil	6.9	11.0	0.9
Salmon, Chinook	1.0	0.9	trace	Herring Oil	6.3	4.2	0.8
Salmon, Chinook, Smoked [b]	0.2	0.3	-	Menhaden Oil	13.2	8.6	1.5
Salmon, Chum	0.2	0.4	trace	Salmon Oil	13.0	18.2	1.1
Salmon, Coho, Farmed	0.4	0.8	trace	Sardine Oil	10.1	10.7	1.3
Salmon, Coho, Wild	0.4	0.7	0.2				
Salmon, Pink	0.4	0.6	trace				
Salmon, Pink, Canned [c]	0.9	0.8	trace	**Nuts and Seeds**			
Salmon, Sockeye	0.6	0.7	trace	Butternuts, Dried	-	-	8.7
Sardine, Atlantic, Canned in Oil [d]	0.5	0.5	0.5	Flaxseed			18.1
Seabass, Mixed Sp.	0.2	0.4	-	Walnuts, English	-	-	9.1
Seatrout, Mixed Sp.	0.2	0.2	trace				
Shad, American	1.1	1.3	0.2				
Shark, Mixed Sp.	0.3	0.5	trace	**Plant Oils**			
Snapper, Mixed Sp.	trace	0.3	trace	Canola (Rapeseed)	-	-	9.3
Swordfish	0.1	0.5	0.2	Flaxseed Oil	-	-	53.3
Trout, Mixed Sp.	0.2	0.5	0.2	Soybean Lecithin Oil	-	-	5.1
Trout, Rainbow, Farmed	0.3	0.7	trace	Soybean Oil	-	-	6.8
Trout, Rainbow, Wild	0.2	0.4	0.1	Walnut Oil	-	-	10.4
Tuna, Fresh, Bluefin	0.3	0.9	-	Wheatgerm Oil	-	-	6.9
Tuna, Fresh, Skipjack	trace	0.2	-				

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

Asthma: A Chronic Inflammatory Disease

The National Heart, Lung, and Blood Institute (NHLBI) defines asthma as follows:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[11]

Asthmatic episodes are triggered by a variety of stimuli including allergens, environmental irritants, viral infections, exercise or other poorly defined factors.

Burden of Illness

Asthma continues to be a major public health concern for Americans, accounting for an estimated 14.5 million lost workdays for adults and 14 million lost school days in children annually. It is estimated that, annually, this costs the United States $14.0 billion in direct health care costs and indirect costs due to lost productivity.[12] A survey by the National Center for Health Statistics (NHIS) and the Centers for Disease Control and Prevention (CDC) estimated that, in 2001, 20.3 million Americans had asthma (6.3 million children), or 73.4 per 1,000 persons. Children between the ages of 5 and 17 years had the highest prevalence rate with an estimated 98.1 per 1,000 persons, with rates decreasing with age. Females had an approximately 30 percent higher prevalence rate (82.6 per 1,000 persons) than men (63.6 per 1,000 persons); the prevalence rate was 22.7% higher in blacks than in whites. Although there was a decline in asthma prevalence from 1997 to 1999 after a long period of steady increase, rates in 2000 and 2001 indicate a return to the rising trend.[13]

During 2000, 465,000 hospital discharges were due to asthma, with over 43% of discharges in patients under the age of 15. The discharge rate was highest in blacks (32.9 per 10,000). It was estimated that 4,487 people died of asthma in 2000, with black women having the highest mortality rate (4.2 per 100,000[13]).

Asthma Onset and Diagnosis

Asthma most commonly arises in childhood, but may have its onset at any age. For all age groups, the clinical diagnosis of asthma is prompted by the presence of symptoms including wheezing, coughing, episodic breathlessness, and chest tightness. However, identical features are present in many other diseases, confounding the diagnosis of asthma. Episodic wheezing and cough are among the most common symptoms encountered in childhood illnesses, particularly in those under the age of 5.[14] In this age group, the most common cause of asthma-like symptoms is viral respiratory infection;[14] alternative causes of recurrent wheezing include cystic fibrosis, mild recurrent inflammation, primary ciliary dyskinesia syndrome, primary immune deficiency, congenital heart disease, and foreign body aspiration.[15] Wheezing disorders unrelated to these

conditions can also be observed in children under the age of 5 years, and which do not necessarily develop into full-blown asthma later on in life. Further complicating the diagnosis of asthma in this age group is the difficulty in obtaining objective measurements of lung function. Thus, diagnosis is particularly difficult in children under the age of 5, and is based largely on clinical judgment and an assessment of symptoms and clinical findings. Prognostic factors include a family history of asthma or eczema, and the presence of respiratory symptoms (e.g., wheeze).[15]

The longterm prognosis for childhood asthma is quite variable. Although longitudinal studies have reported that asthma in childhood has a good prognosis, most studies do not take into account the severity of childhood symptoms. A longterm follow-up study by The Melbourne Epidemiological Study of Childhood Asthma followed children with asthma through to adolescence and adulthood.[16-20] A classification system based on wheezing frequency, which correlated well with clinical and spirometric features of airway obstruction, was used to assess disease. Results demonstrated that most of the children with persistent asthma had continuing symptoms into adult life, as well as reduced lung function. The amount of wheezing in early adolescence seemed to be a predictor of severity in later life, with 73% of those with few symptoms at 14 continuing to have little or no asthma at 28 years. Similarly, 68% of those with frequent wheezing at 14 still suffered from recurrent asthma at 28 years, and the distribution of severity at age 42 was found not to have changed from that at age 35.[20] Ulrik reported that, although the majority of patients with asthma have a good prognosis, those patients with severe disease are at risk of impaired growth of lung function during childhood and excessive decline in lung function in adulthood.[21]

Recently, a study by Castro-Rodriquez and colleagues reported that a clinical picture of children under the age of 3 years which included persistent wheezing and at least one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis), was strongly predictive of subsequent asthma after the age of six.[22] However, how early symptoms and disease severity predict disease progression into adulthood remains to be determined.

Although asthma most often arises in childhood, the annual incidence of asthma after the age of 20, and for the rest of the lifespan, is estimated to be approximately 100 per 100,000.[23] Adult-onset asthma may be triggered by occupational or environment exposures, respiratory infections, or smoking. Complicating the diagnosis, particularly in older adults, is the existence of other common conditions with asthma-like symptomatology, for example, chronic obstructive pulmonary disease (COPD). COPD is typically associated with a long history of smoking and may have an inflammatory component that is responsive to anti-inflammatory drug intervention, thus blurring the boundary with asthma.[15]

Inflammation in the Pathogenesis of Asthma

Asthma is a chronic inflammatory disease. The inflammatory process is a complex process involving a number of cell types, including mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells.[24] Although the relative contribution of these cells and their mediators varies depending on disease severity, treatment and duration, there are some universal features of the inflammatory response in the airway. In general, upon antigen stimulation, or during acute asthma exacerbations, these cells become activated, releasing mediators that act either directly or indirectly on the airway to perpetuate the asthmatic inflammatory response. Mediators of

inflammation include cytokines and growth factors, as well as the eicosanoids. Chemokines, a large family of small cytokines, are responsible for regulating the trafficking of the leukocytes into the airway.

The inflammatory response can be divided into the early phase response (acute, spasmogenic asthma) and the late phase response (chronic, day-to-day asthma). The acute or early phase inflammatory response occurs immediately upon exposure of a sensitized individual to an allergen or other environmental trigger. The early response is initiated by binding of immunoglobulin E (IgE) antibodies to allergen-specific IgE receptors located predominately on mast cells, macrophages and basophils. Binding signals the cell to release preformed mediators including histamine and tryptase, and newly generated mediators including eicosanoids such as the series-2 prostaglandins (PGE_2) and series-4 leukotrienes. Together, these mediators induce contraction of airway smooth muscle and stimulate afferent nerves, mucus hypersecretion, and vasodilation. The series-2 prostaglandin PGE_2 appears to have a prominent role in the hyperresponsiveness of asthma.

Within hours of the response, activated airway cells release cytokines and chemokines, stimulating the release of inflammatory leukoctyes, especially eosinophils and their precursors. The cytokines include IL-1 to IL-5 along with interferon (IFN)-? and TNF-a. The chemokines act as chemoattractants, regulating the recruitment of inflammatory cells into the airway. Although this recruitment involves virtually all cell types, the allergic response is particularly selective for eosinophils, basophils, and lymphocytes. Eosinophilic infiltration of the airway remains a consistent feature of acute inflammation and is also found in mucosal airway tissue from many patients with chronic persistent asthma.[14] The eosinophils are sources of inflammatory mediators which can injure the airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine release. In addition, the eosinophils can release cysteinyl leukotrienes, such as LTC_4, to contract airway smooth muscle. The T-helper lymphocytes are important in the asthmatic inflammatory response since they are prominent in the airways, and produce high levels of cytokines in response to antigen stimulation or during acute asthma exacerbations.[25] The prostaglandins, particularly PGE_2, modulate the formation of cytokines by T-helper cells. The T-helper cells, particularly the Type 1 T-helper cells, produce IL-2 (IL-2 also causes an increase in TNF) and interferon-gamma, whereas the Type 2 T-helper cells produce the cytokines, IL-4 and IL-5. IL-4 acts to commit B-lymphocytes to the synthesis of IgE. There is also evidence that PGE_2 can act directly on B-lymphocytes, to stimulate the formation of IgE.[26,27] The ability to synthesize IgE antibodies to environmental allergens (i.e., atopy) remains a major risk factor in asthma pathogenesis.[14]

Trends in Asthma Management

The primary goal of asthma management is to control symptoms with minimal adverse effects from pharmacotherapy. In 1997, the NHLBI's National Asthma Education and Prevention Program (NAEPP) convened an expert panel to review the different classes of medications used for the short-term relief or long-term control of asthma symptoms;[11] the report has been recently updated.[14] In brief, the Expert Panel Report 2 concluded that the most effective agents available for longterm control of asthma are those agents that attenuate airway inflammation.[11,14] Since airway inflammation is multifactorial, involving several cell types, cytokines, and mediators, the drugs used to decrease inflammation may act at several different steps in the inflammatory process.[11,14] Agents that modify the asthma process, with some

influencing inflammation, include: beta-2 adrenergic agonists, corticosteroids, leukotriene modifiers, mast-cell stabilizing agents, and theophylline.

The beta-2 adrenergic agonists act by relaxing airway smooth muscle. The so-called "short-acting" beta-2 agonists (e.g., terbutaline, pirbuterol, albuterol) are used to reverse and/or inhibit bronchoconstriction related to an acute asthmatic exacerbation. However, the newer "long-acting" beta-2 agonists (e.g., salmeterol, formoterol) are designed to work as an adjunct to inhaled corticosteroid therapy, providing longterm control of symptoms.

The corticosteroids act by decreasing and preventing bronchial inflammation and airway hyperreactivity. According to the Expert Panel Report 2, corticosteroids are the most potent and effective agents for the longterm control of asthma.[11,14] They are not, however, effective for use in acute asthmatic exacerbations.[11,14]

Leukotriene modifiers comprise two pharmacologic classes of compound: 5-lipooxygenase pathway inhibitors (e.g., zileuton) and leukotriene receptor antagonists (LTRAs: e.g., montelukast, zafirlukast). Only zafirlukast and montelukast are approved for use in children.[14]

The mast-cell stabilizing agents include cromolyn sodium and nedocromil. They inhibit both the early and late phases of bronchoconstriction. These agents interfere with the early and late reaction to allergens by stabilizing mast cell membranes, preventing the release of inflammatory cell mediators, as well as the recruitment and chemotaxis of eosinophils and other inflammatory cells.[11,14] Both agents are recommended as an alternative, but not preferred, medication for the treatment of mild persistent asthma.[14]

Theophylline is a bronchodilating agent used principally as adjuvant therapy in asthma management.[11,14] It is structurally related to caffeine and acts by relaxing smooth muscle in the bronchial airways and in the pulmonary blood vessels. In addition, theophylline has been shown to have immunomodulatory, anti-inflammatory, and bronchoprotective effects.[28,29]

Although early intervention with anti-inflammatory therapy may improve the short-term outcome of asthma, longterm studies are needed to determine if early intervention with anti-inflammatory drugs alters the natural course of the disease, particularly in subjects at high risk for developing asthma.

Asthma and Diet

The recent increase in the incidence of asthma is thought to be due to environmental factors rather than a change in genetic susceptibility.[24] A number of such factors, including air pollution, tobacco smoke, allergen exposure and diet, have been proposed as possible explanations.[30] Although there is a relative abundance of observational and scientific evidence for the link between avoidance of environmental triggers and the reduction in the incidence and severity of asthma, the association between diet, and particularly the consumption of the omega-3 fatty acids, has just recently begun to be studied.[31-33] This interest was sparked in no small part by Horrobin's hypothesis that the low incidence of asthma in Eskimos stems from their consumption of large quantities of oily fish, rich in the omega-3 fatty acids EPA and DHA.[34] Yet, to determine the precise nature of the potentially protective role of omega-3 fatty acid intake in this particular population, alternate or complementary explanations for Horrobin's observations likely require investigation as well (e.g., reduced air pollution and allergen exposure). Finally, research has also focused on evaluating aspects of the biological model suggesting that omega-3 fatty acids' impact on asthma comes from its ability to influence those mediators of inflammation presumed to play a prominent role in the pathogenesis of asthma.

Chapter 2. Methods

Overview

The UO-EPC's evidence report on omega-3 fatty acids and asthma 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) refined the research questions, as well as highlighted key variables requiring consideration in the evidence synthesis. Evidence tables presenting the key study characteristics and results were developed. Summary tables were derived from the evidence tables. The methodological quality 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 seven questions:

- *What is the evidence for the efficacy of omega-3 fatty acids to improve respiratory outcomes among individuals with asthma? (Question 1)*

- *What is the evidence that the possible value (efficacy/association) of omega-3 fatty acids in improving respiratory outcomes is dependent on the: specific type of fatty acid (DHA, EPA, DPA, ALA, fish, fish oil); specific source (fish, plant, food, dietary supplement [fish oil, plant oil]); its serving size or dose (fish or dietary supplement); amount/dose of omega-6 fatty acids given as a cointervention; ratio of omega-6/omega-3 fatty acids used; fatty acid content of blood lipid biomarkers; absolute fatty acid content of the baseline diet; relative fatty acid content of the baseline diet; tissue ratios of fatty acid (omega-6/omega-3) during the investigative period; intervention length; anti-oxidant use; and, the manufacturer and its product(s) (purity; presence of other potentially active agents)? (Question 2)*

- *What is the evidence that, in individuals with asthma, omega-3 fatty acids influence mediators of inflammation which are thought to be related to the pathogenesis of asthma? (Question 3)*

- *Are omega-3 fatty acids effective in the primary prevention of asthma? (Question 4)*

- *Among individuals with asthma, do omega-3 fatty acids alter the progression of asthma (i.e., secondary prevention)? (Question 5)*

- *What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acid use to treat or prevent asthma (DHA, EPA, DPA, ALA, fish oil, fish)? (Question 6)*

- *What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations of asthmatic individual such as diabetics? (Question 7)*

Four questions (1, 2, 3, and 5) concern treatment or secondary prevention, one centers on primary prevention (4), and two focus on adverse events, side effects, or counter-indications (6, 7).

Analytic Framework

The analytic framework (Figure 2) illustrates the context of each of the variables of interest to the present systematic review. These include focal (e.g., clinical) population(s), interventions/exposures, intermediate outcomes, clinical outcomes, and adverse events, side effects or counter-indications. The three populations of interest include those with a diagnosis of asthma, those at elevated risk to develop asthma, and "healthy" individuals who, under certain circumstances, may develop asthma.

Not all associations within the analytic framework were investigated. Regarding those individuals with asthma, the key questions focused on the impact of the omega-3 fatty acid intervention/exposure on:

- respiratory outcomes (Question 1);

- mediators of inflammation thought to play a key role in the pathogenesis of asthma (Question 3);

- the progression of asthma (Question 5); and,

- the likelihood of adverse events, side effects, or counter-indications (Questions 6 and 7).

Another question focused on whether or not covariates (e.g., omega-3 fatty acid type or source; omega-6 fatty acid intake as a cointervention) could account for the observed effect on respiratory outcomes (Question 2). The level of fatty acids in the human body, for example the fatty acid content in phospholipids of cell membranes of polymorphonuclear or mononuclear leukocytes, was also investigated insofar as it could act as an effect modifier with respect to respiratory outcomes (Question 2). While it could be assumed that a positive influence on respiratory outcomes may result from the exposure's effect on mediators of inflammation (e.g., leukotrienes; Question 3), the direct association between mediators of inflammation and respiratory outcomes was not assessed.

For questions relating to treatment efficacy, the primary respiratory outcome was forced expiratory volume in one second (FEV_1), considered by many to be the gold standard measure of respiratory functioning. This decision was made in consultation with our TEP. Secondary respiratory outcomes assessed ultimately depended on what outcomes were measured in the included studies. For questions related to secondary prevention, a longterm perspective on respiratory functioning is required.

The question relating to primary prevention (Question 4) involves two populations: those with an elevated risk of developing asthma and those healthy individuals who may develop it. Of primary significance to this question is the prevalence or incidence of asthma as well as its severity. Investigation of both the primary and secondary prevention questions could conceivably include examining the links involving effect modifiers (e.g., risk factors) or mediators of inflammation.

Figure 2. Analytic Framework for omega-3 fatty acids in asthma. **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.**
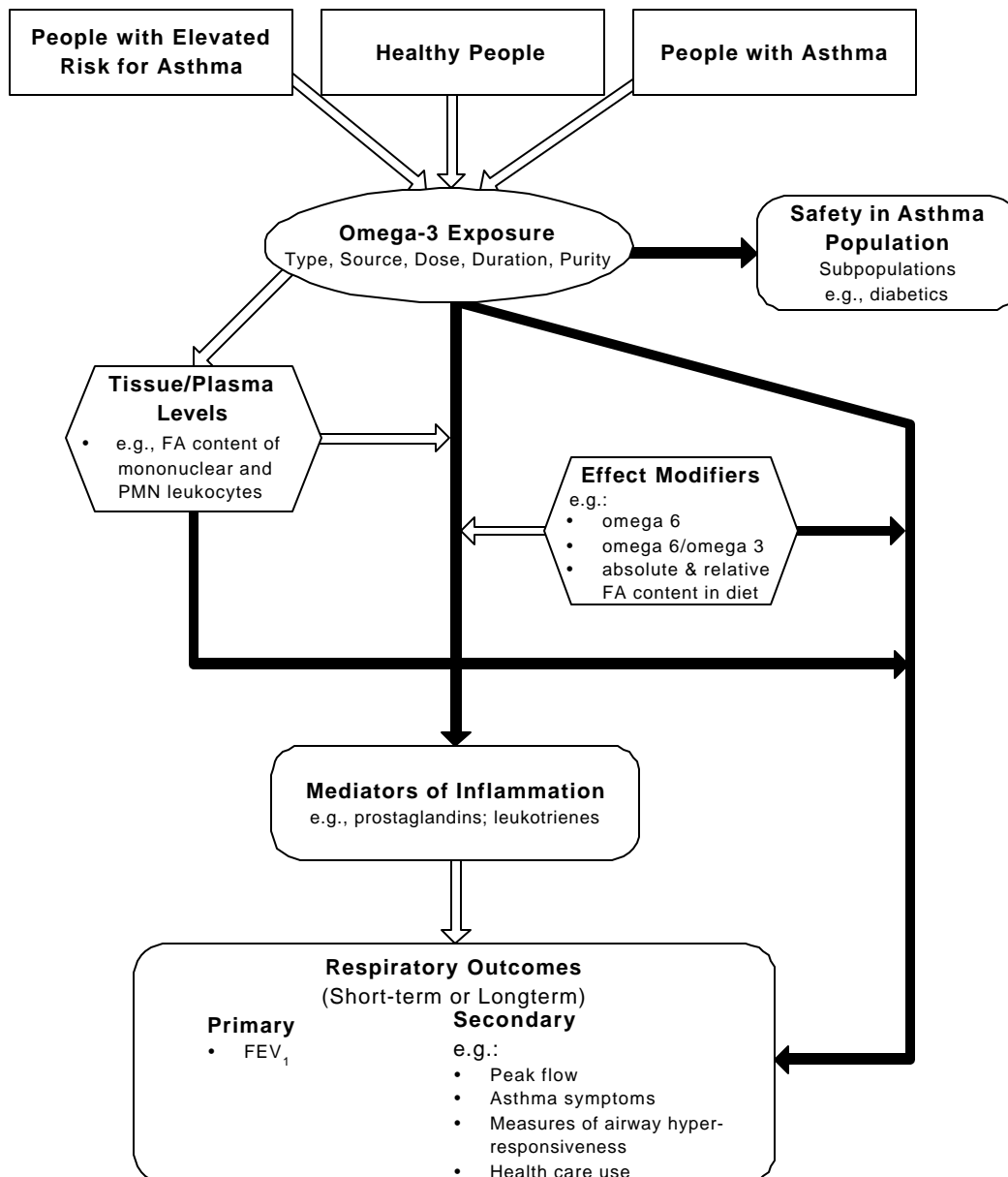
Study Identification

Search Strategy

A specific strategy was developed in consultation with clinical content experts in asthma, and combined with the core omega-3 fatty acids search strategy established in collaboration with the project librarians, biochemists, nutritionists, and clinicians from the three EPCs involved in the 2-year, Health Benefits of Omega-3 Fatty Acids project. Consultation among these sources provided the biochemical names and abbreviations of omega-3 fatty acids, names of commercial omega-3 fatty acids products, and food sources of omega-3 fatty acids.

The following electronic databases were searched: Medline (1966 - April Week 1 2003), Premedline (April 9, 2003), Embase (1980 - 2003 Week 14), Cochrane Central Register of Controlled Trials (1st Quarter 2003), CAB Health (1973 - March 11 2003), and Dissertation Abstracts (1861 to Dec 2002). All databases were searched via the Ovid interface using Search Strategy 1 (Appendix A), except CAB Health, which was searched through SilverPlatter using Search Strategy 2 (Appendix A). Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH term "dietary fats," which was limited by study design to increase its specificity. In databases that support such limits, searches were limited to material involving humans. A total of 1,467 bibliographic records were downloaded, with duplicate records identified and removed using citation management software (Reference Manager®).

Reference lists of included studies, book chapters, and narrative or systematic reviews retrieved after having passed the first level of relevance screening, were manually searched to identify additional unique references. Through contact with content experts, attempts were made to identify both published and unpublished studies. On behalf of the three EPCs investigating the evidence concerning the health benefits of omega-3 fatty acids, a letter was written to industry representatives to obtain additional evidence (Appendix B). Unsuccessful attempts were made to contact the lead author of a recent Cochrane Collaboration systematic review of fish oils in asthma to obtain unpublished data they maintained to have received from investigators.[35] Records obtained from these additional searches were downloaded using Reference Manager® and added to the references previously retrieved. A final set of 1,010 unique references was identified.

Eligibility Criteria

Published and unpublished studies, involving any research design (e.g., randomized controlled trials [RCTs]), and enrolling human populations of any age, were eligible for inclusion if each also met the following criteria: 1) It had to specifically investigate foods or extracts known to contain omega-3 fatty acids as a treatment, a primary prevention, or a secondary prevention. 2) The study populations in treatment or secondary prevention studies required a stated diagnosis of asthma, while the study populations in primary prevention studies could be identified as either at elevated risk for asthma or healthy (i.e., without asthma). In treatment or secondary prevention investigations, ineligible were populations exclusively exhibiting a subset of the symptoms or signs of asthma (e.g., wheeze), that is, without a clearly stated diagnosis of asthma per se. 3) In primary prevention studies, some method had to have

been employed to identify asthma. Studies where an asthmatic response was experimentally induced in nonasthmatic populations were excluded.

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, and delivered in any fashion (e.g., capsules, liquid, PUFA-rich diet), constituted a relevant exposure/intervention. Studies investigating "polyunsaturated fatty acids" were acceptable providing an explicit evaluation was also made of the omega-3 fatty acid content. No restrictions were placed on the types or doses of pre- or on-study cointerventions (e.g., asthma medication, omega-6 fatty acids, other dietary supplements). In primary prevention studies, some method had to have been employed by which the omega-3 fatty acids exposure was identified.

A treatment study was included if it investigated a respiratory outcome, mediators of inflammation, or safety. A primary prevention study typically needed to estimate asthma prevalence or incidence. Case-control studies were also eligible, providing they employed outcomes pertinent to primary prevention. A secondary prevention study required a longterm assessment of respiratory function such that what could be observed, for example, is the longterm maintenance of a significant decrease in the pre-exposure frequency or dose of rescue medication required for asthma exacerbations. Studies of symptom relief, assessing short-term decreases in exacerbation rates, for example, do not constitute examples of secondary prevention. These parameters were derived in consultation with our TEP.

Study Selection Process

The results of literature searches were posted to the UO-EPC's internet-based software system for review. To enhance the speed and efficiency of conducting and managing the systematic review process, this software, which resides on a secure website, was used to enable the electronic capture and internal comparison (relative to explicit criteria) of multiple reviewers' responses to relevance screening questions, and to requests to abstract specific data (e.g., study quality) from bibliographic records or full reports.

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 broad screened the title, abstract, and key words from each bibliographic record for relevance by liberally applying the eligibility criteria. The record was retained if it appeared to contain pertinent study information. If the reviewers did not agree in finding at least one unequivocal reason for excluding it, it was entered into the next phase of the review. The reasons for exclusion were noted using a modified QUOROM format (Appendix D).[36] The screening process also aimed to identify the exact asthma topic-related question a record addressed, in addition to determining whether it might pertain to any of the other topics being systematically reviewed by the three EPCs over the 2-year project.

Print or electronic copies of the full reports 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.[37] To be considered relevant at this second level of screening, all eligibility criteria had to be met. Disagreements were resolved by forced consensus and, if necessary, third party intervention. Excluded studies were noted as to the reason for their ineligibility (Appendix E, List of Excluded Studies)

Data Abstraction

Following a calibration exercise involving two studies, three reviewers independently abstracted the contents of each included study using an electronic Data Abstraction form developed especially for this review (Appendix C). The studies were divided evenly, with half assigned to each of two reviewers. Once a reviewer completed their work, they then checked all of the data abstracted by their counterpart. 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 arms, cohorts, or phases; funding source);

- population (e.g., age; percent males; diagnosis description, including severity, duration, and concomitants; comorbid conditions);

- intervention/exposure (e.g., omega-3 fatty acid types, sources, doses, and intervention/exposure length), and comparator(s);

- cointerventions (e.g., asthma medications, omega-6 fatty acids); and,

- withdrawals and dropouts.

Data relating to outcomes (i.e., respiratory, mediators of inflammation, safety) and two covariates (fatty acid content of blood lipid biomarkers, tissue ratios of fatty acid during the investigative period) were abstracted by a third reviewer, all of whose work was then checked by one of the first two reviewers.

Summarizing the Evidence

Overview

The evidence is presented three ways. Evidence tables in the appendices offer a detailed description of the included studies (e.g., study design, population characteristics, intervention/exposure characteristics), with a study represented only once. The tables are organized by research design and question (Table 1: treatment RCTs; Table 2: treatment studies employing designs other than an RCT; Table 3: primary prevention RCT; Table 4: observational primary prevention studies), and each includes a Part A and B.

A question-specific summary table embedded in the text reports each study 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 given that it

can address more than one research question. Also question-specific is the 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 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 less rigorous research designs. After a calibration exercise involving five studies with appropriate designs borrowed from other systematic reviews, two assessors independently evaluated study quality. Disagreements were resolved via forced consensus.

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[38] 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[39] 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). Primarily to ease the burden on quality assessors who would otherwise have to master many scales or items, constructs cutting across these designs were sought. A validated instrument developed by Downs and Black was identified,[40] with five items selected for use with all study designs other than RCTs. These included clear descriptions of the study hypothesis or objective, study participants, characteristics of participants lost to followup, and the interventions/exposures of interest, in addition to whether the outcome measures were valid and reliable (Appendix C). As with the Jadad instrument, the maximum score was 5, with a higher score indicating greater study quality. However, no guidelines exist to suggest what a poor quality study's score would be based on this five-item subset of Downs and Black's 27-item instrument.[40]

Study Applicability

In this report, the primary focus is on the U.S. population, as specified in the scope of work for this series of evidence reports on the health benefits of omega-3 fatty acids. Given the geographical location of the UO-EPC, however, the definition of study applicability was expanded slightly to include the rest of North America.

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). Regarding the questions of treatment or secondary prevention, the broadest definition of the population of interest is the otherwise "healthy'" North American with asthma who, while potentially presenting with various

concomitants of asthma (e.g., atopy), represents a somewhat broad demographic picture (e.g., gender, race), lives a "typical" North American lifestyle (e.g., background diet), receives "typical" doses and types of asthma treatment, and does not exhibit major comorbid conditions (e.g., diabetes). For prevention studies, the broadest definition of the population of interest is the "typical" healthy North American, with or without an elevated risk for asthma, and living a "typical" North American lifestyle. Applicability decreases as the definition of the sample study population narrows in terms of the factors represented in the schemes.

One allowable exception to the "somewhat broad demographic picture" relates to age. As introduced in Chapter 1, several factors distinguish "asthma" viewed across the lifespan. These include the different age-related clinical pictures of asthma, and the difficulties associated with identifying these different clinical entities. For example, asthma in young children, particularly those under the age of 5, needs to be distinguished from symptoms or signs marking wheezing disorders, which may not develop into full-blown asthma later on in life. In adults, one of the difficulties is distinguishing asthma from COPD. Often, what appears to be asthma in current or ex-smokers is actually COPD. It was thus decided that not all ages required representation in a study's definition of population for it to be considered representative of a broad demographic picture; it was also resolved that, in synthesizing study results, it would be best to describe pediatric and adult data separately. This decision was made in consultation with our TEP.

After a calibration exercise involving five studies with appropriate designs again borrowed from another systematic review, two assessors independently evaluated study applicability. Disagreements were resolved via forced consensus.

Summary Matrix

For a given research question, and where appropriate, a summary matrix situates the pertinent studies in terms of their respective study quality (internal validity) and applicability (external validity) grades. Given that all allocation concealment grades for treatment RCTs were "unclear," the Jadad total quality score became the definition of internal validity in these summary matrices. A three-level scheme was then 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 1 or 2), with a similar approach taken for the studies employing other research designs (A = total quality score of 4 or 5; B = total score of 3; C = total score of 1 or 2). This scheme was established by the 3 EPCs for practical reasons, to afford the incorporation of quality scores within the summary matrix. The three-level applicability scheme applies to all study designs, with studies assigned an "X" (i.e., insufficient information) being excluded from summary matrices.

Qualitative Data Synthesis

For all studies included in the systematic review, an overarching qualitative synthesis describes the progress of each citation through the stages of the review, as well as presents certain report and study design characteristics (e.g., distributions of research design by research question). Then, for each question, a qualitative synthesis is derived separately for evidence derived from RCTs and studies employing other designs. Each synthesis includes a narrative summary of the key defining features of the study (e.g., a priori description of inclusion/exclusion criteria), population (e.g., diagnosis-related), intervention/exposure (e.g.,

types of omega-3 fatty acid), cointerventions (e.g., asthma medication), outcomes, study quality, applicability, and individual study results. A brief study-by-study overview typically precedes a qualitative synthesis.

Evidence from other research designs was included to see whether it confirms the RCT picture of efficacy, because RCTs may not have been conducted, or to provide safety data likely as pertinent as those obtained from RCTs. Yet, research designs other than RCTs (e.g., non-randomized controlled trials [non-RCTs]) are recognized for their greater susceptibility to bias (e.g., selection bias) and confounding, and particularly if they do not include a control group (e.g., noncomparative case series). Thus, for the purposes of interpreting the results, greater emphasis was placed on RCT evidence given its status as the gold standard by which an intervention/exposure's efficacy or effectiveness is investigated.[41] "Greater emphasis" entails assigning greater significance to RCT results although a poor quality RCT is not necessarily superior to a high quality non-RCT. Not all RCTs successfully distribute confounding influences equally across study arms, for example. 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. In this review, a "noncomparative case series" is considered equivalent to a "before-after study."

Quantitative Data Synthesis

Given its greater potential to control for possible confounding factors, only RCT evidence was considered for inclusion in quantitative data synthesis. However, none of the planned meta-analyses, including planned subgroup (i.e., effect modifiers: Question 2) and sensitivity analyses (i.e., study quality; publication bias), were felt to be appropriate given the limitations of the study designs as well as the heterogeneity or failed specificity of both the populations and interventions. These limitations and problems are outlined in the Discussion.

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 1,010 records entered into the initial screening for relevance, 851 were excluded. Reflecting the specific eligibility criteria, the reasons for exclusion were: a. not a primary study (e.g., a review; n = 246); b. does not involve human participants (n = 170); c. does not involve omega-3 fatty acids as an exposure/intervention (n = 250); and, d. the purpose of the exposure/intervention was not the treatment or prevention of asthma (n = 185). All but five of the remaining 159 reports were then retrieved and subjected to a more detailed relevance assessment.[42-46] One report was retrieved, but it was not translated in time to include it in the systematic review.[47] The second relevance screening then excluded 122 reports for the following reasons: a. not a primary study (e.g., a review; n = 70); b. does not involve human participants (n = 4); c. does not involve omega-3 fatty acids as an exposure/intervention (n = 14); and, d. the purpose of the exposure/intervention was not the treatment or prevention of asthma (n = 34). In total, 31 reports, describing 26 unique studies, were deemed relevant for the systematic review, with five studies each described by two reports.

Two reports referred to Huang et al.'s primary prevention (observational) study.[48,49] A published preliminary report[50] outlined the protocol for Mihrshahi et al.'s longterm primary prevention RCT whose 18-month results were recently published.[51] The results of Hodge et al.'s treatment RCT[52] were first disseminated in an abstract;[53] and, Kirsch et al.'s treatment RCT had its clinical outcome data reported in one publication[54] and its mediators of inflammation data in another.[55] Finally, two published reports of a treatment RCT appeared to overlap substantially. When the lead author of the Arm et al. reports was contacted he confirmed that the two reports described a single RCT, although one of them[56] provided response to allergen-challenge data from the participants described in the previous publication,[57] as well as from several other subjects. These data had been unavailable for inclusion in the earlier report, in which clinical data and some mediators of inflammation data are presented. To avoid entering duplicate study participant data, we followed the author's recommendation and focused on the first report[57] for everything except the response to allergen-challenge data, which we obtained from the second document.[56] To avoid confusion in the text, tables, or figures, only one report is used to refer to a given study and its data. It is the one reporting the most data pertaining to the study. Some information regarding the study design of an RCT exclusively described by an abstract[58] were taken from the Cochrane review,[35] which had obtained additional details from a source unavailable to the present review team.

Report and Study Design Characteristics of Included Studies

Of the included studies, two were abstracts[53,58] and the rest were articles published in scientific journals. Only one study was not described by at least one published report.[58] The one relevant study identified by manual search was published.[59] All but five reports (all published) were written in English. Two required translation from Russian[60,61] two from Japanese,[47,62] and one from Polish.[63] As reported earlier, one Japanese publication was retrieved for the purposes of assessing its relevance, yet it was not translated in time to include it in this report.[47] Given its abstract, which allowed it to pass the initial relevance screening, it appears to have been a non-RCT examining the effects of EPA on asthma symptoms, fatty acids in serum, and the generation of various leukotrienes in response to leukocytes.

RCTs and less rigorous types of design were found to address five of the seven research questions. The latter were either controlled (i.e., non-RCT) or uncontrolled (i.e., noncomparative case series; cohort study).

Ten RCTs and nine studies employing other designs address Question 1 (i.e., impact on respiratory outcomes). Of the RCTs, two exclusively randomized children,[52,64] one included both older adolescents and adults,[57] one did not report any age data,[65] and six focused on adults (Summary Table 1).[54,58,66-69] The study including both older adolescents and adults is hereafter included with the adult RCTs.[57] The one failing to report demographic data is kept separate from all syntheses.[65] Two studies employing a design other than an RCT focused on children[63,70] and seven enrolled adults (Summary Table 2).[59,61,62,71-74] One adult study was a non-RCT,[61] with all other designs being noncomparative case series ("before-after studies"). Both pediatric studies involved non-RCT designs.[63,70]

Question 2 (effect modifiers) relies on data from 12 of the 19 studies addressing Question 1, including eight RCTs[54,57,58,65-69] and four studies employing a design other than an RCT (Summary Table 3).[59,62,72,74] Each of the latter four studies involved noncomparative case series. None of the 12 studies enrolled children, since the pediatric studies did not meet the criteria established with respect to this question (at least two studies per outcome, with at least one exhibiting a significant effect in favor of the omega-3 fatty acids exposure). Question 3 (mediators of inflammation) is addressed by 11 studies, including five RCTs and six studies employing a design other than an RCT. Of the RCTs, one involved children[52] and four included adults (Summary Table 4).[54,57,66,68] Each of the studies employing a design other than an RCT enrolled adults (Summary Table 5).[59,60,62,71,73,74] One study employed a non-RCT design,[60] with the others involving noncomparative case series.

Six studies investigated Question 4 (primary prevention). Of these, one was an RCT looking at the impact of omega-3 fatty acids on neonates (Summary Table 6),[51] and five were studies employing an observational design (Summary Table 7) that focused on adults,[75] adolescents,[48] young children and adolescents,[76] and children.[77,78] Question 5 could not be addressed since this review failed to identify any secondary prevention studies. Eight RCTs and two studies employing a design other than an RCT provided safety data to address Question 6 (Summary Table 8). Question 7 could not be evaluated since no study reported adverse events associated with a specific subpopulation (e.g., diabetics).

Question 1: What is the evidence for the efficacy of omega-3 fatty acids to improve respiratory outcomes among individuals with asthma?

As observed in Summary Tables 1 and 2 (below) derived from Evidence Tables 1 and 2 (Appendix E), respectively, two types of evidence, RCTs and studies employing a design other than an RCT, met eligibility criteria for treatment studies investigating Question 1 regarding respiratory outcomes. A qualitative synthesis of the RCT evidence precedes that derived from the other study designs. Data pertaining to key variables such as cointerventions (e.g., asthma medication use), background diet, or past and present smoker status are described in Evidence Tables in addition to qualitative syntheses following this overview of the relevant RCTs.

Overview of Relevant RCTs

Adult and pediatric studies are organized separately. Arm et al.'s RCT of a small sample of English adolescents and relatively young adults (ages 15-42 years) with mild asthma (13/20 exercise-induced) compared high-dose omega-3 fatty acids (5.4g/day EPA/DHA) (n = 12 completers) with visually identical olive oil capsules (n = 8 completers) provided over 10 weeks.[57] Respiratory outcomes included: AM peak expiratory flow (PEF), PM PEF, PEF lability, total symptoms score (e.g., nocturnal wheeze), bronchodilator use, airways histamine responsiveness, airways response to exercise challenge, and, both acute and late airways responses to allergen challenge. Emelyanov et al. randomized a larger, Russian sample population of mild-to-moderate asthmatic adults (all atopic; all house-dust mite sensitive; ages 18-56 years) to receive, for 8 weeks, either low-dose green-lipped mussel extract (200 mg/day EPA/DHA, plus 400 mg/day olive oil) (n = 23) or olive oil capsules (600 mg/day olive oil) (n = 23).[69] Respiratory outcomes included: FEV_1, AM PEF, PM PEF, daytime wheeze, nighttime awakenings, use of inhaled beta-2 agonists, and, decrease in the concentration of exhaled hydrogen peroxide in expired breath condensate.

Okamoto et al. conducted a very small efficacy study in Japan involving a wide range of adults (22-84 years of age) with moderate asthma (7 were atopic), who were randomized to receive 4 weeks of either ALA derived from perilla seed supplementation (n = 7) or corn oil rich supplementation as the control (n = 7).[66] Each intervention was delivered in 10-20 g/day servings of oil used as salad dressing and/or mayonnaise. Respiratory outcomes included: FEV_1, AM PEF, forced vital capacity (FVC), and the maximal expiratory flow at 25% of the forced vital capacity (V_{25}). Thien et al.'s English trial of pollen-sensitive young adults (n = 37; ages 19-42 years) with hay fever compared the efficacy, over 6 months, of capsules with high-dose EPA/DHA (5.4 g/day) derived from fish oil (n = 15 completers), and, visually identical olive oil capsules (n = 10 completers).[67] Respiratory outcomes included: AM PEF, PM PEF, diurnal PEF, respiratory symptom scores, bronchodilator use, and, histamine responsiveness.

Kirsch et al. compared high-dose (4 g/day EPA ethyl ester and trace amounts of DHA) (n = 6) and low-dose omega-3 fatty acids (0.1 g/day EPA ethyl ester and trace amounts of DHA) (n = 6) in a very small RCT involving older Americans (42-73 years) with moderate asthma (9 with allergic rhinitis).[54] The two types of intervention were delivered via gelatin capsules, for 8 weeks. Respiratory outcomes included: FEV_1, total lung capacity (TLC), forced mid expiratory

flow (FEF_{25-75}), airflow resistance, self-reported asthma severity ratings, and, observer-reported asthma severity ratings.

McDonald et al.'s very small two-phase crossover RCT of Australian adults (n = 15) with moderately severe asthma (ages 28-72 years) investigated the effects of receiving 10 weeks of either high-dose omega-3 fatty acid supplementation via fish oil (4.5 g/day EPA/DHA) (n = 15) or control capsules with 15 g/day of olive oil.[58] Respiratory outcomes included: AM PEF, PM PEF, bronchodilator use, and, asthma symptom scores. Stenius-Aarniala et al.'s somewhat larger, three-phase crossover RCT of likely Scandinavian adults across a similarly wide age spectrum (19 to 61 years; n = 36) compared 20 mL daily of fish oil (omega-3 fatty acid content undefined) with equivalent amounts of olive oil, and, evening primrose oil.[68] Participants experienced relatively stable, moderately severe asthma. The intervention was delivered for 10 weeks from concealed bottles, yet there was no attempt to conceal taste. Respiratory outcomes included AM PEF and PM PEF.

Hodge et al. randomly assigned Australian children, ages 8 to 12 years (asthma severity unreported) to receive, over 6 months, either omega-3 fatty acids (1.2 g/day EPA/DHA from fish oil capsules; ALA from canola diet) (n = 20 completers) or omega-6 fatty acid supplementation (matched capsules with safflower, palm, and olive oils; sunflower oils) (n = 19 completers).[52] Respiratory outcomes included: FEV_1, asthma severity scores, and, dose-response ratio to histamine challenge. Nagakura et al. randomized Japanese children (asthma severity unreported) from a wider age range (4-17 years), and compared EPA/DHA from fish oil capsules (n = 15) with visually identical olive oil capsules (n = 15).[64] Doses were weight-adjusted, and the intervention period lasted 10 months. Respiratory outcomes included observer-evaluated asthma symptom scores, and, bronchial hyperresponsiveness to acetylcholine challenge.

Dry and Vincent's RCT (n = 12) did not provide data regarding the age of their population of allergic asthmatics, so it was impossible to group it with either the adult or pediatric trials.[65] They compared low-dose (1 g/day) EPA/DHA (n = no data) with an undefined placebo (n = no data) after nine months of a 12-month intervention period. FEV_1 was their sole respiratory outcome.

Qualitative Synthesis of RCT Evidence Regarding Respiratory Outcomes

Trial characteristics. Ten RCTs published between 1988 and 2002 were identified as addressing Question 1 (Summary Table 1; Evidence Table 1; Appendix E). Seven studies involved adults,[54,57,58,66-69] two enrolled children,[52,64] and one did not identify its study population's age range.[65]

Only one adult trial[54] and one pediatric trial[52] reported both inclusion and exclusion criteria. One study exclusively provided inclusion criteria,[67] whereas three presented only exclusion criteria.[58,68,69] One of the latter studies was the one that was only published as an abstract. Four RCTs did not provide either inclusion or exclusion criteria.[57,64-66]

All but two trials employed a parallel-arm design, with each of the eight involving two study arms. The crossover trials included two[58] and three phases,[68] respectively. The former compared omega-3 fatty acids to a control containing olive oil, whereas the latter included an exposure to evening primrose oil in addition to a control containing olive oil.

The ten studies were typically small, with a mean number of 27.2 (range: 12-46) participants. A total of 75 children and 197 adults were randomized. The studies lasted an average of 26.6

(range: 4-52) weeks, with a mean intervention length of 19.7 (range: 4-52) weeks. Only two trials did not report the length or details concerning a run-in period, with an average run-in length for the remaining eight studies of three (range: 2-8.7) weeks.[65,66] Of the two crossover trials, only the two-phase trial reported a washout period, yet details concerning its protocol were not included in its brief abstract.[58]

The trials were conducted in various countries, with two undertaken in each of Japan,[64,66] Australia,[52,58] and England.[57,67] The remaining trials took place in France, the United States, Russia, and Finland. In nine of the studies, a single site was involved. The report for the tenth study did not provide this information.[65] Both RCTs undertaken in England reported funding source information. Both received some private funding, with one also supported by industry,[57] and the other receiving the oil capsules from industry in addition to some support from a medical charity.[67] The pediatric Australian study was supported by government and a private source,[52] the American trial received government funding from two granting institutions,[54] and the Finnish publication only reported having received their omega-3 fatty acid exposure from industry.[68] Both trials conducted in Japan,[64,66] the trial conducted in France,[65] the trial conducted in Russia,[69] and one of the trials conducted in Australia,[58] did not provide information concerning funding source. There were no noticeable differences with regards to trial characteristics between the adult and pediatric trials.

Summary Table 1: RCT evidence of omega-3 fatty acids to improve respiratory outcomes in asthma

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Jadad Total Quality / Allocation Concealment (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Arm, 1988, England[56,57]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	1/9	4 (Grade: A)/ unclear	III
Emelyanov, 2002, Russia[69]	23	200 mg EPA+DHA + 400 mg olive oil	23	600 mg olive oil	4/7	5 (Grade: A)/ unclear	III
Kirsch, 1988, USA[54,55]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA ethyl ester (trace DHA)	0/6	3 (Grade: B)/ unclear	I
McDonald, 1991, Australia[58*]	15	2.7 g EPA + 1.8 g DHA	15	15 g olive oil	0/4	3 (Grade: B)/ unclear	III
Okamoto, 2000a, Japan[66]	7	10-20 g perilla seed oil (ALA: NR)	7	10-20 g corn oil	4/4	2 (Grade: C)/ unclear	III
Stenius-Aarniala, 1989, Finland[68*]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	0/2	2 (Grade: C)/ unclear	III
Thien, 1993, England[67]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	0/6	4 (Grade: A)/ unclear	III
CHILDREN							
Hodge, 1998, Australia[52]	NR	0.72 g EPA 0.48 g DHA + ALA (NR) via canola diet	NR	Omega-6 fatty acids: 1.8 g safflower oil + 1.8 g palm oil + 0.4 g olive oil + sunflower diet (NR)	0/3	3 (Grade: B)/ unclear	III
Nagakura, 2000, Japan[64]	15	17.0-26.8 mg/kg EPA; 7.3-11.5 mg/kg DHA (300 mg fish oil)	15	300 mg olive oil	2/2	4 (Grade: A)/ unclear	III
NOT REPORTED							
Dry, 1991, France[65]	NR	1.0 g EPA+DHA	NR	"Placebo" (NR)	1/1	2 (Grade: C)/ unclear	X
n = number of enrolled participants; NR = not reported; S = significant; *Crossover trial							

Population characteristics. One RCT did not report any age, gender distribution, or racial/ethnic background data.[65] For the two pediatric trials, the average age of the participants was 10.6 (range: 4-17) years.[52,64] Excluding two studies failing to report mean age data,[58,65] yet including data from one exclusively describing study completers,[67] the mean age of the participants in the five adult studies was 44.6 (range: 18-84) years. The two pediatric populations involved 47.7% males, whereas the corresponding figure for adult trials was 36% (range: 13.3-52.6%), including data solely for completers from one study.[67] Little information was reported identifying the racial/ethnic makeup of trial populations. Although neither

pediatric trial explicitly provided this information, the likely backgrounds were Asian[64] and Caucasian/European.[52] Not one adult trial explicitly described these data, yet it could be inferred that, at least for six of seven studies, participants were likely drawn from Caucasian/European,[57,58,67,69] Asian,[66] and Scandinavian[68] backgrounds. The American RCT did not specify its racial/ethnic composition.[54]

One of the two pediatric studies,[52] and five of the eight adult trials,[54,65,66,68,69] provided a definition of asthma to classify study participants. While the descriptions varied, a few used standard approaches. For example, Stenius-Aarniala et al.'s Finnish study used the American College of Chest Physicians and the American Thoracic Society's 1975 criteria.[68] One pediatric[52] and five of the eight adult studies[54,58,66,68,69] provided a description of their diagnostic method. While one of these reported the use of some pulmonary function testing,[58] the other four described having used a strategy that combined a clinical history with assessments of pulmonary function.

One pediatric trial employed ratings to establish a definition of asthma severity, yet it never interpreted their participants' baseline level of asthma severity.[52] The other study involving children did not describe a method to determine severity or provide a statement about the participants' asthma severity. Six of the eight adult trials interpreted their participants' severity level. Of the four studies identifying a moderate level of severity, only two provided a definition.[54,68] Two reports merely provided a label such as "moderate" or "severe," for example.[58,66] One group of investigators assigned a mild-to-moderate severity rating using a defined approach.[69] The only study identifying mild asthmatics did not describe the method by which this was achieved.[57] Two adult trials did not define their participants in these terms.[65,67] Not one of the ten included studies attempted to define the severity of asthma at baseline, or on-study, in light of how well it was controlled by medication.

The duration of asthma for the only pediatric study reporting these data was an average of 10.1 years.[64] Only three adult trials[54,66,69] provided these data, with a mean duration of 15.7 years.

The RCT reports provided different ways to describe some of the typical concomitant conditions or possible triggers of asthma. In the single pediatric trial reporting such information, 36 of the 39 participants were considered atopic.[52] The Okamoto et al.,[66] Arm et al.,[57] and Emelyanov et al.[69] studies identified 50% (7/14), 88% (22/25), and 100% (46/46) of their randomized adult participants as atopic, respectively. In addition, the Arm et al. trial included an undefined number of subjects with exercise-induced asthma,[57] and the Emelyanov et al. study included participants who were also house dust-mite sensitive.[69] In the study by Thien et al., the participants were pollen-sensitive, had hay fever, and some exhibited a sensitivity to fungal spores; the authors claimed that the possible effect of these sensitivities on the results would be eliminated by virtue of the randomization process.[67] No data were reported regarding the study arms to which were allocated this undefined number of participants with asthma who were also spore-sensitive. The population in the Dry and Vincent study was considered to be allergic asthmatic, yet no definition was provided.[65] Three-quarters (9/12) of Kirsch et al.'s participants were identified as having allergic rhinitis.[54] Stenius-Aarniala et al.'s sample contained relatively stable asthmatics, four of whom were aspirin-sensitive and another four of whom had positive, yet undefined, skin-prick tests.[68] The McDonald et al. study did not describe their participants with respect to any of these conditions.[58]

In spite of the possibility that one of the major concomitant conditions in asthmatics could be pollen sensitivity, almost no information was reported on the seasons in which the studies were

conducted. One trial evaluated pollen-sensitive participants with hay fever before, during, and after peak pollen season.[67] Another study conducted by the same group of investigators assessed response to allergen challenge outside pollen season, with participants exhibiting pollen sensitivity to a skin-prick test excluded from evaluations during pollen season.[57] Two studies enrolled participants having been admitted to hospital for asthma,[64,66] with investigators in one acknowledging that having such a controlled environment would minimize exposure to inhalant allergens for both study arms.[64] All other studies were conducted with outpatients.

The number and types of concurrent condition known to have been excluded from the RCTs are limited. Few studies described this information. Hodge et al.'s study excluded children with other significant diseases (undefined) and those with dietary salicylate sensitivity.[52] Stenius-Aarniala et al.'s adult trial screened out those with fish allergy, diabetes, or coagulation disorders.[68] Kirsch et al. excluded those with status asthmaticus, pneumonitis, pneumothorax, or other major lung disease in the previous year.[54] Emelyanov et al. screened out current or ex-smokers, clinically significant heart, renal, liver and intestinal disorders, and, women of childbearing potential using inadequate contraception.[69]

A few attempts were made at determining whether or not certain asthma risk factors, or those with the potential to influence asthma control, were present in studies, and whether participants characterized in these terms were any more likely to have been associated with a given study arm. Most of the important data were never provided for full samples, however, let alone to shed light on cross-arm differences.

The cross-arm equivalence of asthma severity was reported in four study documents,[52,54,57,69] while such information was not reported on five occasions.[58,65-68] In one pediatric trial, the mean baseline asthma severity score was higher in the omega-3 fatty acid group.[64] In seven trials, no data were provided that would clarify that study arms were similar, or the same, on the basis of concomitant conditions or triggers.[58,64-69] Only two reports indicated that there was an equal distribution of children with atopy[52] or adults with allergic rhinitis.[54] One reported similar distributions of both atopic and exercise-induced asthmatics across study arms.[57] Two trial reports each indicated that the asthma durations of participants in their respective study arms were slightly, but not significantly, different.[64,69] No other report included similar information.

Data concerning participants' smoker status or history were only presented in four reports. One trial excluded all current and ex-smokers,[69] whereas a second study identified their participants as nonsmokers.[67] Ex-smokers constituted almost half (7/15) of the randomized adults in one study.[58] In another study, three of the 29 trial completers were current smokers, and 12 of 29 trial completers were nonsmokers over the previous two years.[68]

Information concerning present or past smoker status was thus provided for only two of the four trials that included older adults. The age range for these two studies was 28 to 72 years in one study,[58] and 19 to 61 years in the other one.[68] The age ranges for the two studies where samples might have included some ex-smokers were 42 to 73 years in one study,[54] and 22 to 84 years in the other.[66] Finally, current or ex-smokers might have been included in any of the trials, with the exception of the pediatric trials.

No information was reported in any of the adult studies concerning the possibility of COPD in any of the participants. Also, no information was reported in the two pediatric trials concerning the possibility of wheezing syndromes. Information regarding exposure to environmental smoke was also unreported, as were data pertaining to a possible history of early respiratory infections in the pediatric populations.

Given the dearth of data concerning these variables, little definitive can be said about their roles as confounders. Finally, in spite of the likelihood that the background diets of participants vary as a function of geographic location, no information of this type was contained in study reports.

Intervention/exposure characteristics. The source of the omega-3 fatty acid intervention varied across the RCTs. One pediatric trial[64] and five adult trials[57,58,65,67,68] described the source as fish oil. The specific types of fish from which fish oil exposures were derived were not described. The other study involving children defined the intervention as fish oil, a canola (ALA) diet, and eating fish at least once per month.[52] The remaining adult studies employed either a marine source (green-lipped mussel),[69] capsules containing EPA ethyl ester along with trace amounts of DHA,[54] or perilla seed diet supplementation.[66] The type of omega-3 fatty acid employed in six studies, including one pediatric trial, included a combination of EPA and DHA.[57,58,64,65,67,68] The other pediatric study employed both an EPA and DHA combination, and a canola-based ALA diet.[52] The remaining adult studies used olive oil in combination with EPA/DHA,[69] EPA ethyl ester with trace amounts of DHA,[54] or ALA.[66]

The most frequently used control was olive oil, and olive oil combined with EPA/DHA was the most widely investigated intervention.[57,58,64,67-69] Other comparisons included: low-dose EPA/DHA compared with an undefined placebo;[65] a high dose (4 g/day) of EPA/DHA compared with a low dose (0.1 g/day) of EPA/DHA;[54] EPA/DHA capsules and ALA supplementation as well as at least one fish meal a month, compared with control capsules (safflower, palm, and olive oils); omega-6 fatty acid supplementation compared with no fish consumption;[52] and, ALA supplementation compared with corn oil, the latter identified as a source of omega-6 fatty acids.[66]

If, as established in consultation with our TEP, greater than or equal to 3 g is taken to define a high adult daily dose or serving of omega-3 fatty acids, then four adult studies met this criterion: 5.4 g/day EPA/DHA versus olive oil;[57,67] 4.5 g/day EPA/DHA versus olive oil;[58] and, 4 g/day EPA ethyl ester, with an undefined amount of DHA, versus a low dose of omega-3 (0.1 g/day).[54] One adult trial studied a low dose of omega-3 fatty acids (200 mg/day EPA plus 400 mg/day olive oil) compared with 600 mg/day of olive oil.[69] Another study examined what they claimed to be a low dose of omega-3 fatty acids (amounts of EPA/DHA undefined) compared with olive oil.[68] One adult RCT reported only the amount of oil to be consumed (10 to 20 g/day) in each of the ALA and corn oil (omega-6 fatty acid) study arms, but not the actual amounts of ALA.[66] One adult study reported comparing a low dose of omega-3 fatty acids (1 g/day) with an undefined placebo.[65]

One pediatric trial compared a dose of omega-3 fatty acids (1.22 g/day of EPA/DHA, plus an undefined amount of ALA from diet supplementation) with omega-6 fatty acid capsules and dietary supplementation.[52] Another study that enrolled children used a dose of omega-3 fatty acids, adjusting the dose for body weight (17-26.8 mg/kg/day EPA and 7.3-11.5 mg/kg/day DHA), and compared this intervention to olive oil.[64] With little or no data available in study reports with which to adjust doses by weight, it was decided that the definition of a high ($\geq$ 3g/d) versus low dose for adults could not be applied to children. A 1.22 g/d dose in a child could be equivalent to a 3 g/d dose in an adult on a per kg body weight basis.

Various methods were used to deliver the omega-3 fatty acid exposure. Six of ten trials, including one that studied children, solely employed capsules with standardized doses.[54,57,58,64,67,69] One study did not describe the therapeutic vehicle, although it was likely to

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have been capsules as well.[65] A pediatric trial had parents provide oils, margarine, and salad dressing containing ALA, in addition to fish oil capsules.[52] An adult trial had participants use bottles of oil, salad dressing, and mayonnaise containing ALA,[66] while another had adults deliver their own fish oil by way of spoonfuls poured from concealed bottles.[68] In these three RCTs, there was thus no way to guarantee a constant within-participant intake of oils or omega-3 fatty acids and, in turn, an unvarying within- or between-study arm intake of oil (as calories/energy), or a stable difference in the interventions received by the different study arms. This means that the definition of the intervention, and the control exposure, changed in some unmeasured ways. At the same time, recorded consumption data strongly suggest that intake varied amongst study participants.

In one pediatric trial, the consumption of food products was not monitored, and the children ingested at least 25% fewer than the allocated fish oil capsules.[52] In another trial, while the participants were directed to consume 10 to 20 mL/day of oil, great variability was observed in the actual consumption, and only 21 of 29 completers consumed more than 15 mL/day.[68] To compound matters, the authors of this study acknowledged that the lack of any attempt to conceal the taste of the fish oil might have impacted the results.[68] Overall, how these failed standardizations of dosing may have affected the study results was not discussed in any reports. The implication of this state of affairs is highlighted in Chapter 4.

In not providing a definition of its placebo, another study also failed to demonstrate unequivocally that it had controlled for caloric intake.[65] Finally, failure of an adult trial to present information to the contrary, suggests that it also may have failed to control across study arms for this important variable.[54] As a result, when it comes to the intervention, half of the included RCTs failed to establish unequivocally that they had eliminated the possibility of confounding.[52,54,65,66,68]

The exact schedule used to determine the delivery of the exposures was not provided in any report. Only one pediatric trial stated how many capsules would be taken at a given time, with the schedule calling for three times of day.[64] One adult trial reported a morning and evening schedule.[69] Reports of trials that employed dietary supplementation with oils, dressings and mayonnaise did not specify at which meals the foods should be consumed, or whether they should be apportioned in some way.[52,66,68]

Few trial reports indicated that the participants were instructed to maintain their background diet over the course of the study. One adult study conducted in Japan, involving perilla seed supplementation, mandated that participants maintain an unchanged diet,[66] while an Australian trial of adults told the participants to keep their dietary fish intake constant.[58] An English investigation asked participants to maintain their usual diet.[57] None of the RCTs provided omega-6 fatty acids or any other supplement as a cointervention, and none attempted to alter the ratio of omega-6 to omega-3 intake.

Eight of ten trials indicated the manufacturer of at least one omega-3 fatty acid product used in their study.[52,54,57,64,65,67-69] Only one study reported on the purity of their omega-3 fatty acid exposure.[54]

Cointervention characteristics. There were no data regarding the presence or treatment of concurrent conditions in any of the ten RCTs. There was a scarcity of information reported concerning the dosing levels of asthma medication.

Two trials established exclusion criteria concerning the use of asthma medication. One pediatric study excluded children on oral corticosteroids, although on-study inhaled

corticosteroid use was permitted.[52] An adult trial excluded anyone receiving inhaled corticosteroids or having been hospitalized for asthma during the run-in period.[69] The latter study also mandated that no participants receive on-study oral or inhaled corticosteroids; only rescue beta-2 agonist medication was allowed. The remaining eight studies did not set exclusion criteria pertaining to prestudy asthma medications.

Seven reports did not indicate whether participants had had to maintain a constant on-study dose of corticosteroid medications.[52,57,58,64-66,68] One adult trial did demand that participants maintain a constant dose of inhaled corticosteroids across the study,[67] while another asked that all types and doses of medications other than oral corticosteroids be kept constant during the trial.[54]

Only three studies explicitly stated that participants used on-study oral corticosteroids.[54,64,68] Of these, two reports mentioned that there was no change in the use of this medication during their study,[64,68] while the third acknowledged that oral corticosteroid use may have changed over the 8 weeks of intervention.[54] Compliance data for the first two studies were not reported. Also, these two studies failed to report data concerning the cross-arm equivalence of oral corticosteroid use.[64,68] The third trial reported that all six participants used oral corticosteroids in the high-dose omega-3 fatty acid group, and four of six participants used oral corticosteroids in the low-dose omega-3 fatty acid group.[54] In this study, the dosing of oral corticosteroids could be altered by physicians according to pre-established criteria ($\leq$5 mg/week).[54]

Eight RCTs reported that participants took on-study inhaled corticosteroids.[52,54,57,64-68] One of these included a single user in the low-dose group,[54] a second reported that eight of 25 completers had taken them,[67] and another did not indicate whether any adults had used them.[58] Few data were provided to indicate whether inhaled corticosteroid use was kept constant across the study, or whether study arms were balanced for either the number of users or the dose. Five trials suggested that inhaled corticosteroid use did not change across the study.[52,64,65,67,68] Three trials provided no data.[57,58,66] Regarding the equivalence of inhaled corticosteroid use across study arms, four trials reported no data,[57,65,66,68] one observed more users in the omega-3 fatty acid arm (n = 4) than in the control arm (n = 1),[67] and one indicated that while there were three users per study arm, the control participants received a slightly higher mean dose.[64]

Of note, with regards to the use of other asthma medications, a trial reported that its study arms differed significantly in the amount of rescue medications required for acute on-study asthma attacks.[64] A vast spectrum of other medications was used, including inhaled beta-2 agonists (Evidence Table 1). One study reported that similar numbers of participant across study arms had used oral theophylline, beta-2 agonists, and cromolyn.[54]

Outcome characteristics. The most frequently employed respiratory outcomes (Evidence Table 1) were AM PEF, employed in six RCTs,[57,58,66-69] followed by FEV_1[52,54,65,66,69] and PM PEF, with five studies each,[57,58,67-69] and then by subjective asthma symptom scores[54,57,58,67] and total bronchodilator use, each with four representations.[57,58,67,69] One study reported results for four respiratory outcomes, yet no data were provided in the abstract.[58] Only once did either of the pediatric studies use one of the above-noted outcomes. While the pulmonary function tests appeared to be based on standard methodologies, the symptom ratings and bronchodilator use data were captured via diary cards. The psychometric performance of subjective rating instruments was not established in the reports. Very few studies reported intention-to-treat analyses or statistical tests assessing the between-arm difference in (%) change from baseline in

outcomes. Instead, they preferred to perform and report separate analyses of individual study arm data. Nine of ten trials described withdrawals and dropouts.

   Study quality and applicability. No variability was observed regarding the assessed adequacy of allocation concealment. All trials received a rating of "unclear." The mean Jadad total quality score was 3.2 (range: 2-5), indicating good quality. The mean quality for the two pediatric studies was slightly higher (3.5). The greatest inconsistency involving a Jadad item was for blinding. Of ten studies in total, two of the RCTs received the lowest (0) rating and four of the RCTs received the highest (2) rating. Virtually no variability characterized the applicability rating, with eight of ten trials obtaining a level III rating. This indicates the extremely limited potential for generalization to the typical North American population with asthma. Given the uniform picture of allocation concealment, quality grades based exclusively on the Jadad total quality scores were entered into the summary matrix.

   While four of the RCTs exhibited high quality, as defined by the Jadad total score, none received an allocation concealment rating other than "unclear," indicating that at least one possible threat to internal validity cannot be ruled out. Moreover, the generalizability of the results of these four RCTs to the North American standard set for this review was extremely limited. The only trial with strong generalizability potential also exhibited good study quality.[54] It was a small trial, however (n = 12).

Summary Matrix 1: Study quality and applicability of RCT evidence regarding respiratory outcomes*

		Quality								
		A			**B**			**C**		
Applicability	**I**				Author	Year	N			
					Kirsch	1988	12			
	II									
	III	Author	Year	N	Author	Year	N	Author	Year	N
		Arm	1988	25	McDonald	1991	15	Okamoto	2000a	14
		Emelyanov	2002	46	Hodge[†]	1998	45	Stenius-		
		Nagakura[†]	2000	30				Aarniala	1989	36
		Thien	1993	37						

N = number of randomized participants; *Dry, 1991 (total quality grade: C) not entered since received an "X" (insufficient information) for applicability; [†]Pediatric trial

Qualitative Synthesis of Individual RCT Results

   Adult and pediatric study results are organized separately, and the most frequently investigated outcomes are presented first. Regarding FEV_1 as the gold standard measure of pulmonary function, two of three adult RCTs showed no benefit relating to omega-3 fatty acid exposure.

   In an adult study conducted in Japan, involving a very wide range of ages (22 to 84 years) and investigating the efficacy of ALA derived from perilla seed supplementation compared with corn oil rich supplementation, Okamoto et al. observed a significantly greater increase in FEV_1 in the omega-3 fatty acid group.[66] Yet, Kirsch et al.'s trial, which compared high-dose (4 g/day EPA ethyl ester and trace amounts of DHA) and low-dose omega-3 fatty acids (0.1 g/day EPA ethyl ester and trace amounts of DHA) in a sample population of older Americans (42 to 73 years), found a nonsignificant change in FEV_1 in either study arm.[54] Emelyanov et al.'s Russian

study of an adult population (18 to 56 years), which compared low-dose green-lipped mussel extract (200 mg/day EPA/DHA, plus 400 mg/day olive oil) and olive oil capsules (600 mg/day olive oil), showed nonsignificant between-arm differences in changes in FEV_1.[69]

For AM PEF, two studies reported a significant benefit, and three reported no benefit. Emelyanov et al.'s study, which compared low-dose green-lipped mussel extract with olive oil capsules, showed a significantly greater increase in AM PEF in the omega-3 fatty acids arm,[69] whereas Okamoto et al.'s perilla seed supplementation trial (ALA vs. corn oil) observed a significant increase in AM PEF only in the treatment arm.[66] However, Arm et al.'s English trial of a sample of relatively young adults, which compared high-dose omega-3 fatty acids (5.4g/day EPA/DHA) with visually identical olive oil capsules, reported a nonsignificant between-arm difference in changes in AM PEF.[57] Thien et al.'s English trial of pollen-sensitive young adults with hay fever, which compared high-dose EPA/DHA (5.4 g/day) derived fish oil capsules with visually identical olive oil capsules, observed a nonsignificant between-arm difference in AM PEF during the pollen season.[67] In addition, Stenius-Aarniala et al.'s three-phase crossover study of likely Scandinavian adults from across a wide age spectrum (19 to 61 years), which compared 20 mL daily of fish oil (omega-3 fatty acid content undefined) with equivalent amounts of olive oil and evening primrose oil, reported a nonsignificant difference between phases for AM PEF.[68] While providing neither the data nor the results of statistical testing, McDonald et al.'s study of Australian adults, who received either high-dose omega-3 fatty acid supplementation via fish oil (4.5 g/day EPA/DHA) or control capsules with 15 g/day of olive oil, reported a nonsignificant between-arm difference in change in AM PEF.

All five studies revealed a nonsignificant benefit for PM PEF. The Arm et al. study,[57] as well as Thien et al.'s,[67] each of which compared high-dose omega-3 fatty acids (5.4g/day EPA/DHA) with visually identical olive oil capsules in young adults, reported a nonsignificant between-arm difference in changes in PM PEF. The findings from Emelyanov et al.'s study,[69] which compared low-dose green-lipped mussel extract with olive oil capsules, and the findings from Stenius-Aarniala's crossover trial[68] concurred. The results of McDonald et al.'s study were similar, yet no data were reported.[58] The two trials that investigated high-dose omega-3 fatty acids (vs. olive oil) observed a nonsignificant between-arm difference in diurnal PEF variability during the pollen season in pollen sensitives with hay fever,[67] or outside pollen season.[57]

Four trials evaluated the impact of omega-3 fatty acids on self-reported bronchodilator use, with only the Emelyanov et al. investigation showing a significantly greater decrease in use (puffs/day) in its low-dose green-lipped mussel study arm.[69] Both English studies of high-dose omega-3 fatty acids failed to find a significant between-arm difference either during[67] or outside[57] pollen season. McDonald et al.'s unreported data regarding high-dose EPA/DHA were in agreement.[58]

Four RCTs failed to find a benefit expressed in terms of between-arm differences in changes in self-reported asthma symptom scores, including both high-dose omega-3 fatty acids studies conducted during or outside pollen season,[57,67] Kirsch et al.'s project investigating high versus low doses of EPA in an older American population,[54] and McDonald et al.'s trial of high-dose omega-3 fatty acids.[58]

Kirsch et al.'s additional assessment of observer-reported asthma severity ratings revealed nonsignificant changes in both study arms.[54] Regarding other self-reported measures, Emelyanov et al. reported a significantly greater decrease in daytime wheeze in the omega-3 fatty acid arm, but a nonsignificant between-arm difference in changes in nighttime awakenings.[69]

Two studies each failed to find a significant between-arm difference in changes in airways histamine responsiveness (specific airways conductance: sGAW) in either the high-dose EPA/DHA or olive oil control arms, both during and outside pollen season.[57,67] Other, single-study evaluations are organized by whether or not their results attained statistical significance.

Okamoto et al.'s investigation of the impact of perilla seed (vs. corn oil) supplementation observed a significantly greater increase in FVC in the omega-3 fatty acid arm.[66] They also observed a significant increase in V_{25} only in the omega-3 fatty acid arm. Emelyanov et al. identified a significantly greater decrease in the concentration of exhaled hydrogen peroxide in expired breath condensate in the green-lipped mussel arm.[69]

Kirsch et al. compared high- and low-dose omega-3 fatty acids and found a nonsignificant change in FEF_{25-75}, TLC, and airflow resistance in each study arm.[54] Arm et al. compared high-dose omega-3 fatty acids with visually identical olive oil capsules, and reported nonsignificant changes in the maximal percent decreases in specific airways conductance in response to exercise challenge in both study arms.[57] They also reported a nonsignificant change in the acute airways response to allergen challenge in both study arms.[57] However, they reported a significant suppression at 2 hours, then at 3 to 7 hours on late airways response to allergen challenge, but only in the omega-3 fatty acids arm.

Hodge et al.'s investigation of Australian children (ages 8 to12 years) receiving either omega-3 fatty acids (1.2 g/day EPA/DHA from fish oil capsules; ALA from canola diet) or omega-6 fatty acid supplementation (matched capsules with safflower, palm, and olive oils; sunflower oils) revealed a nonsignificant change in FEV_1 or parent-endorsed asthma severity scores in each study arm.[52] In a study randomizing Japanese children from a wider age range (4 to 17 years), and comparing EPA/DHA from fish oil capsules with visually identical olive oil capsules, Nagakura et al. reported a significant decrease in observer-evaluated asthma symptom scores only in the treatment arm.[64] Their doses were weight-adjusted. Nagakura et al. also reported a significant decrease in bronchial hyperresponsiveness to acetylcholine challenge only in the treatment arm. Finally, Hodge et al.'s study revealed a nonsignificant change in the dose response ratio to a histamine challenge in both study arms.[52] Dry and Vincent compared low-dose (1 g/day) EPA/DHA with an undefined placebo at nine months, and found a significantly greater increase in FEV_1 in the omega-3 fatty acid arm of a study failing to define its sample's age.[65]

Overview of Relevant Studies With Designs Other Than an RCT

Adult and pediatric studies are organized separately. Masuev divided participants, in a very small Russian cohort exhibiting both an acute and late asthmatic response to allergen challenge, into two matched subgroups. One then received 6 g/day of EPA and DHA capsules over 8 weeks (n = 5) and the other took olive oil capsules (n = 3) over this same period.[61] In this non-RCT, participants had bronchial asthma, and were hypersensitive to house dust. Change in PEF after 4-8 hours was the sole outcome.

Ashida et al.'s similarly small Japanese noncomparative case series (n = 5) received perilla seed supplementation (ALA amount undefined) for 2 weeks.[59] The oil intervention was delivered as replacement salad dressing and/or mayonnaise. Four participants exhibited bronchial asthma, and the other, cough variant asthma. Outcomes included AM PEF, PM PEF, and, an asthma symptoms score (e.g., cough). In a small noncomparative case series (n = 8), Hashimoto et al. exposed a small number of Japanese adults with mild to moderate asthma, and

hyperlipidemia, to 1,800 mg/day of EPA over 8 weeks.[62] The mode of delivery was not reported. Respiratory outcomes included AM PEF, PM PEF, and various undefined ones: symptom score, asthma score, therapeutic score, sleep score, and, daily life score.

In a very small noncomparative case series (n = 7) receiving a 30-day, capsule-based exposure to 3g/day of EPA and DHA, Villani et al. observed atopic adults in Italy with mild seasonal asthma (from airborne allergens).[72] Respiratory outcomes included: PEF (undefined), FEF_{25-75}, TLC, change in fall in FEV_1 in response to bronchial challenge, airways responsiveness to bronchial challenge, residual volume (RV), and, slow vital capacity. Okamoto et al.'s somewhat larger noncomparative case series of mild asthmatics (half were atopic) in Japan (n = 26) was exposed to perilla oil supplementation (10-20 g/day; ALA amount undefined) in salad dressing or mayonnaise over 4 weeks, with the background diet unchanged.[71] They distinguished responders from nonresponders as those participants with significantly decreased LTC_4 generation by peripheral leukocytes (undefined).[71] The goal was to see whether these two groups were distinguishable on the basis of the following respiratory outcomes: FEV_1, AM PEF, FVC, and, V_{25}.

Picado et al. exposed a small noncomparative case series of aspirin-intolerant asthmatics (n = 10), first to 6 weeks of placebo (lactose) capsules plus a poorly defined eucaloric diet (e.g., 32% fat), then to another 6 weeks of an experimental diet including 3 g/day of omega-3 fatty acids (i.e., undefined EPA/DHA), via capsules, and the same eucaloric diet.[74] Respiratory outcomes included: PEF (undefined), oral corticosteroid use, bronchodilator use, and, pulmonary symptom score. In an attempt to alter the intake ratio of omega-6/omega-3 fatty acids in atopic asthmatics, Broughton et al. exposed an American noncomparative case series (n = 26) to 4 weeks of low fish oil supplementation (~0.7 g/day EPA/DHA), followed by another 4 weeks of high fish oil supplementation (~3.3 g/day EPA/DHA), yielding a low (1:0.1) and high (1:0.5) ratio exposure, respectively.[73] The investigators assessed the change from baseline in the magnitude of the provocative dose of methacholine required to cause a 20% fall in each of FEV_1, FVC, PEF, and FEF_{25-75}. They also evaluated the differences between responders and nonresponders on these bases.

In a relatively large pediatric non-RCT with Polish children (n = 60), Machura et al. investigated the impact on bronchial asthma of a 12-week exposure to either fish oil supplementation (15 mL fish oil/day; n = 37) or a control (15 mL of sunflower oil; n = 23).[63] Respiratory outcomes included: FEV_1, PEF (undefined), FEF_{25-75}, the number of days with increased severity of asthma symptoms, and, loss of asthma control. In a second pediatric non-RCT, conducted in Russia over an undefined period, Gorelova and Semikina compared 4.5 g/day of fish oil in capsules (omega-3 fatty acid content undefined; n = 23) plus a poorly defined hypoallergenic diet with the same diet and an undefined control (n = 10).[70] Their outcome was bronchodilator use.

Qualitative Synthesis of Evidence Regarding Respiratory Outcomes from Study Designs Other Than an RCT

Study characteristics. Nine studies with either a non-RCT or noncomparative case series design, published between 1988 and 2000, were identified as being pertinent to Question 1 (Summary Table 2; Evidence Table 2, Appendix E). Six exclusively involved adults,[59,62,71-74] one enrolled older adolescents and adults 17 to 40 years-of-age,[61] and is considered along with the adult studies, and two evaluated children.[63,70]

Only two of the adult studies presented clearly defined inclusion and exclusion criteria,[62,73] another adult study provided both, albeit vaguely described,[72] and four adult studies exclusively described inclusion criteria.[59,61,71,74] For example, one of the studies excluded adults with a history of bleeding disorders or delayed clotting time.[73] Both pediatric investigations failed to report any selection criteria.[63,70]

One non-RCT, after identifying adults exhibiting both an acute and late asthmatic response to allergen challenge, divided the eight responders into two groups matched for age, gender, and asthma duration.[61] Four adult studies each employed a single-phase, noncomparative case series design.[59,62,71,72] Two adult investigations each selected a noncomparative case series, which they then exposed to two interventions in a fixed sequence.[73,74] Both pediatric studies used a non-RCT design.[63,70] The first one matched the groups for age, diagnosis, and asthma treatment (no data);[70] the second one did not report how, or if, the groups were matched.[63]

Summary Table 2: Evidence from other study designs of omega-3 fatty acids to improve respiratory outcomes in asthma

Author, Year, Location	Omega-3 Fatty Acid Cohort/Phase		Comparator Cohort/Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Total Quality (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Ashida, 1997, Japan[59†]	5	15 g perilla seed oil (ALA: NR)	NA	NA	3/3	3 (Grade: B)	III
Broughton, 1997, USA[73†]	26	"Low" EPA + DHA intake: ~0.7 g (mean)	26	"High" EPA + DHA intake: ~3.3 g (mean)	5/16	3 (Grade: B)	I
Hashimoto, 1997, Japan[62†]	8	1.8 g EPA	NA	NA	5/7	3 (Grade: B)	III
Masuev, 1997b, Russia[61††]	5	6.0 g EPA+DHA	3	6.0 g olive oil	1/1	4 (Grade: A)	III
Okamoto, 2000b, Japan[71†]	26	10-20 g of perilla seed oil (ALA: NR)	NA	NA	5/5	4 (Grade: A)	III
Picado, 1988, Spain[74†]	10	3.0 g EPA+DHA + eucaloric diet	10	3.0 g lactose + eucaloric diet	3/4	5 (Grade: A)	III
Villani, 1998, Italy[72†]	7	3.0 g EPA+DHA (1:1 ratio)	NA	NA	3/7	4 (Grade: A)	III
CHILDREN							
Gorelova, 1998, Russia[70††]	23	4.5 g fish oil (NR) + hypo-allergenic diet	10	Control (NR) + hypo-allergenic diet	1/1	2 (Grade: C)	III
Machura, 1996, Poland[63††]	37	3.0 g EPA+DHA (15 mL fish oil)	23	15 mL sunflower oil	2/6	3 (Grade: B)	III
n = number of enrolled participants; NR = not reported; NA = not applicable; S = significant; †Noncomparative case series; ††non-RCT							

The nine studies typically involved few participants, with a mean number of 20.3 (range: 5-60).[35] A total of 93 children and 90 adults were enrolled. On average, more children than adults were studied (mean: 46.5 participants). Five studies involved no more than ten adults.[59,61,62,72,74]

For the eight studies that reported data on study length and intervention length, the average study length was 7.7 (range: 2-14) weeks and the mean intervention length was 6.0 (range: 2-12) weeks. Only four of the eight studies had intervention periods that lasted longer than 8 weeks.[61-63,74] Two adult investigations reported the length of a run-in period (each 2 weeks), with neither detailing a protocol.[62,74] Neither of the studies employing a two-phase, noncomparative case series design included a washout between their two exposure periods.[73,74]

The studies were conducted in six different countries, with Japan represented three times[59,62,71] and Russia twice.[61,70] The remaining locations were Poland, Italy, the United States, and Spain. Where data were available, a single site conducted the study. Only two adult studies reported a funding source: a university and industry,[73] and a professional society.[74] Other than the fact that only the pediatric studies exclusively undertook controlled studies, there were no noticeable differences between these and the adult studies with regards to study characteristics.

Population characteristics. Neither pediatric study reported a mean age or a percentage of male participants.[63,70] However, they did provide an age range: children aged 1 to 12 years for one study,[70] and children aged 7 to 17 years for the other one.[63] For the six adult studies that reported data on the age of the participants, the average age was 48.0 (range: 17-84) years.[59,62,71-74] The average percentage of males in the five investigations that provided these data was 27.6% (0%-57%).[59,62,71,72,74] No authors explicitly stated the racial/ethnic background of the study participants, yet it is likely that Caucasian/Europeans and Asian populations were represented five[61,63,70,72,74] and three[59,62,71] times, respectively. Americans constituted the final population, yet its racial/ethnic composition was not described.[73]

Two adult studies indicated having employed a standard definition of asthma,[71,74] one pediatric study provided a vague definition,[70] and the remaining studies provided no definition at all. For example, Okamoto et al.[71] employed the International Consensus on Diagnosis and Treatment of Asthma criteria, whereas, another study indicated that their participants were in "relative remission," although this term was not defined.[61] A description of the diagnostic method used to identify asthma was reported on only four occasions, and with varying degrees of detail.[71-74] The one pediatric study enrolling children as young as 1 year-of-age did not provide information regarding how, or if, asthma and wheezing disorders were distinguished.[70] None of the adult studies that involved the older populations indicated how, or if, asthma and possible COPD were differentiated.[59,62,71,74]

Four of nine studies indicated the asthma severity of the included study population. This included one study that described subgroups of children with mild or severe asthma,[63] one study with adults diagnosed with mild-to-moderate asthma,[62] and two studies that enrolled adults with mild asthma.[71,72] Only one study described the criteria used to classify asthma severity.[71] For four of seven adult studies that reported an asthma duration, the average was 12.9 (range: 3-24.7) years.[59,61,63,71,74] One pediatric study reported that the average duration of asthma was 7.36 years for their subgroup with mild asthma, and 9.25 years for their subgroup with moderately-severe asthma.[63] None of these studies attempted to define the severity of asthma at baseline, or on-study, in light of how well it was controlled by medication. Of the two pediatric studies with a control group, no information was provided regarding how, or if, the groups were matched on the basis of asthma severity.[63,70]

Typically, without clear definition, studies identified their asthma population as having the following concomitant conditions: atopy,[71,73] atopic dermatitis,[70] atopy with allergic asthma,[63] atopy with aero-allergens,[72] hypersensitivity to dust,[61] aspirin-intolerant asthma and nasal polyps (50%),[74] and cough variant asthma (20%).[59] One adult investigation evaluated participants with allergic dermatitis (50%) concurrent with hyperlipidemia in its full sample.[62] Of the two non-RCTs with children, the report information indicated that there was matching across groups for atopic dermatitis,[70] and to some extent for atopy.[63] In the second pediatric study, it was unclear whether, as with the treatment group, the control group contained any children with allergic asthma.[63] No information was reported regarding concurrent conditions (or related medications), or the seasons in which the studies took place. One study involved adults hospitalized for asthma.[59]

Regarding the reporting of asthma risk factors, or those with the potential to influence asthma control, very little information was provided. Only one adult study reported having enrolled non-smokers, yet no details were provided regarding their smoking history.[73] Data concerning exposure to environmental smoke or a history of early respiratory infections in children were not provided, although one study excluded adult participants if they had had an upper respiratory infection less than 6 weeks prior to the study.[73] The two non-RCTs involving children reported no data as to whether their groups were equivalent on any of these or other bases.[63,70] Consequently, nothing can be concluded about the influence of these potential confounders on individual study results.

Intervention/exposure characteristics. Two noncomparative case series employed perilla seed oil as their source of omega-3 fatty acids,[59,71] four used fish oil,[63,70,73,74] and three likely used fish oil, given the omega-3 fatty acids that were identified. However, this information was not explicitly stated.[61,62,72] Both pediatric studies employed fish oil.[63,70] Only one study described the specific type of fish from which part of their intervention was derived (i.e., sardine).[74] Four of nine investigations identified the type of omega-3 fatty acid as EPA and DHA,[61,72-74] two used EPA exclusively,[62,63] two employed ALA,[59,71] and one did not report the exact type(s) of omega-3 fatty acids.[70]

The two pediatric non-RCTs compared: fish oil capsules plus a poorly defined hypoallergenic diet with a hypoallergenic diet and no description of the placebo capsules;[70] and fish oil with sunflower oil, the latter considered a source of omega-6 fatty acids.[63] In the first non-RCT, the investigators wished to establish a lower omega-6/omega-3 ratio of fatty acids, yet the data reported were contradictory.[70] Also, the 4.5 g/day dose was of fish oil, not omega-3 fatty acids. As a result, it was unclear how either exposure was defined in this investigation.

In the two noncomparative case series where the participants received two exposures in sequence, the exposure were: placebo capsules and a eucaloric (32% fat) diet, followed by the same diet, fish oil capsules, and sardine oil in one;[74] and, a low omega-3 fatty acid intake of fish oil capsules followed by a high omega-3 fatty acid intake in the other.[73] In the latter study, fish oil regimens were individualized based on an analysis of prestudy omega-6 fatty acid intake, yielding a low omega-6/omega-3 fatty acid ratio of 1:0.1 in the low fish oil exposure and a high omega-6/omega-3 fatty acid ratio of 1:0.5 in the high fish oil exposure.[73] The non-RCT that selected participants on the basis of an acute and late asthmatic response to allergen challenge subsequently assigned participants to receive either EPA and DHA (likely by way of fish oil), or an olive oil control.[61]

If greater than or equal to 3 grams per day is considered to be a high daily dose or serving of omega-3 fatty acids, then five studies attained this level: 6 g/day,[61] 3.3 g/day in one noncomparative case series' high-dose phase;[73] 3 g/day in the other noncomparative case series' second phase;[74] 3 g/day in a pediatric non-RCT;[63] and, 3 g/day in a noncomparative case series.[72] One adult noncomparative case series received 1,800 mg/day.[62] Three studies did not define their omega-3 fatty acid dose or serving.[59,70,71]

The most frequently used method for delivering the fish oil was standardized dosing capsules.[61,70,72,73] In one study, the method by which participants received the sardine oil was not specified.[74] In another study, the hypoallergenic diet given along with the fish oil capsules was poorly defined, with no clear indication of the types or amounts of food consumed, or whether consumption varied across the study.[70] One study described a range for the daily intake of perilla seed supplementation (10-20 g in salad dressing and/or mayonnaise), precluding a precise definition of a serving size or amount of ALA for any participant on any given day.[71] The investigators reported that the adults consumed an average of 14.65 g/day, suggesting variability in intake among study participants.

A second investigation mandated 15 g/day of perilla seed oil consumption, yet there was no report of how, or if, the investigators attempted to control the intake.[59] One pediatric[63] and one adult[62] study did not describe how their omega-3 fatty acid exposure was delivered. In the reports of the four studies that did not use a completely controlled dosing vehicle, no information was provided to establish a description of the omega-3 fatty acid content.[59,70,71,74] Thus, for six of the studies employing a design other than an RCT it was impossible to establish the exact definition of the omega-3 fatty acid exposure. In the two pediatric non-RCTs, no data were provided showing that the oil intake was matched, suggesting a likely, between-group difference in caloric intake.[63,70] This potential source of confounding was not addressed.

Only one study described the exact timing of the intervention (i.e., at each main meal),[63] while a second study mentioned that the intervention was in the morning.[73] Few study reports indicated that participants had been instructed to maintain their background diet.[59,71] One noncomparative case series was told that they could maintain a free diet (undefined).[72] Two studies altered the diet of their participants: one to a hypoallergenic diet (undefined),[70] and one to an eucaloric diet (poorly defined).[74]

No study mandated the intake of omega-6 fatty acids as a cointervention, despite one investigation's attempt to alter the omega-6/omega-3 fatty acid ratio through the consumption of omega-3 fatty acids,[73] and another study's attempt to do so through a hypoallergenic diet and fish oil capsules.[70] The first investigation also excluded adults if they were consuming fish oil supplements or more than one fish meal per week.[73]

No report indicated the manufacturer of the omega-3 fatty acid intervention although the use of MaxEPA® suggests the involvement of Seven Seas, Ltd.[73] Information concerning the purity of the supplementation was never provided.

Cointervention characteristics. There were no data regarding any additional treatment received by the participants in the only study that had a clearly identified concurrent condition (i.e., hyperlipidemia).[62] There was a dearth of information reported regarding the types and dosing of asthma medication.

One noncomparative case series excluded adults if they were taking any asthma medication.[72] Another excluded those taking more than 5 mg/day of prednisone or longterm steroids (undefined) started less than one month prior to the study.[62] A third study asked that no

nonsteroidal anti-inflammatory drugs (NSAIDS) be taken,[73] and a fourth asked participants to maintain a fixed dose of inhaled corticosteroids and bronchodilator medication during the study.[74] No other study described whether their participants maintained a constant on-study dose of inhaled or oral corticosteroids. Two studies reported the number of users of each of these drugs.[59,71] In one of these, the range of allowable inhaled corticosteroid doses varied greatly across participants (400-1200 ug/day).[59] Seven of ten adults in one noncomparative case series were corticosteroid dependent, with two taking prednisolone.[74] However, whether their on-study doses were maintained was not reported. Other asthma medications were also poorly described, such that it was impossible to determine whether on-study doses were kept constant, or whether the types and doses were equivalent across groups in the controlled studies.

Outcome characteristics. The most frequently employed respiratory outcomes were PEF (undefined, yet likely AM),[61,63,72-74] AM PEF,[59,62,71] and FEV_1.[63,71,73] Given the limited descriptions in the individual study reports, it was difficult to determine whether all the pulmonary function tests were based on standard methodologies. The psychometric performance of symptom rating scales was never described. Relative to RCTs, few dropouts or withdrawals were observed.

Study quality and applicability. The mean total quality score was 3.6 (range: 2-5), likely indicating good quality. Of note, five of nine studies provided very limited descriptions of study participants.[59,60,62,70,73] The quality grades associated with quality scores were entered into the summary matrix. Little variability characterized the applicability rating, with eight of nine studies assigned a level III rating (Summary Matrix 2). This indicates the extremely limited potential for generalization to the typical North American population with asthma.

Four studies exhibited high quality, defined by a total quality score of 4 or 5. However, the generalizability of the results of these four studies to the North American standard set for this review was extremely limited. The only study with strong generalizability potential also exhibited good study quality.[73]

Summary Matrix 2: Study quality and applicability of evidence regarding respiratory outcomes from study designs other than an RCT

		Quality								
		A			**B**			**C**		
Applicability	**I**				**Author**	**Year**	**N**			
					Broughton	1997	26			
	II									
	III	**Author**	**Year**	**N**	**Author**	**Year**	**N**	**Author**	**Year**	**N**
		Masuev	1997b	8	Ashida	1977	5	Gorelova*	1998	33
		Okamoto	2000b	26	Hashimoto	1977	8			
		Picado	1988	10	Machura	1996	60			
		Villani	1998	7						
N = number of randomized participants; *Pediatric trial										

Qualitative Synthesis of Individual Study Results From Study Designs Other Than a RCT

Adult and pediatric study results are organized separately. Masuev divided participants, in a Russian cohort exhibiting both an acute and late asthmatic response to allergen challenge, into two matched subgroups. One received 6 g/day of EPA and DHA capsules over 8 weeks and the other took olive oil capsules over this same period.[61] In this non-RCT, they noted a significant increase in PEF 4 to 8 hours after allergen challenge (i.e., late response period) only in the omega-3 fatty acids group.

Ashida et al.'s Japanese noncomparative case series received perilla seed supplementation (ALA amount undefined) for 2 weeks, and they reported a significant increase in AM PEF.[59] Hashimoto et al. exposed Japanese adults with mild to moderate asthma and hyperlipidemia, to 1,800 mg/day of EPA over 8 weeks.[62] They reported a significant increase in AM PEF. Hashimoto et al.[62] found a significant increase in PM PEF, as did Ashida et al.[59] On the other hand, Picado et al. exposed a noncomparative case series of aspirin-intolerant asthmatics from Spain, first to 6 weeks of placebo (lactose) capsules plus a poorly defined eucaloric diet (e.g., 32% fat), then to another 6 weeks of an experimental diet including EPA/DHA capsules and the eucaloric diet.[74] They reported a significant decrease in (likely AM) PEF only in response to the fish oil, as well as a significant between-exposure difference in PEF at final followup. In a noncomparative case series with a 30-day exposure to 3g/day of EPA and DHA in Italian adults allowed to maintain a free diet, Villani et al. found a nonsignificant change in (likely AM) PEF.[72] They also reported a nonsignificant change in TLC, FEF_{25-75}, SVC, in addition to a significant decrease in RV.

Hashimoto et al. reported a significant decrease in both symptom scores and asthma scores (each undefined).[62] Ashida et al. reported a significant decrease in asthma symptoms score (cough, wheeze, daytime activity, sputum volume, dyspnoea).[59] Yet, a nonsignificant change in pulmonary symptom score (cough/dyspnoea) was associated with both the fish oil and control exposures in Picado et al.'s noncomparative case series.[74] Hashimoto et al. observed a significant decrease in a therapeutic score (undefined) along with nonsignificant changes in sleep score (undefined), and a daily life score (undefined).[62]

Picado et al. reported a significant increase in bronchodilator use only within the last 2 weeks of the fish oil exposure.[74] During this period, bronchodilator use was significantly higher during

the fish oil exposure. On the other hand, the investigators found a nonsignificant between-exposure difference in oral corticosteroid use. Villani et al. noted a significant reduction in the maximum fall in FEV_1 and in the airways responsiveness to bronchial challenge.[72]

In an attempt to alter the intake ratio of omega-6/omega-3 fatty acids, Broughton et al. exposed an American case series to 4 weeks of low fish oil supplementation (~0.7 g/day EPA/DHA), followed by another 4 weeks of high fish oil supplementation (~3.3 g/day EPA/DHA), yielding a low (1:0.1) and high (1:0.5) ratio exposure, respectively.[73] With the low-ratio exposure, they observed a significant reduction from baseline of 51%, 89%, 65% and 92% in the provocative dose of methacholine required to cause a 20% fall in FVC, FEV_1, PEF, and FEF_{25-75}, respectively. With the high-ratio exposure, they noted a nonsignificant difference from baseline in the magnitude of the provocative dose required to cause a 20% fall in each of FVC, FEV_1, PEF, and FEF_{25-75}. With the high-ratio exposure they also observed that, in responders (i.e., those with nonsignificant reductions in respiratory measures with increased challenge), the respiratory responses were never reduced by 20%, regardless of the methacholine dose (no data provided); nonresponders (i.e., those with respiratory reductions with increased challenge) had significantly greater difficulty breathing at 1.375 units methacholine, and demonstrated a reduced respiratory capacity in three of four respiratory outcomes (no data provided) with the high-ratio exposure. Only FEF_{25-75} improved (no data provided).

Okamoto et al.'s noncomparative cases series in Japan was exposed to perilla oil supplementation (ALA amount undefined) in salad dressing or mayonnaise over 4 weeks, with background diet unchanged.[71] They distinguished responders from nonresponders as those participants with significantly decreased leukotriene C4 generation by peripheral leukocytes (undefined).[71] In an attempt to distinguish the two subgroups they reported: significantly lower baseline FVC, FEV_1, and V_{25} for responders; while there was a significant increase in AM PEF for both subgroups in response to the exposure, the values were significantly lower for responders during the study; significant increases in FEV_1 and FVC following the exposure were observed only for responders, and, significant differences between responders and nonresponders in these two outcomes were noted at final followup. However, without additional evidence to support them, Broughton et al. and Okamoto et al.'s observations concerning responders likely shed little direct light on whether omega-3 fatty acid supplementation provides a clinical benefit.

In a pediatric non-RCT with Polish children, Machura et al. investigated the impact of a 12-week exposure to either fish oil supplementation or a control (sunflower oil).[63] They found a nonsignificant difference in PEF between both the mild, or the severe, subgroup and the control. They also observed a significantly higher FEF_{25-75} only in the mild asthma subgroup relative to the control, in addition to a nonsignificant difference in FEV_1 between the mild asthma subgroup and the control, and the severe asthma subgroup and the control. Machura et al. noted a significant difference between the severe, but not the mild, asthma subgroup and the control in both the number of days with increased severity of asthma symptoms and the loss of asthma control.[63] In a pediatric non-RCT conducted in Russia over an undefined period, which compared 4.5 g/day of fish oil in capsules (omega-3 fatty acid content undefined) plus a poorly defined hypoallergenic diet with the same diet and an undefined control, Gorelova and Semikina observed significantly lower bronchodilator use in the omega-3 fatty acid arm.[70]

Question 2: What is the evidence that the possible value (efficacy/association) of omega-3 fatty acids in improving respiratory outcomes is dependent on specific effect modifiers?

Specific effect modifiers identified in consultation with our TEP were candidates for planned investigations with respect to respiratory outcomes. They included the: specific type of fatty acid; specific source; serving size or dose; amount/dose of omega-6 fatty acids given as a co-intervention; ratio of omega-6/omega-3 fatty acids used; fatty acid content of blood lipid biomarkers; absolute fatty acid content of the baseline diet; relative fatty acid content of the baseline diet; tissue ratios of fatty acid (omega-6/omega-3) during the investigative period; intervention length; anti-oxidant use; and, the manufacturer and its product(s).

Qualitative Synthesis of Evidence Regarding the Assessment of Effect Modifiers

Question 2 pertains exclusively to respiratory outcomes. A reasonable alternative when it is impossible to experimentally manipulate the above-noted variables would be, for example, to assess their potential impact as covariates via subgroup analysis. However, in the present evidence base there were very few direct evaluations of these variables, and meta-analysis of any kind was considered to be inappropriate (Chapter 4). Therefore, a third, albeit less than ideal approach was adopted. It distinguished between studies yielding statistically significant results and studies with other (i.e., null, or, significant in the opposing direction) results for a specific outcome on the basis of specific operational definitions, or levels, of independent variables. To illustrate, a high (but not low) dose of omega-3 fatty acids would have to be consistently and exclusively associated with a particular benefit (e.g., significantly increased FEV_1) in order to prompt further empirical testing to assess whether dose magnitude reliably influences results.

To investigate the impact of certain covariates in this way, it is assumed that, given the small size of the included studies, at least two studies investigating an outcome are required, with at least one demonstrating a significant result. Four outcomes were therefore evaluated: FEV_1; AM PEF; PM PEF; and, bronchodilator use. A fifth outcome might have been assessable had the operational definitions of "symptom scores" been more consistent or better described.

Both RCT evidence (n = 8) and evidence from noncomparative case series (n = 4) were included in the present appraisal, with greater emphasis placed on the former given its far greater potential to control for confounding influences (Summary Table 3; Evidence Tables 1 and 2: Appendix E). One RCT could not be classified;[65] all other studies involved adult participants. Quality data were excluded from the summary table given their noncomparable definition for the two types of design (i.e., RCTs vs others); a summary matrix was not possible. While the results of direct tests (e.g., high vs. low dose)[54] have already been presented in relation to Question 1, they are briefly revisited. After the predefined covariates are addressed, the possible influence of study-defined covariates (e.g., patterns of asthma severity; patterns of on-study corticosteroid use) is assessed. Given that all studies have already been synthesized qualitatively with reference to Question 1, these summaries (e.g., population characteristics) are not repeated.

Of the six studies in this review that investigated FEV_1, two pediatric controlled studies produced nonsignificant clinical effects, thereby precluding an evaluation of covariates.[52,63] The population characteristics were similar between the two studies (nearly all were atopic) and accounted for two of the three largest samples (n = 45 and n = 60, respectively) included in the present systematic review. The children in these studies received the intervention for a substantial period of time (6 months and 12 weeks, respectively).

Of the four RCT studies involving adult participants, two demonstrated significant,[65,66] and two demonstrated nonsignificant,[54,69] increases in FEV_1 in response to an omega-3 fatty acid intervention. Three different definitions of the intervention (ALA; EPA/DHA; EPA ethyl ester, with trace amounts of DHA), and 4 different definitions of comparator, were observed. Three of the four studies used a marine source (fish oil; mussel extract), whereas, one RCT used perilla seed oil.[66]

Summary Table 3: An indirect assessment of the impact of effect modifiers on the value of omega-3 fatty acids to improve four respiratory outcomes in asthma, organized by research design

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		Results Favoring Omega-3 Fatty Acids	Research Design	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Arm, 1988, England[56,57]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	NS: AM PEF NS: PM PEF NS: BDU	RCT	III
Dry, 1991, France[65*]	NR	1.0 g EPA+DHA	NR	"Placebo" (NR)	S: FEV_1	RCT	X
Emelyanov, 2002, Russia[69]	23	200 mg EPA+DHA + 400 mg olive oil	23	600 mg olive oil	S: AM PEF S: BDU NS: FEV_1 NS: PM PEF	RCT	III
Kirsch, 1988, USA[54,55]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA ethyl ester (trace DHA)	NS: FEV_1	RCT	I
McDonald, 1991, Australia[58]	15	2.7 g EPA + 1.8 g DHA	15	15 g olive oil	NS: AM PEF NS: PM PEF NS: BDU	RCT, 2-phase crossover	III
Okamoto, 2000a, Japan[66]	7	10-20 g perilla seed oil (ALA: NR)	7	10-20 g corn oil	S: FEV_1 S: AM PEF	RCT	III
Stenius-Aarniala, 1989, Finland[68]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	NS: AM PEF NS: PM PEF	RCT, 3-phase crossover	III
Thien, 1993, England[67]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	NS: AM PEF NS: PM PEF NS: BDU	RCT	III
Ashida, 1997, Japan[59]	5	15 g perilla seed oil (ALA: NR)	NA	NA	S: AM PEF S: PM PEF	Non-comparative case series	III
Hashimoto, 1997, Japan[62]	8	1.8 g EPA	NA	NA	S: AM PEF	Non-comparative case series	III
Picado, 1988, Spain[74]	10	3.0 g EPA+DHA + eucaloric diet	10	3.0 g lactose + eucaloric diet	S: AM PEF NS: BDU[†]	Non-comparative case series (placebo, then fish oil)	III
Villani, 1998, Italy[72]	7	3.0 g EPA+DHA (1:1 ratio)	NA	NA	NS: AM PEF	Non-comparative case series	III
n = number of enrolled/randomized participants; NR = not reported; NA = not applicable; S = significant; NS = nonsignificant; BDU = bronchodilator use; [*]Age not reported [†]S greater BDU in last 2 weeks within the omega-3 fatty acids phase							

A significant effect for FEV_1 was not exclusively associated with the use of a high dose of omega-3 fatty acids or with serving size. The only clearly defined high-dose (EPA ethyl ester) versus low-dose comparison produced a nonsignificant result.[66] Perilla seed oil, which was considered to be a source of high-dose omega-3 fatty acids, resulted in a significant increase in FEV_1; however, the amount of ALA contained in the perilla seed oil was not reported.[66] None of the four studies used omega-6 fatty acids as a cointervention or evaluated the impact of an

omega-6/omega-3 fatty acid ratio. A single study evaluated the on-study fatty acid content of blood lipid biomarkers or tissue ratios of fatty acid; however, the statistically significant findings were associated with nonsignificant clinical effects for FEV_1 and five other respiratory outcomes.[54] For example, only the high dose of EPA ethyl ester significantly increased the total quantity of EPA while significantly decreasing that of AA and DHA in the phospholipids of polymorphonuclear and mononuclear leukocytes. The ratio of EPA to AA in polymorphonuclear leukocytes rose from 0.3 to 0.4 after intake of the high dose, and was attributable to an increase in EPA and an approximately 60% suppression of AA. The effects of EPA on AA and EPA content in mononuclear leukocytes were less prominent than those in the polymorphonuclear leukocytes.

Both the longest (12 months)[65] and the shortest intervention periods (4 weeks)[66] significantly increased FEV_1. No study mandated or evaluated the use of antioxidants; no patterns of covariation relating the manufacturer and the results were observed. As well, no study reported data concerning the purity of the exposure, the presence therein of other potentially (added) active agents (e.g., anti-oxidants), or the relative or absolute fatty acid contents of the baseline diet.

Regarding other study-defined covariates, a few patterns were noted. The two studies that demonstrated a nonsignificant effect for FEV_1 each mandated some form of control of on-study use of asthma medications.[54,69] One study [69] permitted only beta-2 agonists, whereas, the other[54] kept constant all types and doses of asthma medications except oral corticosteroids. The likely goal was to increase the likelihood that any positive clinical effects could be attributed to the intervention and not this cointervention (Chapter 4).

One RCT with a nonsignificant result for FEV_1 was the only study to control for smoking.[69] Since smoking is a factor with the potential to influence asthma control and thereby affect the likelihood of being able to meaningfully attribute possible benefits to the omega-3 fatty acid intervention, Emelyanov et al. excluded current and ex-smokers from the study.[69] In addition, two RCTs, one with significant results and the other with nonsignificant results, included an older population but did not take into account the possibility that some of the sample population might have been current or ex-smokers, or might have had COPD rather than asthma.[54,66]

In the single pediatric study that employed AM PEF as an outcome, a nonsignificant effect was observed.[63] Of the adult studies, four RCTs[57,58,67,68] and one noncomparative case series[72] produced a nonsignificant result, whereas, two RCTs[66,69] and three noncomparative case series[59,62,74] each demonstrated a benefit related to the omega-3 fatty acid exposure. The investigators of a two-phase, noncomparative case series (placebo and eucaloric diet, followed by 3g/day of EPA and DHA with the same eucaloric diet) reported a significant result.[74]

The only non-marine source (perilla seed oil) produced two significant results, one in an RCT[66] and the second in a noncomparative case series.[59] However, both studies were very small. Marine-derived oils produced both significant and nonsignificant results, with all but one[74] using an olive oil control group.

A particular serving size or dose did not exclusively produce a significant result. Four of five studies, of varying design[57,58,67,72] and employing a high dose (i.e., 3-5.4 g/day) as it was operationally defined in this review, failed to find a significant benefit. The sole significant result was found in a noncomparative case series.[74] Three of the RCTs employed an olive oil control.[57,67,68] Although significant effects were associated with an RCT[65] and a noncomparative case series[62] exposed to a low dose of omega-3 fatty acids, the comparators were too discordant to permit a meaningful comparison of these studies. One significant[66] and one nonsignificant

result[68] were observed in studies failing altogether to provide clear omega-3 fatty acid content data pertaining to their exposure. No study evaluated the impact on AM PEF of omega-6 fatty acids included as a co-intervention, in turn making it impossible to investigate the influence of an omega-6/omega-3 fatty acid intake ratio. Likewise, none of the studies assessed the relative or absolute fatty acid contents of the baseline diet.

One, two-phase noncomparative case series[74] and three RCTs[57,67,68] assessed the on-study fatty acid content of blood lipid biomarkers or tissue ratios of omega-6/omega-3 fatty acids. Results yielded a significant[74] and three nonsignificant effects[57,67,68] relating to AM PEF. A two-phase noncomparative case series also revealed a significant increase in EPA and DHA, concomitant with a nonsignificant change in AA in the fish oil supplementation phase.[74] One RCT assessed the AA and EPA compositions in plasma and in neutrophil membranes.[67] The study found that only EPA increased significantly, and exclusively, in the omega-3 fatty acids arm. There was a nonsignificant change in AA content in both the EPA/DHA and olive oil study arms. A crossover RCT comparing EPA/DHA to olive oil and to evening primrose oil investigated the percent distribution of fatty acids in plasma cholesterol esters.[68] Results indicated that EPA, DHA, and palmitic acid each increased significantly in the EPA/DHA arm, but no change was observed for AA. Another RCT assessed the fatty acid composition of phospholipid membranes, and reported a nonsignificant change in the relative AA and DHA compositions in both study arms (EPA/DHA vs. olive oil), concomitant with a significant increase in EPA exclusively in the treatment arm; the latter rose to 2.6% of the total neutrophil content.[57] There was insufficient variability in these observations to be able to distinguish between studies producing significant and nonsignificant benefits in AM PEF.

Looking exclusively at the two RCTs that yielded a significant effect[66,69] and the four RCTs that yielded a nonsignificant effect,[57,58,67,68] the latter employed a longer intervention period (mean = 14 weeks) than did the former (mean = 6 weeks). None of the studies reporting AM PEF results employed antioxidants as a cointervention or reported information concerning the purity or presence of other potentially active agents in their omega-3 fatty acid interventions. There was insufficient information regarding the manufacturers of the fatty acids to assess this variable's possible relationship with specific results.

Concerning other population, intervention, or co-intervention covariates, it was observed that the adult studies associated with null results included younger study participants (mean = 32.7 years; range 15-72)[57,58,67,68,72] compared with studies that produced significant results (mean = 52.9 years; range 18-84 years)[59,62,66,69] Among the studies finding no benefit for AM PEF, three of the sample populations fell between the ages of 15 and 49 years.[57,67,72] Any study conducted in Japan, and likely involving an Asian population, was exclusively associated with a significant effect for AM PEF.[59,62,66] The two studies that included in-patients were both conducted in Japan and both studies reported a significant benefit associated with omega-3 fatty acids[59,66]. Three of five studies that yielded nonsignificant results, as well as one study that produced a significant resulted in favor of omega-3 fatty acids, enrolled participants who did not receive on-study oral corticosteroids.[57,67,72] The mean sample sizes associated with significant and nonsignificant effects were 16.6 and 24 participants, respectively. While none of the five studies with significant results reported any withdrawals or dropouts, four of the five studies with null findings each reported at least five withdrawals or dropouts.[57,58,67,68]

No pediatric studies utilized PM PEF as an outcome. The two adult studies that reported a significant effect each involved noncomparative case series.[59,62] The two studies employed different omega-3 fatty acid exposures (ALA[59]; EPA[62]), and enrolled an average of 6.5

participants. Five RCTs yielded nonsignificant results.[57,58,67-69] The five RCTs averaged 31.8 participants. Nonsignificant results were associated with a longer intervention period (12.8 weeks vs. 5 weeks) and a younger population (35.4 [range: 15-72] years vs. 60.9 [range: 38-78] years). No other patterns of difference were observed.

Only one pediatric study employed on-study bronchodilator use as an outcome.[70] Of the two adult studies that demonstrated a significant result, the RCT showed a benefit associated with the omega-3 fatty acids arm,[69] whereas, the other study found significantly greater bronchodilator use exclusively in the last 2 weeks of the fish oil supplementation phase in a noncomparative case series.[74] There were an insufficient number of studies yielding a significant result to afford a meaningful evaluation of predefined or study-defined covariates.

Question 3: What is the evidence that, in individuals with asthma, omega-3 fatty acids influence mediators of inflammation which are thought to be related to the pathogenesis of asthma?

As observed in Summary Tables 4 and 5, and derived from Evidence Tables 1 and 2 (Appendix E), respectively, two types of evidence addressing Question 3 met eligibility criteria for treatment studies. A qualitative synthesis of the RCT evidence precedes data derived from other designs. The evidence comes from in vitro studies using samples taken from asthma patients. These samples were then investigated using procedures to influence the production of mediators of inflammation.

Overview of Relevant RCTs

No RCTs other than a subset of those addressing Question 1 were found to address Question 3. Given these RCTs had their basic study parameters described, then synthesized with respect to Question 1, many of these descriptions are not repeated. Instead, only notable patterns are highlighted, with the reader encouraged to consult the qualitative synthesis pertaining to Question 1, and, the Evidence Tables for more detail.

Qualitative Synthesis of RCT Evidence Regarding Mediators of Inflammation

Notable patterns. Five RCTs published between 1988 and 2000 were identified as being relevant to address Question 3 (Summary Table 4; Evidence Table 1: Appendix E). The studies were conducted by Arm et al,[57] Kirsch et al.,[54] Okamoto et al.,[66] Stenius-Aarniala et al.,[68] and, Hodge et al.[52] Only the last study enrolled children.

A minority of studies reported both inclusion and exclusion criteria.[52,54] The studies were typically small, with an average of 26.4 (range: 12-45) participants. A total of 45 children and 87 adults were randomized. The trials lasted an average of 18.2 (range: 4-32) weeks, with a mean intervention length of 11.6 (range: 4-26) weeks.

Summary Table 4: RCT evidence of omega-3 fatty acids to influence mediators of inflammation in asthma

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Jadad Total Quality / Allocation Concealment (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Arm, 1988, England[56,57]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	3/5	4 (Grade: A)/ unclear	III
Kirsch, 1988, USA[54,55]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA EPA ethyl ester (trace DHA)	9/17	3 (Grade: B)/ unclear	I
Okamoto, 2000a, Japan[66]	7	10-20 g perilla seed oil (ALA: NR)	7	10-20 g corn oil	2/2	2 (Grade: C)/ unclear	III
Stenius-Aarniala, 1989, Finland[68*]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	2/8	2 (Grade: C)/ unclear	III
CHILDREN							
Hodge, 1998, Australia[52]	NR	0.72 g EPA 0.48 g DHA + ALA (NR) via canola diet	NR	Omega-6 fatty acids: 1.8 g safflower oil + 1.8 g palm oil + 0.4 g olive oil + sunflower oil diet (NR)	0/1	3 (Grade: B)/ unclear	III
N = number of randomized participants; NR = not reported; S = significant; *Crossover trial							

The average age of adult participants was 36.8 (range: 15-84) years, and the pediatric trial included children with an average age of 10.25 (range: 8-12) years. Almost no racial/ethnic information was provided, leaving the reader to infer from the trial locations that the backgrounds of the participants likely varied considerably. Three of the adult studies included participants with asthma of moderate severity,[54,66,68] whereas, the remaining trial enrolled participants with mild asthma.[57] None of these studies defined severity in light of how well-controlled the asthma was by medication. Only two of the adult studies reported the duration of asthma (mean duration = 20.9 years; 15 years[66] and 26.08 years[54]). Three of five trials reported having roughly equivalent proportions of asthma concomitants (e.g., atopy) across study arms.[52,54,57] Cross-study arm equivalence for level of asthma severity was reported in three of the studies.[52,54,57] In one trial, three of the 29 study completers were present smokers and 12 of the 29 were non-smokers over the previous 2 years.[68] No other information concerning risk factors or factors influencing asthma control could be extracted from this set of studies.

The source of the omega-3 fatty acid intervention varied across the RCTs (Summary Table 4). The most frequently used control was olive oil, and together with EPA/DHA, constituted the most widely investigated comparison.[57,68] If a high daily dose or serving of omega-3 fatty acids for adults is defined as 3 grams of omega-3 fatty acids, then two adult studies met this criterion.[54,57] Another study only reported the amount of oil to be consumed in each of the ALA (10-20 g/day) and the corn oil (omega-6 fatty acid) study arms, but not the gram amounts of omega-3 fatty acids consumed.[66] Various methods were used to deliver the omega-3 fatty acid exposure, ranging from standardized dosing with capsules,[54,57] to uncontrolled

dosing/servings.[52,66,68] Little or no information was reported regarding dosing/serving schedules or the apportionment of food across meals.[52,66,68] A few reports indicated that participants were told to maintain their background diet during the study period.[57,66] No RCT provided omega-6 fatty acids or any other supplement as a co-intervention. None of the studies attempted to alter the ratio of omega-6 to omega-3 intake.

There were no data regarding the presence or treatment of concurrent conditions in any of the five RCTs. There was a scarcity of information reported concerning the dosing levels of asthma medications. Four reports did not indicate that participants had to maintain a constant on-study dose of especially the corticosteroid medications.[52,57,66,68] One trial asked that all types and doses of medication other than oral corticosteroids be kept constant during the trial.[54] Only two studies explicitly stated that participants used on-study oral corticosteroids.[54,68] Of these, one report mentioned that there was no change in the use of this medication during their study period,[68] whereas, the second study acknowledged that oral corticosteroid use may have changed over the 8-week intervention period.[54] The first study reported no data concerning the cross-arm equivalence of oral corticosteroid use.[68] The second indicated that all six participants in the high-dose omega-3 fatty acid dose group, and four of the six participants in the low-dose group, used oral corticosteroids.[54] All five RCTs reported participants having taken on-study inhaled corticosteroids.[52,54,57,66,68] Two of the reports suggested that inhaled corticosteroid use did not change across the study period;[52,68] two of the studies provided no data,[57,66] and one study reported a single user.[54] Three of the studies failed to provide data regarding the equivalence of inhaled corticosteroid use across the study arms.[57,65,66]

Outcome characteristics. The most frequently studied foci regarding mediators of inflammation (Evidence Table 1: Appendix E) involved the generation of leukotrienes B_4 and B_5 by various leukocytes. The methods by which the human samples were collected, processed, and analyzed were reported with varying degrees of detail and complexity.

Study quality and study applicability. As was the case with Question 1, the lack of variability in ratings of allocation concealment (i.e., all "unclear") permitted quality grades derived from Jadad total scores to be entered into the summary matrix. The mean total quality score was 2.8 (range: 2-4), placing it lower than the larger set of RCTs addressing Question 1 from which these five studies were drawn. The quality score for the only pediatric trial was slightly higher than the present average (3). Two of the five RCTs received a "O" for blinding.[66,68]

Summary Matrix 3: Study quality and applicability of RCT evidence regarding mediators of inflammation

		Quality								
		A			**B**			**C**		
					Author	Year	N			
	I				Kirsch	1988	12			
	II									
Applicability		Author	Year	N	Author	Year	N	Author	Year	N
	III	Arm	1988	25	Hodge*	1998	45	Okamoto	2000a	14
								Stenius-Aarniala	1989	36
N = number of randomized participants; *Pediatric trial										

For four of five studies, applicability grades indicated very restricted generalizability. The only RCT (n = 12) with strong applicability exhibited good quality.[54]

Qualitative Synthesis of Individual RCT Results

In an adult study conducted in Japan that involved participants with a wide range of ages (22-84 years) and that investigated the efficacy of ALA derived from perilla seed supplementation compared with corn oil rich supplementation, Okamoto et al.[66] observed a significantly greater decrease in the generation of leukotriene B_4 by peripheral leukocytes in the omega-3 fatty acid arm. Kirsch et al. compared high-dose (4 g/day EPA ethyl ester, and trace amounts of DHA) with low-dose (0.1 g/day EPA ethyl ester, and trace amounts of DHA) omega-3 fatty acids in an older American sample population (42-73 years) and observed significant decreases in the generation of leukotriene B_4 by 10^6 polymorphonuclear leukocytes and by 10^6 mononuclear leukocytes only in the high-dose study arm.[54] In a relatively young adult English population, Arm et al. compared high-dose omega-3 fatty acids (5.4g/day EPA/DHA) with identical olive oil capsules, and reported a nonsignificant suppression in the calcium ionophore-induced generation of leukotriene B_4 by 10^6 polymorphonuclear leukocytes in either study arm.[57]

Kirsch et al. reported significant increases in the generation of leukotriene B_5 by 10^6 polymorphonuclear leukocytes and by 10^6 mononuclear leukocytes in each of the high-dose and low-dose study arms.[54] Arm et al. compared high-dose omega-3 fatty acids (5.4g/day EPA+DHA) with identical olive oil capsules, and reported no calcium ionophore-induced generation of leukotriene B_5 by 10^6 polymorphonuclear leukocytes before either intervention or after the control intervention, yet some was observed after the omega-3 fatty acid exposure.[57]

Arm et al. also reported a significant suppression of total leukotriene B compound generation by 10^6 polymorphonuclear leukocytes only in the omega-3 fatty acid arm.[57] Okamoto et al. observed a significantly greater decrease in the generation of leukotriene C_4 by peripheral (undefined) leukocytes in the omega-3 fatty acid arm.[66] Kirsch et al. found nonsignificant changes in the generation of PGE by 10^6 polymorphonuclear leukocytes and by 10^6 mononuclear leukocytes in either the high-dose or low-dose omega-3 fatty acid study arm.[54]

Kirsch et al. also identified a significant suppression of polymorphonuclear leukocyte chemotaxis to complement fragment 5a (C5a), leukotriene B_4 (3 ng/ml), leukotriene B_4 (30 ng/ml), 10^{-7} fMLP (M), and 10^{-6} fMLP (M) only in the high-dose omega-3 fatty acid dose arm.[54] They also reported nonsignificant changes in the suppression of mononuclear leukocyte chemotaxis to C5a, leukotriene B_4 (3ng/ml), and, leukotriene B_4 (30ng/ml).[54] Arm et al. compared high-dose omega-3 fatty acids (5.4g/day EPA/DHA) with visually identical olive oil capsules, and reported a significant suppression of neutrophil chemotaxis (# neutrophils per five high power fields) to leukotriene B_4, only in the omega-3 fatty acid arm.[57] They also reported a significant suppression of neutrophil chemotaxis (# neutrophils per five high power fields) to fMLP (M) only in the omega-3 fatty acid arm. Kirsch et al. reported a nonsignificant change in the suppression of mononuclear leukocyte chemotaxis to 10^{-7} fMLP (M) and to 10^{-6} fMLP (M).[54]

A three-phase crossover study of likely Scandinavian adults from across a wide age spectrum (19-61 years), compared 20 mL daily of fish oil (omega-3 fatty acid content undefined) with equivalent amounts of olive oil and evening primrose oil.[68] Results demonstrated significantly higher plasma PGE_2 levels in the fish oil phase and significantly lower plasma $PGF_{2-alpha}$ levels in the olive oil phase compared with the other two phases. In addition, nonsignificant between-

phase differences in plasma levels of TxB_2 and 6-keto-$PGF_{1-alpha}$, and urine levels of PGE_2, $PGF_{2-alpha}$, TxB_2, and 6-keto-$PGF_{1-alpha}$, were observed.

Hodge et al.'s investigation of Australian children (ages 8-12 years) receiving either omega-3 fatty acid (1.2 g/day EPA/DHA from fish oil capsules; ALA from canola diet) or omega-6 fatty acid supplementation (matched capsules with safflower, palm, and olive oils; sunflower oils), revealed a nonsignificant between-study arm difference in changes in TNF-a production.[52]

Overview of Relevant Studies With Designs Other Than an RCT

Five of the studies addressing Question 1 also investigated Question 3. Given these investigations had their basic study parameters described, then synthesized with respect to Question 1, many of these descriptions are not repeated here. Instead, only notable patterns are highlighted.

One non-RCT was found, which had not addressed Question 1. Masuev selected 34 Russian participants, 17 with bronchial asthma, and 10 with infection-dependent asthma.[60] Two groups were formed, matched for age, sex, and asthma severity (undefined). The first group (n = 27) received 6g/day of EPA and DHA (with an undefined amount of vitamin E) in capsule form, and the other group took 6g/day of an olive oil control. The intervention period was 2 months. Relevant outcomes included: 5-hydroxyeicosatetraenoic acid (5-HETE) production, and, 5-hydroxyeicosapentaenoic acid (5-HEPE) production.

Qualitative Synthesis of Evidence Regarding Mediators of Inflammation From Study Designs Other Than an RCT

Notable patterns. Six relevant studies published between 1988 and 2000 addressed Question 3 (Summary Table 5; Evidence Table 2: Appendix E). All exclusively involved adults. Five were the noncomparative case series evaluated by Ashida et al.,[59] Broughton et al.,[73] Hashimoto et al.,[62] Okamoto et al.,[71] and, Picado et al.[74] The Broughton et al. and Picado et al. noncomparative case series each involved two intervention phases. The sixth relevant study is Masuev's above-noted non-RCT.[60]

Summary Table 5: Evidence from other study designs of omega-3 fatty acids to influence mediators of inflammation in asthma

Author, Year, Location	Omega-3 Fatty Acid Cohort/Phase		Comparator Cohort /Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Total Quality (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
Ashida, 1997, Japan[59†]	5	15 g perilla seed oil (ALA: NR)	NA	NA	2/2	3 (Grade: B)	III
Broughton, 1997, USA[73†]	26	"Low" EPA+ DHA intake: ~0.7 g (mean)	26	"High" EPA+ DHA intake: ~3.3 g (mean)	4/7	3 (Grade: B)	I
Hashimoto, 1997, Japan[62†]	8	1.8 g EPA	NA	NA	0/2	3 (Grade: B)	III
Masuev, 1997a,	27	6.0 g eiconol: EPA+DHA (NR)	7	6.0 g olive oil	1/1	2 (Grade: C)	III

Russia[60††]							
Okamoto, 2000b, Japan[71†]	26	10-20 g perilla seed oil (ALA: NR)	NA	NA	1/1	4 (Grade: A)	III
Picado, 1988, Spain[74†]	10	3.0 g EPA+DHA + eucaloric diet	10	3.0 g lactose + eucaloric diet	1/1	5 (Grade: A)	III
n = number of enrolled participants; NR: not reported; NA = not applicable; S = significant; †Noncomparative case series; ††non-RCT							

A minority of studies reported both inclusion and exclusion criteria.[62,73] The six studies typically involved few participants (n = 109), with a mean number of 18.2 (range: 5-34). Three of the studies involved no more than 10 adults.[59,62,74] The studies lasted an average of 7.8 (range: 2-14) weeks and the mean intervention length was 5.5 (range: 2-8.7) weeks. Only one study did not last at least 4 weeks.[59] Neither of the studies employing a two-phase noncomparative case series included a washout between their exposure periods.[73,74]

In the six studies, the average age of participants was 51.2 (range: 19-84) years.[59,60,62,71,73,74] No authors explicitly stated the racial/ethnic background of any of their participants, yet it is likely that Caucasian/Europeans[60,74] and Asian populations[59,62,71] were represented twice and three times, respectively. Americans constituted the final population yet its racial/ethnic composition was not reported.[73]

Only two studies indicated having employed a standard definition of asthma.[71,74] Only three reported their diagnostic method.[71,73,74] None of the studies involving the oldest populations indicated how, or if, asthma and possible COPD were differentiated.[59,62,71,74] Only one of the studies described criteria classifying asthma severity.[71] None of these studies attempted to define the severity of asthma at baseline, or on-study, on the basis of how well it was controlled by medication. In the non-RCT, no information indicated whether the groups had been matched on the basis of asthma severity.[60]

Conditions concomitant to asthma were poorly defined. One of the studies evaluated participants with allergic dermatitis (50%) concurrent with hyperlipidemia in its full sample.[62] No information was reported regarding other concurrent conditions (or related medications) or the seasons within which the studies took place. One study involved adults hospitalized for asthma.[59] Regarding the reporting of asthma risk factors, or those with the potential to influence asthma control, very little information was provided. Only one study reported having enrolled non-smokers yet no details were provided regarding their smoking history.[73] Consequently, nothing can be concluded about the influence of these potential confounders on individual study results.

Various sources of omega-3 fatty acids were used. If a high daily dose or serving of omega-3 fatty acids for adults is defined as greater than or equal to 3 g of omega-3 fatty acids, then three studies met this criterion.[60,73,74] Two studies did not define their omega-3 fatty acid dose or serving.[59,71] One study described a range of intake for the daily use of perilla seed oil-supplemented salad dressing and/or mayonnaise (10-20 g), precluding a precise definition of a serving size for any participant on any given day.[71] The investigators reported that the adults consumed only 14.65 g/day, likely suggesting variability in intake among study participants. A second investigation mandated 15 g/day of perilla seed oil consumption yet there was no report of how, or whether, the investigators attempted to control the intake.[59] One study did not describe how their omega-3 fatty acid exposure was delivered.[62] In the studies that did not use a completely controlled dosing vehicle, no information was provided to establish a description of

the omega-3 fatty acid content.[59,71,74] For four studies it was thus impossible to establish exactly the definition of the omega-3 fatty acid exposure.

Two studies indicated that participants were told to maintain their background diet.[59,71] One study altered the diet of their participants to an eucaloric diet (poorly defined).[74] No study mandated the intake of omega-6 fatty acids as a cointervention, although one study did attempt to alter the omega-6/omega-3 fatty acid ratio through the consumption of omega-3 fatty acids.[73] Information concerning the purity of the supplementation was never provided.

There are no data concerning the treatment received by participants in the study in which participants were reported to have a clearly identified concurrent condition (i.e., hyperlipidemia).[62] There is a dearth of information reported regarding the types and dosing of asthma medication. One noncomparative case series excluded individuals taking more than 5 mg/day of prednisone, or longterm steroids (undefined) that were started less than one month prior to the study.[62] A second study requested that no NSAIDS be taken,[73] and a third asked participants to maintain a fixed dose of inhaled corticosteroids and bronchodilator medication during the study.[74] No other study described whether their participants maintained a constant on-study dose of inhaled or oral corticosteroids. A few studies reported the number of users of each of these drugs;[59,71] in the one study,[59] the range of allowable inhaled corticosteroid doses varied greatly across participants (400-1200 ug/day). Seven of ten adults in one noncomparative case series were steroid-dependent, with two of the adults taking prednisolone;[74] however, whether their on-study doses were maintained was not reported. Other asthma medications were also poorly described and hence it was impossible to determine whether on-study doses were kept constant, or, whether the types and doses were equivalent across groups in the only controlled study.

Outcome characteristics. The most frequently employed intermediate outcomes were the various leukotriene series. Given the limited descriptions in the individual study reports, it was difficult to determine whether all the pulmonary function tests were based on standard methodologies.

Study quality and applicability. The mean total quality score was 3.3 (range: 2-5), likely indicating good quality. Of note, two of six studies provided very limited descriptions of study participants lost to followup.[60,73] The quality grades associated with quality scores were entered into the summary matrix. Little variability characterized the applicability rating, with five of six studies assigned a level III rating (Summary Matrix 4). This indicates the extremely limited potential for generalization to the typical North American population with asthma.

Summary Matrix 4: Study quality and applicability of evidence regarding mediators of inflammation from study designs other than an RCT

		Quality								
		A			**B**			**C**		
Applicability	**I**				**Author**	**Year**	**N**			
					Broughton	1997	26			
	II									
	III	**Author**	**Year**	**N**	**Author**	**Year**	**N**	**Author**	**Year**	**N**
		Okamoto	2000b	26	Ashida	1977	5	Masuev	1997a	34
		Picado	1988	10	Hashimoto	1977	8			
N = number of randomized participants										

Two noncomparative case series exhibited high quality, defined by a total quality score of 4 or 5.[71,74] However, the generalizability of the results of these studies to the North American standard set for this review was extremely limited. The only study with strong generalizability potential also exhibited good study quality.[73]

Qualitative Synthesis of Individual Study Results From Study Designs Other Than a RCT

In a non-RCT of Russian adults exposed either to 6g/day of EPA and DHA or olive oil for 2 months, Masuev[60] investigated likely less potent mediators of inflammation. They found a significant decrease in 5-HETE production and an undefined change in 5-HEPE production related to the omega-3 fatty acids exposure.

Okamoto et al.'s noncomparative case series of Japanese adults exposed to perilla oil-supplemented (ALA amount undefined) salad dressing or mayonnaise over 4 weeks (background diet unchanged) found that leukotriene C_4 generation by peripheral leukocytes decreased significantly in adults defined as responders and increased significantly in those defined as nonresponders.[71] At final follow-up, leukotriene C_4 levels differed significantly for these two subgroups. Ashida et al.'s noncomparative case series of Japanese adults also received perilla seed oil supplementation (ALA amount undefined) for 2 weeks, and they reported a significant decrease in the generation of leukotriene C_4 as well as leukotriene B_4 by peripheral leukocytes.[59]

Broughton et al. exposed a noncomparative case series of American adults to 4 weeks of low-dose fish oil supplementation (~0.7 g/day EPA and DHA), followed by another 4 weeks of high-dose fish oil supplementation (~3.3 g/day EPA and DHA), in an attempt to alter the intake ratio of omega-6/omega-3 fatty acids, yielding a low (1:0.1) and high (1:0.5) ratio exposure.[73] The authors reported a significant increase in urinary total leukotriene E_4 excretion associated with the low-ratio exposure. In addition, they noted: a nonsignificant change in urinary total leukotriene E_5 excretion associated with the low-ratio exposure; a nonsignificant change in urinary leukotriene E_4 excretion with the high-ratio exposure for responders (nonsignificant fall in respiratory measures with increased methacholine challenge) or nonresponders (respiratory reductions with increased challenge); a nonsignificant change in leukotriene E_4 excretion when responders and nonresponders were combined; significantly lower urinary leukotriene E_4 excretion with the high-ratio exposure; and, a significant increase in urinary leukotriene E_5 excretion with the high-ratio exposure for responders and nonresponders. Hashimoto et al. exposed a noncomparative case series of Japanese adults with mild to moderate asthma and hyperlipidemia, to 1800 mg/day of EPA over 8 weeks and reported a nonsignificant change in the urinary excretion of leukotrienes B_4 and E_4.[62]

Picado et al. exposed a noncomparative case series of aspirin-intolerant asthmatics first to 6 weeks of placebo (lactose) capsules plus a poorly defined eucaloric diet (e.g., 32% fat), then another 6 weeks with an experimental diet including EPA/DHA capsules and the eucaloric diet. They reported a significant decrease in concentrations of TxB_2 only with the fish oil exposure.[74]

Question 4: Are omega-3 fatty acids effective in the primary prevention of asthma?

As observed in Summary Tables 6 and 7, and derived from Evidence Tables 3 and 4 (Appendix E), one RCT and 5 observational studies addressed the question of primary prevention. A qualitative description of the former precedes the latter.

Qualitative Synthesis of RCT Evidence Regarding Primary Prevention

Given that there is only one RCT, its study parameters and results are described together. A factorial design was employed to test the separate and combined effects of an active diet containing omega-3 fatty acids (500 mg/day of tuna fish oil from age 6 months, along with other omega-3 fatty acids such as canola oils and margarine prior to age 6 months), and, active house dust mite reduction.[51] The study required four groups to achieve this. The diet was placebo-controlled (Sunola oil) but the control used for the dust mite reduction primarily involved advice. One co-objective of the study was to alter the omega-6/omega-3 fatty acid ratio in the active diet arm. Pregnant women (n = 616; 36 weeks gestation) were randomized to one of four groups in this 5-year study, with their unborn children at risk for asthma given that at least one parent or sibling exhibited asthma or its symptoms.

Summary Table 6: RCT evidence of omega-3 fatty acids to prevent asthma in children

Author, Year, Location	Omega-3 Fatty Acid Group		Comparator Group		# of S Unique Results Favoring Omega-3 Fatty Acids	Jadad Total Quality/ Allocation Concealment (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
Mihrshahi, 2003, Australia[50,51]	312	0.8 mg EPA + 3.6 mg DHA per kg body weight (500 mg fish oil) + canola oil/ margarine (ALA: NR)	304	500 mg Sunola oil + PUFA oils/ margarine	2/10	2 (Grade: C)/ adequate	III
n = number of randomized participants; S = significant; PUFA = polyunsaturated fatty acids							

Mihrshahi et al. recently reported the results of an 18-month interim analyses even though they explicitly recognized the difficulty in identifying asthma in such a young population.[51] They found a nonsignificant difference between the active and control diet groups in the diagnosed prevalence of asthma. The statistically significant benefits of the omega-3 fatty acid intervention, relative to controls, were observed with respect to very few variables reflecting problems with wheeze (i.e., lower number of episodes "ever;" wheeze lasting more than a week). The intervention did not influence health care utilizations relating to problems with wheeze, or the use of asthma medications, including inhaled corticosteroids. Dust mite reduction neither independently, nor by way of interaction with the omega-3 fatty acid intervention, had a positive effect on respiratory outcomes. They also found that, in terms of reaching the children's plasma, the omega-3 fatty acid intervention significantly altered the omega-6/omega-3 fatty acid ratio

relative to controls. Jadad-defined study quality was low, yet the concealment of allocation was adequate. Applicability was restricted.

Overview of Relevant Observational Studies

Hodge et al. employed a stratified case-control design to evaluate a cross-section of Australian school children aged 8 to 11 years.[77] Stratification yielded four groups, that is, children with current asthma (wheeze and airways hyperresponsiveness; n = 71), airways hyperresponsiveness only (n = 55), wheeze only (n = 79), and normal airways (neither wheeze nor airways hyperresponsiveness; n = 263). Inclusion in one of the four groups was determined by respiratory functions testing and physician examination. A parental questionnaire focused on diet over the last 12 months, including fish (i.e., oily vs non-oily) consumption. Satomi et al.'s cross-sectional study observed children in grades 1, 3, and 5 in coastal and inland areas of Japan.[78] Current diet (e.g., reddish fish vs pale fish vs other marine foods) was assessed via parental questionnaire, and, health status was likely determined by physician examination. Children with (n = 706) and without asthma (n = 6,882) were identified.

Huang et al. investigated Taiwanese adolescents aged 13 to 17 years in a cross-sectional study.[48] Both a food-frequency questionnaire and a 24-recall method were employed to assess current diet (e.g., seafish vs. oily fish vs. shellfish). A health status questionnaire and a physician diagnosis identified participants who were asthmatic (n = 35), had allergic rhinitis (n = 115), wheezed (n = 11), or exhibited none of these conditions (n = 1,030). The cross-sectional study by Takemura et al. investigated elementary and junior high school children and adolescents in Japan.[76] A quantitative food frequency questionnaire evaluated current fish intake, and, a physician diagnosis yielded those with (n = 1,673) and without asthma (n = 22,109). Each of the studies including children or adolescents was primarily concerned with asthma prevalence.

The Nurses Health Study's prospective cohort (U.S.) was evaluated for a possible association of risk of adult-onset asthma, and, the frequency of intake of various types of food.[75] A semi-quantitative food frequency questionnaire was employed to index food intake over the past year (e.g., dark meat fish vs other fish). Over 1,200 cases of adult-onset asthma were identified.

Qualitative Synthesis of Observational Study Evidence Regarding Primary Prevention

Study characteristics. Adult and pediatric studies are described separately. All studies were published between 1994 and 2003 (Summary Table 7; Evidence Table 4: Appendix E). The study evaluating both young children and adolescents is included with the pediatric investigations.

Summary Table 7: Observational study evidence of omega-3 fatty acids for primary prevention of asthma

Author, Year, Location	Number with asthma	Types of Control (n)	Unadjusted or Adjusted Associations of Dietary Fish Intake and Asthma Prevalence	Study Quality (Internal Validity)	Applicability (External Validity)
ADULTS					
Troisi, 1995,	1446	NA	▪ NS relationship between 6-y risk of	3 (Grade: B)	II

USA[75]			asthma and frequency of intake of dark meat fish • NS adjusted risk reduction associated with all levels of omega-3 fatty acid intake		
ADOLESCENTS					
Huang, 2001, Taiwan[48,49]	36	• Allergic rhinitis (n=115) • No asthma or rhinitis (n=1,030)	• S association between higher frequencies of oily fish intake and asthma prevalence	3 (Grade: B)	III
ADOLESCENTS & CHILDREN					
Takemura, 2002, Japan[76]	1673	• Not currently asthmatic (n=22,109)	• S higher asthma prevalence (adjusted) for consumers of 1-2 fish meals/wk than for consumers of 1-2/mo (overall, and only in males)	3 (Grade: B)	III
CHILDREN					
Hodge, 1996, Australia[77]	71	• Normal airways (n=263) • Airways hyper-responsiveness only (n=55) • Wheeze only (n=79)	• S lower (unadjusted) risk of asthma in eaters of fresh fish and oily fresh fish • S lower (adjusted) risk of asthma in consumers of oily fish	2 (Grade: C)	III
Satomi, 1994, Japan[78]	706	• Not asthmatic (n=6,882)	• S negative correlation between asthma prevalence and frequency of fish consumption (e.g., reddish fish)	4 (Grade: A)	III
n = number of evaluated participants; NA = not applicable; S = significant; NS = nonsignificant					

All but one study reported both inclusion and exclusion criteria, with one pediatric study failing to explicitly state exclusion criteria.[78] Two studies provided very few details regarding their sampling procedure.[76,78] The full sample sizes varied, ranging from a cross-section of 808 school-age children[77] to 121,700 nurses in the Nurses Health Study.[75] Two studies were funded by government,[48,77] one by a medical association,[76] one by the NIH,[75] and one did not report a funding source.[78]

Population characteristics. The adult study followed a cohort of exclusively female nurses aged between 34 and 68 years.[75] Approximately half of the participants in the other studies were male. Of the two studies that included adolescents, one examined individuals between the ages of 6 and 15 (mean: 10.41) years,[76] and the ages of the participants in the other study ranged between 3 and 17 (mean: 14.7) years.[48] Children in the two pediatric investigations ranged in age between 6 and 11 (mean: NR) years,[78] and 8 and 11 (mean: 9.5) years.[77] While it could be surmised that the three studies that involved Asian populations,[48,76,78] the Australian project[77] likely included those of primarily Caucasian/European descent, whereas, the American study provided no race/ethnicity details.[75]

Each study evaluating asthma prevalence included a subset of asthmatic participants. The only study to assess incidence of asthma excluded all asthmatic individuals prior to following a

cohort of nurses prospectively.[75] Of those including asthmatic participants, the asthma sample sizes ranged from 36 adolescents[48] to 1,673 children and adolescents.[76] Three of the latter four samples of asthmatics[76-78] included an average of 60.2% males, exceeding the 50% value for their full sample populations. Methods to identify asthma varied, and included questionnaires asking about a physician-assigned diagnosis of asthma,[48,75,78] a modified American Thoracic Society questionnaire,[76] and testing combined with a clinical assessment.[77] Asthma severity data were not reported for any study. Only the report of the Nurses Health Study described the range of asthma medications used by the participants.[75] These included various types of corticosteroid.

The four pediatric studies each defined a control sub-sample of individuals without asthma,[48,76-78] with their sizes ranging from 263 children[77] to 22,109 children and adolescents.[76] Only two reports described whether, and how, its sub-populations varied. Hodge et al. found more children with atopy in their asthmatic group than in their other subpopulations; in addition they found no difference between groups with respect to a history of early respiratory infections or parental history of asthma.[77] Takemura et al. reported that, relative to non-asthmatics, the asthmatic children and adolescents were younger, more likely to be male, and more likely to have parents with a history of asthma.[76]

Exposure characteristics. The exposures of interest to the present systematic review involved the dietary intake of various types of fish, indicating the possible presence of EPA and DHA. However, the specific amounts (in grams) of these omega-3 fatty acids were never reported. Four studies reported the types of fish, arguing that certain fish (reddish;[78] oily;[48,77] dark meat[75]) contained greater amounts of omega-3 fatty acids. One study did not report the types of fish.[76] The timeframe of food intake varied between respondents but was reported to be within: the past year;[75,77] the current diet;[76,78] and, both the last month, and, 24-hour recall.[48] Every study employed at least a semi-quantitative questionnaire with which to collect data, although one also included interviews with the participating adolescents.[48] The various questionnaires provided different response options (e.g., "never" to "daily;"[77] "less than once a month" to "more than 4-5 times a week;"[78] "almost never" to "at least 3-4 times a week").[76] Assessments involving children required that parents provide the data.[48,76-78] While investigators were invariably focused on fresh fish consumption (vs canned products), no studies factored into their analysis the ways in which the fish were prepared or the impact of the preparation method (e.g., frying) on the omega-3 fatty acid content.

Outcome characteristics. The key outcomes were the prevalence[48,76-78] and incidence[75] of asthma and its core symptoms.

Study quality and applicability. The mean total quality score was 3.2 (range: 2-4), likely indicating good quality. All five studies failed to describe their exposures adequately, and two failed to satisfactorily describe their study participants.[76,77] The quality grades associated with quality scores were entered into the summary matrix. Virtually no variability characterized the applicability rating, with four of five studies assigned a level III rating (Summary Matrix 5). This indicates the extremely limited potential for generalization to the typical healthy North American population, or to those at risk for asthma.

Summary Matrix 5: Study quality and applicability of observational study evidence regarding primary prevention

		Quality								
		A			**B**			**C**		
	I									
Applicability	**II**				**Author**	**Year**	**N**			
					Troisi*	1995	1446			
	III	**Author**	**Year**	**N**	**Author**	**Year**	**N**	**Author**	**Year**	**N**
		Satomi	1994	706	Huang	2001a	36	Hodge	1996	71
					Takemura	2002	1673			
N = number of randomized participants; *Adults (nurses) only										

One observational study exhibited high quality, defined by a total quality score of 4.[78] However, its applicability was extremely limited. The only study with reasonable applicability also exhibited good quality.[75]

Qualitative Synthesis of Individual Observational Study Results

In a cross-section of Australian children aged 8 to 11 years, Hodge et al. found that, when results were unadjusted, the risk of asthma was significantly lower in consumers of fresh fish or oily fresh fish (high in omega-3 fatty acids).[77] The focus was on consumption over the past year. Current asthma was observed in 8.8% of children who ate oily fish, compared with 15.6% of those eating non-oily fish, and 23% of those who never ate fresh fish. When the results were adjusted for specific risk factors (atopy, parental asthma, parental smoking, ethnicity, country of birth, early respiratory illness), only children who ate oily fresh fish had a significantly reduced risk of asthma. In these children, the risk was one-quarter that of those who did not eat oily fish. But, the consumption of fresh fish of any kind did not significantly reduce the risk of airways hyperresponsiveness alone or of wheeze alone either before or after adjusting for the above-noted risk factors.

Similarly, observing children in grades 1, 3, and 5 in coastal and inland areas of Japan, Satomi et al. reported a significant negative correlation between asthma prevalence and frequency of fish consumption in the current diet.[78] After excluding the effects of multiple confounders positively correlated with asthma prevalence (air conditioning in home, dusty home, temperature difference between day and night, at least one parental smoker, maternal intake of fermented beans and mushrooms, and, living near a pasture), asthma prevalence decreased as reddish fish (high in omega-3 fatty acids) intake increased. In addition, the asthma prevalence was lower in those who ate fish at least four times a week as compared to with those who ate it less than once a month.

Yet, both studies including at least some adolescents found a significant positive association between fish intake and asthma prevalence. Based on a univariate analysis of food frequency questionnaire data relating to the previous month, Huang et al. reported that, in adolescents aged 13 to 17 years, higher frequencies of oily fish intake were significantly associated with asthma prevalence.[48] However, oily fish intake did not play a significant role in predicting asthma prevalence in multivariate logistic regression. The study by Takemura et al. investigated elementary and junior high school children and adolescents and found that, using one to two meals per month as the reference standard, and after adjusting for age, gender, and a parental history of asthma, a significantly higher asthma prevalence was observed for those who ate fish one to two times per week compared with those who ate fish one to two times a month.[76] The

risk increased gradually with increasing frequency of fish intake, with a significant positive trend observed. When vegetable and fruit intake were included as additional risk factors, a similar significant and positive association was observed. The significant trend was attributed exclusively to results from male participants. Takemura et al. did not distinguish between the types of fish (e.g., oily vs. non-oily).[76]

The Nurses Health Study data showed that the 6-year risk of adult-onset asthma was unrelated to the frequency of intake of dark meat fish, tuna fish, or shrimp.[75] This nonsignificant association was maintained when results were adjusted for age and smoking status, and also when other factors (body mass index, residential area, number of physician visits, and energy intake) were adjusted for.

Question 5: Among Individuals with Asthma, do Omega-3 Fatty Acids Alter the Progression of Asthma (i.e., Secondary Prevention)?

There were no studies found that investigated this question.

Question 6: What is the Evidence for Adverse Events, Side Effects, or Counter-Indications Associated with Omega-3 Fatty Acid Use to Treat or Prevent Asthma (DHA, EPA, DPA, ALA, Fish Oil, Fish)?

Qualitative Synthesis of Safety Data for All Research Designs

Studies not included in Summary Table 8 did not report any safety issues. No primary prevention studies reported safety concerns. Adverse events or side effects were observed in ten studies, six of which were adult RCTs,[54,57,58,67-69] two of which were pediatric trials,[52,64] and two of which were studies of adults involving study designs other than an RCT.[61,73]

The most serious consequence of involvement in a study occurred when one participant almost died following repeated allergen challenge.[61] In this study, the omega-3 fatty acid exposure had not yet begun. Of the intervention/exposure-related events, the most serious was nausea and vomiting after taking the fish oil capsules, which forced the participant to withdraw.[67] An undefined number experienced occasional, "mild gastrointestinal discomfort" (undefined) while taking fish oil capsules.[73] Three children experienced "discomfort" (undefined) after taking exposure capsules, two of whom were receiving a mixture of oils rich in omega-6 fatty acids (safflower).[52] Consequences of the events relating to the latter two studies were not reported. Seventeen adults and one child across four RCTs each experienced problems swallowing capsules because of their size or number, and were forced to withdraw.[57,58,64,67] Only for the one child was it reported to which study arm they had been randomized (control).[64] An unreported number (<7) left a crossover trial because they could not tolerate the taste of the oil

delivered by spoonfuls poured from masked bottles.[68] An undisclosed number of adults experienced fishy hiccups while taking fish oil, with no indication of the consequences.[73] Two adults developed skin itch (one per study arm: mussel vs olive oil) and another three reported a metallic taste (two receiving olive oil capsules).[69]

One adult withdrew after being hospitalized for acute asthma.[57] Three adults, two of whom were in the high-dose EPA ethyl ester group, had adverse reactions to aspirin or NSAIDS, but no information was reported as to whether they remained in the study.[54]

Three studies likely decided to avoid situations whereby omega-3 fatty acids might exacerbate an existing condition. They excluded adults with a history of bleeding disorders, delayed clotting time and coagulation diseases, and peptic ulcers.[58,68,73]

Summary Table 8: Studies reporting adverse events, side effects, and counter-indications

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		Safety data
	n	Type & Dose/ Day	n	Type & Dose/Day	
ADULTS					
Arm, 1988, England[56,57†]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	Withdrew (timing: NR): size & number of capsules not tolerable (n=3; arm: NR); Withdrew after 3 wk (omega-3 fatty acids): hospitalized for acute asthma (n=1)
Broughton, 1997, USA[73††]	26	'Low' EPA + DHA intake: ~0.7 g (mean)	26	'High' EPA + DHA intake: ~3.3 g (mean)	Fishy hiccups (omega-3 fatty acids arm: NR); Occasional mild gastrointestinal discomfort (omega-3 fatty acids arm: NR); Exclusion criteria: history of bleeding disorder or delayed clotting time
Emelyanov, 2002, Russia[69†]	23	200 mg EPA+DHA + 400 mg olive oil	23	600 mg olive oil	Skin itch (1 per study arm); Metallic taste (omega-3 fatty acids arm: 1; control arm: 2)
Kirsch, 1988, USA[54,55†]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA ethyl ester (trace DHA)	Adverse reactions to aspirin or NSAIDs in high (n=2) & low dose (n=1) arms
Masuev, 1997b, Russia[61†††]	5	6.0 g EPA+DHA	3	6.0 g Olive oil	Withdrew (timing: NR) due to severe clinical apnea in response to repeated allergen challenge (n=1)
McDonald, 1991, Australia[58†*]	15	2.7 g EPA + 1.8 g DHA	15	15 g olive oil	Withdrew (timing: NR): problems swallowing capsules (n=2). Exclusion criteria: peptic ulcers, cardiovascular disease, other potential bleeding disorders
Stenius-Aarniala, 1989, Finland[68†*]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	Withdrew (timing: NR): could not tolerate taste of oil, or, difficulty keeping diary (n=7; breakdowns: NR) Exclusion criteria: coagulation disorders & diabetes
Thien, 1993, England[67†]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	Withdrew in wk 1: nausea & vomiting after taking capsules (omega-3 fatty acids arm: n=1); withdrew after wk 1: size & number of capsules unmanageable (n=6; arm: NR); withdrew in first 2 wk: size & number of capsule unmanageable (n=4; arm: NR); withdrew (timing: NR): difficulty taking capsules & recording data (n=2; arm: NR)
CHILDREN					

Hodge, 1998, Australia[53†]	NR	0.72 g EPA 0.48 g DHA + ALA (NR) via Canola diet	NR	'Omega-6 fatty acids:' 1.8g Safflower oil + 1.8g Palm oil + 0.4g Olive oil + Sunflower diet (NR)	Discomfort after taking capsules: omega-3 fatty acids arm (n=1); omega-6 fatty acids arm (n=2)
Nagakura, 2000, Japan[64†]	15	17.0-26.8 mg/kg EPA; 7.3-11.5 mg/kg DHA (300 mg fish oil)	15	300 mg olive oil	Dropped out: unable to swallow capsules at beginning of study (n=1; arm: control)
n = number of enrolled/randomized participants; NR = not reported; NA = not applicable; [†]RCT; [††]Noncomparative case series [†††]non-RCT [*]Crossover trial					

Question 7: What is the Evidence that Omega-3 Fatty Acids are Associated with Adverse Events in Specific Subpopulations of Asthmatic Individual such as Diabetics?

There were no studies found that investigated this question.

Chapter 4. Discussion

Overview

Twenty-six studies investigated five of the seven questions addressed in this systematic review of the evidence concerning the health effects of omega-3 fatty acids in asthma. The question of secondary prevention and the question of safety related to omega-3 fatty acid use in subpopulations of asthmatic could not be addressed since there were no studies addressing either of these topics. Eleven RCTs (ten treatment; one primary prevention) and 15 studies employing other designs (ten treatment; five primary prevention) were included. Three of the former and six of the latter exclusively involved either children or adolescents. It is likely that, other than Ashida et al.'s noncomparative case series lasting 2 weeks,[59] all treatment studies lasted long enough to demonstrate that a difference could be found in terms of respiratory outcomes and mediators of inflammation. Relevant studies could only be synthesized qualitatively according to the question(s) that they addressed. Reasons for choosing to forego meta-analysis follow from a critical analysis of the evidence base. After the response to each research question is presented, the discussion turns to the broader implications and issues raised by the findings.

The Evidence

There is not enough consistent evidence, or sufficient evidence from methodologically sound and adequately powered studies with which to conclude definitively that omega-3 fatty acids are or are not efficacious in improving respiratory outcomes in adults or children (Question 1). Failure to control for confounding in over half the RCTs also made it difficult, if not inappropriate, to summarize their data. The greater inability to control for confounders in study designs less "naturally" rigorous than RCTs complicated the synthesis of those data.

In light of the available information, the inconsistency among study results may be attributable to the heterogeneity in definitions of the: settings (e.g., hospital vs outpatient; countries); populations (e.g., age; gender; clinical picture of asthma, including its severity and concomitants, or triggers with the potential to impact asthma control); interventions and their contrasts with comparators (e.g., different types and amounts of oil and omega-3 fatty acid contents; controlled vs uncontrolled dosing), and cointerventions (e.g., asthma medication with varying capacities to control asthma in the short-term or longterm). This observation applies to all patterns of results relating to Questions 1, 2, 3, and 4. Explicitly defined study quality was good for the various types of study design, with the prominent limitation for RCTs being limited blinding, and the key limitation for studies using other designs being the poor description of study participants. All but one RCT[54] and one two-phase, noncomparative case series [73] exhibited very restricted applicability to the typical North American population of asthmatics.

Adult RCTs revealed a somewhat contradictory picture of efficacy with respect to this systematic review's primary outcome, FEV_1. One very small adult study (n = 14) that employed uncontrolled dosing of perilla seed oil and corn oil (control) over a short intervention period (n = 4 weeks) reported a significant effect. However, two RCTs each observed no benefit relating to

an omega-3 fatty acids intervention. One compared high and low doses of EPA ethyl ester[54] over 16 weeks in a small study (n = 12), whereas the second investigated the benefit of low dose EPA/DHA (vs. olive oil) over ten weeks in the systematic review's highest quality RCT.[69] The latter involved one of the largest sample populations (n = 46) included in the evidence review. Emelyanov et al. also demonstrated good control of three confounding factors (see Critical Analysis) while providing one of the most rigorous methods to select its asthma population.[69] No studies of adults in a non-RCT or noncomparative case series investigated this outcome. With regard to studies of children, one RCT[52] and a non-RCT[63] observed no benefit in terms of FEV_1. Thus, while it might be tempting to conclude an absence of efficacy based on the solid Emelyanov et al. study,[69] the fact that there were few studies to consider makes the most balanced understanding one that suggests more research is needed before anything definitive can be concluded about the impact of omega-3 fatty acids on FEV_1. Moreover, a change in this outcome perhaps should not have been expected in the Emelyanov et al. trial because they utilized a low dose of omega-3 fatty acids, as well as randomized mild asthmatics. That said, exactly to what the other observed clinical effects (e.g., AM PEF) in their study may be attributed (e.g., another component in Lyprinol) is unclear.

With respect to several other respiratory outcomes, there is likewise no unequivocal response to the question of efficacy for adults or children. For AM PEF in adults, two RCTs,[66,69] including Emelyanov et al.,[69] and three noncomparative case series[59,62] showed a significant benefit for omega-3 fatty acid supplementation. However, four RCTs[57,58,67,68] and a noncomparative case series[72] reported no benefit. The pediatric non-RCT also revealed no benefit.[63]

For PM PEF in adults, five RCTs including Emelyanov et al.,[69] showed no benefit whereas two noncomparative case series noted a significant effect.[59,62] While the RCT evidence likely deserves to be "weighted" more heavily, and suggests no efficacy, this pattern requires interpretation within the larger context of the various outcomes' findings. Based on two RCTs, [57,67] no effect was observed for diurnal PEF variability in adults. Pediatric studies did not employ either of these latter two outcomes.

Results varied with respect to adult bronchodilator use. Three RCTs[57,58,67] reported no benefit (i.e., decreased use) associated with omega-3 fatty acid supplementation. One noncomparative case series with two exposures observed a significant increase in bronchodilator use associated with deteriorating airflow obstruction in the last two weeks of fish oil supplementation (versus placebo).[74] Emelyanov et al.'s adult RCT,[69] and a non-RCT with children,[70] each observed a benefit associated with omega-3 fatty acid use. The latter enrolled children as young as one year of age, however.

Observing results relating to subjective ratings of respiratory function, including asthma symptom scores and severity scores, with each based on widely varying definitions and informants (i.e., participants; professionals; parents), revealed a significantly greater decrease in daytime wheeze for adults receiving omega-3 fatty acids in one RCT,[69] and a significant decrease in symptom and asthma scores in two noncomparative case series.[59,62] Two adult RCTs[57,67] noted no benefit with respect to airways responsiveness to histamine challenge, whereas one adult RCT[57] and a non-RCT of adults[61] each reported some value associated with omega-3 fatty acid use in blunting late airways responses to allergen challenge. The remaining observations from both RCTs and other designs involved one study per outcome, including poorly defined subjective ones (e.g., "daily life score") and several others reflecting pulmonary

function (e.g., FVC). No discernible patterns were observed supporting an unequivocal interpretation of omega-3 fatty acids' efficacy.

Given the largely inconsistent picture of efficacy within and across respiratory outcomes, it is impossible to conclude one way or the other that omega-3 fatty acids are an efficacious adjuvant or monotherapy in improving respiratory outcomes in adults or children. This view is perhaps best illustrated by what was observed with respect to the primary outcome, FEV_1. In general, very few studies were available with which to address the question for adults, and even fewer for children and adolescents. Even though study quality, as operationally defined in the present review, was not an obvious shortcoming of the 20 included treatment studies, the very limited generalizability potential for all but two of them may be taken to suggest that answering Question 1 requires more research conducted with North American samples. Additional observations are highlighted in subsequent sections.

The observations derived from the indirect assessment of the possible influence of predefined or study-defined covariates (Question 2) on the results of treatment studies are highly unreliable. With almost no direct tests of the predictive utility of effect modifiers, or the possibility of subgroup meta-analysis (see below), and with few studies consistently observing significant effects for a given outcome, the evaluation yielded few clear observations. Nevertheless, it did highlight one exposure potentially worth exploring in future empirical investigations of the health effects of omega-3 fatty acids in asthma.

It was noted that perilla seed oil supplementation, provided in an uncontrolled fashion to adults across various studies, exclusively produced significant clinical effects in favor of this omega-3 fatty acids exposure (12/12). This observation is based on results from a small RCT (e.g., FEV_1, AM PEF)[66] and two noncomparative case series (e.g., AM PEF; PM PEF).[59,71] However, one issue requiring resolution is the amount of omega-3 fatty acid content participants actually received from this supplementation. Aside from the perilla seed oil observation, too many tenuous connections were observed to permit their extrapolation. The relationship of variables such as the type, source, or dose of the omega-3 fatty acids could not be investigated with any precision. Nevertheless it seemed to be the case that none of the specific definitions, or levels, of the predefined or study-defined covariates was associated exclusively with a significant effect (e.g., high or low dose). Without the option of meta-analysis, it is difficult to respond adequately to Question 2. It must be concluded that, at present, effect modifiers responsible for any significant asthma-related benefits accruing to omega-3 fatty acids supplementation cannot be identified. This exploration was complicated by the fact that few significant effects were found.

It is likewise unfeasible to conclude one way or the other that omega-3 fatty acids positively influence the lipid mediators of inflammation in adult studies in accordance with the biological model implicating the lipoxygenase and cyclooxygenase pathways in asthma. The effects with respect to any of leukotriene series when omega-3 fatty acids were given were not *consistently* observed across this collection of studies. Possible reasons include poorly designed studies, varying populations, small sample sizes, and, varying or problematic laboratory methods. Moreover, virtually no mediators of inflammation other than the lipid variety were found to have been investigated (e.g., TNF-a). With the omega-3 fatty acids exposure, there was a significantly suppressed generation of LTB_4 by various types of leukocyte observed in two small RCTs totaling 16 participants[54,66] and an even smaller noncomparative case series, (n = 5)[59] but no effect was observed in a larger RCT (n = 25).[57] An inconsistent picture was observed with respect to the increased generation of LTB_5 by various types of leukocyte, with a significant

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increase revealed by one small RCT (n = 12)[54] and a null effect found in a larger RCT (n = 25).[57] One RCT noted the significant suppression of total LTB compounds by leukocytes.[57] Yet, one small RCT (n = 14)[66] and two noncomparative case series[59,71] totaling 31 adults consistently found a significantly suppressed generation of LTC_4 by peripheral leukocytes. In these three studies, perilla seed oil had been delivered via uncontrolled servings.

The nonsignificant generation of PGE by various leukocytes in one small RCT (n = 12)[54] is contrasted with the significantly higher plasma PGE_2 and significantly lower plasma $PGF_{2-alpha}$ reported for omega-3 fatty acid supplementation in a crossover RCT (n = 36), the latter a study that failed to provide a washout in comparing uncontrolled servings of fish oil supplementation, olive oil, and evening primrose oil.[68] This same crossover study also revealed nonsignificant effects with respect to plasma TxB_2, plasma 6-keto-$PGF_{1-alpha}$, in addition to urinary PGE_2, $PGF_{2-alpha}$, TxB_2, and 6-keto-$PGF_{1-alpha}$. Yet, Picado's small (n = 10), two-exposure noncomparative case series reported a significant decrease in TxB_2 associated with omega-3 fatty acids use.[74] In their noncomparative case series (n = 26), Broughton et al. found that significantly lower urinary LTE_4 excretion and significantly higher urinary LTE_5 excretion were associated with high, but not low, dose EPA.[73] Hashimoto et al.'s noncomparative case series noted a nonsignificant change in urinary LTB_4 and LTE_4 excretion.[62]

Two RCTs found a significant suppression of polymorphonuclear leukocyte chemotaxis in response to various stimuli (C5a, LTB_4, and two fMLP concentrations) in a total of 37 adult with asthma,[54,57] while the smaller of the two RCTs (n = 12) also reported a nonsignificant suppression of mononuclear leukocyte chemotaxis to various stimuli (C5a, LTB_4) associated with omega-3 fatty acid use.[54] Finally, Hodge et al. reported a nonsignificant change in TNF-a production in their pediatric RCT that compared omega-3 fatty acid with omega-6 fatty acid supplementation.[52]

The only consistent impacts of omega-3 fatty acids on mediators of inflammation involved the suppression of LTC_4 and of polymorphonuclear leukocyte chemotaxis to various stimuli. However, all of the results must be interpreted with caution given the small sample sizes and the fact that the findings of significant effects for the same outcome involved different intervention-comparator contrasts, as well as varying doses of omega-3 fatty acids. As with the evidence regarding Question 1, considerable clinical heterogeneity characterizes these studies. Their average study quality was good, and, their applicability was very restricted. The implications of these observations are described later.

Dietary fish consumption, including oily fish intake, was assessed primarily through retrospective food-frequency questionnaires, and appeared to serve as a primary prevention for asthma in two pediatric populations (Question 4).[77,78] However, asthma prevalence and fish, or oily fish, intake were significantly and positively related in studies that included adolescents from Asia,[48,76] with one of these studies also including some children.[76] In a prospective study that followed nurses, no association was found between adult-onset asthma and dietary fish intake.[75]

One possible interpretation of the inverse relationship between age and the ability of regular fish intake to protect against asthma is that, the sooner people, especially children at risk, are exposed to omega-3 fatty acids, the more likely they will be protected. It is possible that even low fish (oil) intake has effects on specific immunological factors inherent to the development of asthma in childhood, which may no longer be modifiable later in life.[79] Early in life, omega-3 fatty acids may reduce inflammatory responses to allergens.[52] Eventually, a critical period may be identified.

Mihrshahi et al.'s factorial RCT is, in large part, a study evaluating the impact of an omega-3 fatty acid regimen (vs placebo), initiated prebirth, on neonates at risk for asthma, given that at least one parent or sibling had received this diagnosis.[51] Their interim results indicated a limited benefit accruing to the omega-3 fatty acid exposure, yet 18 months is likely too early in life to reliably identify asthma. Final followup at five years of age should provide a clearer picture of the value of omega-3 fatty acids as primary prevention. Regarding the prevention studies, study quality was better, on average, for the observational studies than for the single RCT; and, as was the case for treatment studies, almost no studies even remotely resembled the North American population standard established in this review. Problems with these prevention studies are enumerated below, including speculation as to why the protective effect was not observed in the studies enrolling adolescents.

No safety profile relating to omega-3 fatty acids as an exposure was reported for primary prevention studies (Question 6); evidence from the remaining studies suggests that the safety profile in treatment studies was good. Most of the adverse events were related to the capsule delivery of oils, rather than to the oils per se.[57,58,64,67] On several occasions, an inability to swallow capsules led to withdrawal from a study. Other participants may have had difficulties taking eighteen capsules a day of oil in two specific RCTs, yet these difficulties were not reported.[57,67] The one moderately serious reaction observed was an undefined number of episodes of nausea and vomiting after ingesting the fish oil capsules, and this led to a withdrawal.[67] Unspecified numbers of children and adults experienced some mild gastrointestinal discomfort, but not all individuals had been receiving the omega-3 fatty acid exposure.[52] Fishy hiccups or burping were a rare complaint. By far the most serious event linked to a treatment study involved severe apnea associated with repeated allergen challenge, not the omega-3 fatty acid exposure.[61]

Thus, either omega-3 fatty acid supplementation in these studies did not constitute a notable safety problem, or safety data were under-reported. Given what has been observed by others,[35] the first interpretation appears to be, at the very least, tenable. While the U.S. Food and Drug Administration has in the past recommended three grams as the maximum daily intake of EPA and DHA, even minor safety concerns associated with larger doses were rare in the present collection of studies. A critical analysis puts into perspective the less than definitive answers to the investigated research questions.

Critical Analysis

Many limitations and problems characterize the present evidence base. To begin with, for the treatment studies, only a small minority of RCTs[52,54,69] and studies using other designs[62,72,73] reported both inclusion and exclusion criteria. Most studies were very small, with many of the RCTs likely being underpowered. Relative to the RCTs, studies with designs exhibiting considerably less potential rigor were even smaller, shorter in duration, and provided less information. Thus, most of the following critique focuses on the RCTs. It must also be recalled that only two treatment studies and one investigating primary prevention demonstrated good and somewhat restricted applicability, respectively. The results of all other studies likely cannot be generalized to the North American reference standard defined in the present review.

The majority of studies were poorly reported, often failing to include key details that could clearly identify the target population, the intervention/exposure it received, or any other

treatments that they may have been receiving for asthma. For example, some of the studies did not present any, complete, or non-contradictory, population information as basic as demographic details (e.g., age; gender distribution), diagnosis-related information beyond a label of "asthma" (e.g., definition, including severity, duration, concomitants/triggers with the potential to influence asthma control; method of diagnosis), or lifestyle/racial/ethnic factors with the potential to influence asthma or the effectiveness of its treatment (e.g., background diet).[65,66] Yet, three of 20 treatment studies did acknowledge that their asthma participants had been in-patients in controlled, hospital environments.[59,64,66] Investigators of a noncomparative case series claimed their asthma participants were in "remission" yet, while they never defined the term, they continued to describe them as if they were currently asthmatic.[72] Some RCT reports stated how many adults or children had been randomized, but did not report numbers of participant per study arm.[52,57,65,67] One RCT reported data and information only for study completers,[67] and the scarcity of information contained in all reports of the treatment studies suggest that this was not the only instance. One pediatric RCT[64] included children under the age of five, whereas a non-RCT enrolled children as young as one year of age.[70] In neither of these reports did the authors assure, with or without data, that they had adequately distinguished between wheezing disorders and asthma. Early transient wheeze is not a reliable predictor of asthma.[51] Some studies involving older adults, with some current or ex-smokers, did not report if they had ruled out COPD.[66,68] Almost no information was made available regarding concurrent conditions (e.g., hyperlipidemia) or their treatment.[62] The latter could have interacted with the participants' asthma treatment.

The same limitations are observed with respect to the reporting of characteristics defining the intervention/exposure (e.g., amounts of omega-3 fatty acid), comparators (e.g., "placebo"), and the allowable or mandated types and doses of cointervention (e.g., types and doses of asthma medication). Some authors defined an intervention/exposure only in terms of the amount of oil known to contain omega-3 fatty acids, while others solely described the amount of omega-3 fatty acid content without any indication of the amount of oil consumed.[59,66,68,71] When whole foods were a component of the on-study intervention/exposure (e.g., hypoallergenic diet), little descriptive information was reported.[52,64,70] Problems relating to the failed control of two confounders (i.e., uncontrolled serving/dose sizes; varying uses of asthma medication with the potential to influence asthma) are described below. Finally, outcomes involving subjective measures of respiratory function tended to be poorly defined, if at all.

What data were reported suggest the presence of flawed methodologies and designs. This observation contradicts the picture of good study quality (i.e., internal validity) for both RCTs and other designs obtained through formal quality assessment. An implication of this discord is addressed later. Nevertheless, restricted, failed or no attempts at blinding, was one of the biggest threats to the internal validity of RCTs. It was the Jadad quality component for which the most studies failed to receive a single point (n = 2/10);[66,68] and, in the case of the Stenius-Aarniala trial, the authors also suggested that their prestudy familiarity with participants likely influenced the latter's improvements in functioning.[68] Very few studies provided information regarding their run-in protocol or duration. Two crossover trials and two noncomparative case series, each of the latter with two exposures, did not include a washout period.[58,68,73,74] In these uncontrolled investigations, participants always received the exposures in the same order.[73,74] The timing of the delivery of the exposures was seldom described.[57,69] Problems associated with some of the delivery methods were presented in the results section regarding safety (e.g., 18 large capsules/day).[57,67] Having so many participants drop out because of such a difficulty raises

questions about the levels of compliance in those who remained in the studies. Also, few treatment studies framed their results in terms of whether they took place during pollen season, a time of great instability in pulmonary functioning for many children and adults.

Very few studies reported having analyzed their data on an intention-to-treat basis.[58,64,69] Some studies reported no withdrawals or dropouts, yet did not indicate that they had analyzed their data in accordance with this principle.[65] Moreover, most treatment studies did not report the results of, or possibly never undertook, tests of significance evaluating between-arm differences in outcomes. They did not present or possibly analyze their data in terms of between-group differences in (percent) change from baseline in a particular outcome. Rather, they tended to present results of data analyzed separately from each group. While this may be appropriate to assess whether, for example, EPA levels in cell membranes actually increased in an omega-3 fatty acids intervention group, independently analyzing study groups' data means failing to benefit from the RCT's capacity to control for the effects of certain key factors that could, in less rigorous designs, make difficult or impossible the relatively unequivocal interpretation of between-group results. The number of significant results reported by studies may be exaggerated as a result.

One option entertained was to have the present review team derive effect sizes and confidence intervals for each study's respiratory outcome data. However, considerable data were not reported in trials, making it difficult to calculate these estimates and their precision. For example, estimation of the effect size requires an estimate of the standard deviation of the difference in outcomes between the treatment and control groups. When the outcome is measured as (percent) change from baseline, incomplete reporting of results may complicate or prevent estimation of this standard deviation. When pretest and posttest means and standard deviations are given, as was the case regarding many of the included trials' outcomes, but standard deviations of the change (from pretest to posttest) are not, one possibility is to use a variance imputation strategy such as that proposed by Follmann et al.[80]

Since observations on individuals are generally correlated, the standard deviation of the change within an individual depends on this correlation. Follmann et al. note that if the population measurement variances are equal pretest and posttest, then "presumably the correlation is at least 0.5, otherwise the pretest-posttest design is less efficient than a test based on just the final measurements." Assuming a correlation of 0.5 (or a correlation estimated from similar trials with more complete reporting of results) then leads to an imputed estimate of the standard deviations of the change. A further assumption that the population change variances are equal in the treatment and control groups then leads to an estimate of the standard deviation of the difference in outcomes between the treatment and control groups. Although this approach may be intuitively appealing, it lacks empirical verification and depends on assumptions of equality of measurement and change variances that may be difficult to verify. Standard deviations imputed in this manner may be very sensitive to the assumed correlation, and resulting effect size estimates may be biased. As a result, it was decided not to follow this strategy. Instead, available results were entered into the respective trials' evidence tables.

That so much important information was missing from reports concerning these next variables' assessment/status and significance, or because available descriptions clearly indicated failures to adequately deal with them, suggest that in planning their studies most investigators did not appreciate the need to control for the threat to the internal validity of their treatment studies posed by at least three key confounders (i.e., population, intervention/exposure, cointervention). If uncontrolled for in treatment studies of any design, these could complicate or

prevent the meaningful interpretability of results regarding the utility of omega-3 fatty acids for asthma. That is, failure to control for their possible influence could make it difficult to unequivocally attribute any result (e.g., significant or null) to the actions of this intervention/exposure. Poor reporting of study details further complicates matters by making it difficult to rule out the possibility that these factors alone or in combination could account for the study results, perhaps as well as the omega-3 fatty acids exposure could. How the following observations relate to the issue of study quality is discussed later.

Asthma is a multi-factorial phenomenon that can be triggered by numerous stimuli or circumstances, including exposure to feathered or furry pets, respiratory infections, smoking, or exposure to secondhand smoke and other pollutants; and, asthma control afforded by medication can deteriorate when an asthmatic is exposed to these. It is thus important in studies evaluating the clinical benefit of an asthma intervention that factors with the potential to influence asthma control be assessed and taken into consideration in trying to understand the results.

For example, if during pollen season a greater number of children seriously affected by pollen are randomized to the placebo arm than to the omega-3 fatty acids intervention arm, then a greater frequency and severity of exacerbations indicating a loss of asthma control in the control group could influence the picture of omega-3 fatty acids' efficacy, when expressed as a between-arm difference in objective or subjective measures of respiratory function. A significant treatment effect might have to be attributed to both the benefit from taking omega-3 fatty acids in the active treatment arm and the significant loss of asthma control in the control group. That said, rarely did a study provide clear information as to whether it had been conducted in or out of pollen season, a time when many asthma reactions are triggered.[67] This raises the possibility that this factor was not adequately controlled for. Only one RCT noted that their study took place out of pollen season,[57] while another intentionally assessed participants both during and outside pollen season.[67]

In general, studies did a poor job of describing how, and if, factors with the potential to influence asthma control were handled. Whether atopic participants, or those with more severe forms of asthma, were distributed equally across study arms was rarely reported.[66] The few RCTs that did report on these factors also demonstrated that randomization does not necessarily neutralize possible key confounding influences by equally distributing participants characterized by these factors across study arms. For example, one RCT noted that the severity ratings were higher at baseline in the omega-3 fatty acids group, which may have contributed to a significant decrease in these scores across treatment.[64] The same pediatric RCT noted, without data, significant between-arm differences in the amount of on-study asthma medication required for acute asthma attacks. Yet, such reports of possible confounders were rare.

Thirty percent of each of the included RCTs and studies with other designs mandated that participants consume certain servings of oil or food rich in omega-3 fatty acids without the use of standardized "dosing" (e.g., capsules). One RCT[66] and two noncomparative case series[59,71] each employed perilla seed oil supplementation, while another RCT delivered its fish and control oils by having it poured from masked bottles.[68] On several occasions, an intake range was specified (e.g., 10-20 g/day) for delivery by spoon[66] or by being poured from a bottle and used as food (e.g., salad oils).[68] A pediatric RCT included a canola diet component,[52] and a non-RCT provided children with a poorly defined hypoallergenic diet.[70] Each report failed to specify exact serving sizes and the amount of omega-3 fatty acids derived from these dietary elements, although one non-RCT report claimed, without data, that their diets were matched for energy intake.[70] The issue of uncontrolled servings/dosing is problematic for the following reason.

Methods of delivering exposures in an uncontrolled fashion preclude knowing exactly what the "exposure" is, and cannot help but lead to variation in individual participants' daily intake across a study. This, in turn, translates into daily changes in a study group's daily consumption, or "exposure," across a study, thereby complicating the interpretation of study results. The exposure is constantly changing within- and between-participants, which is quite different from the situation where a pediatric RCT weight-adjusts its on-study EPA/DHA doses.[64]

In the few instances where consumption data were reported in studies employing uncontrolled servings, they merely illumined that, on average, participants either did not consume the mandated amount, or, in the case of a study employing an instruction pertaining to a range of possible consumption, the maximum allowable amount.[68,71] Nonetheless, a precise and constant definition of the treatment is required to meaningfully interpret study results, and the present treatment studies employing uncontrolled dosing strategies did not achieve this ideal.

Where controlled studies are concerned, uncontrolled servings created other problems, given that control participants also had their exposure delivered in the same, uncontrolled manner. This made it highly unlikely that participants in different study groups received the same amount of oil- or food-as-calories,[66] or that the difference in the amount of omega-3 fatty acid content consumed in the two study arms —reflecting a planned disparity (e.g., 5.4g/day from fish oil vs virtually no g/day from other oils)— was kept constant. Thus, unlike studies of controlled dosing (e.g., identical capsules containing fish oil or olive oil), and notwithstanding compliance, uncontrolled serving/dosing studies fail to provide a precise and constant definition of the exposure as oil/food or omega-3 fatty acid content. The ability to unequivocally interpret study results is thus hindered, while raising serious concerns about the internal validity of the three treatment studies conducted in Japan with perilla seed supplementation and which never failed to find a significant clinical effect.[59,66,71]

The third confounding factor relates to the impact on results of the on-study use of corticosteroids. It is important to know exactly how many corticosteroid users were included in a given study, at what doses, and whether or not these doses were changed (and how) due to improved or failing asthma control. Yet, knowing these patterns of use will not necessarily make it less difficult to meaningfully interpret study results. The reason is that corticosteroid users may have had their doses altered across a study, or, in controlled investigations the distributions of users and of doses across study groups may have been unequal. In these circumstances, the ability of corticosteroids to improve respiratory outcomes particularly over the longterm can mask the benefits associated with omega-3 fatty acid use. For example, in sensing a lessening of their asthma control, participants receiving a placebo in an RCT might have their corticosteroid dose increased. This could improve respiratory functioning to a level equal to that produced by the omega-3 fatty acids intervention given to the other study group. A lack of cross-arm equivalence, either produced because of a change in one study arm, or because more corticosteroid users were enrolled in the control arm to begin with,[67] could eliminate any between-group differences in outcome that would denote a significant clinical effect in favor of the omega-3 fatty acids exposure. Also, within a single group of participants, the effects of increased doses of corticosteroids can bring about improved respiratory functioning thought to be attributable to the omega-3 fatty acids. Failing to know the exact role played by corticosteroids in a study owing to inadequate study design, reporting, or both, makes it impossible to rule out their possible impact on study results.[52]

In the relevant studies of all design types, there was a scarcity of information regarding users of corticosteroids and their doses, including to which arms users had been allocated.[57,62,64] Even

less information was provided concerning whether doses of these drugs were kept constant or how they may have changed across the study for participants; or, whether the number of users and their doses were equivalent across study groups in controlled investigations. Yet, one RCT did ask participants to maintain a constant use of inhaled corticosteroids, although compliance data were not reported.[67] Another trial reporting no clinical effects claimed that similar oral corticosteroid doses had been observed for the two study arms.[54] Finally, having all participants not take corticosteroids might provide one of the clearest tests of the benefits of omega-3 fatty acids,[69] especially since Emelyanov et al.'s RCT of corticosteroid-naïve adults also excluded current or ex-smokers, provided controlled dosing via capsules, controlled for the intake of calories across study arms, and randomized one of the largest samples (n = 46) identified by the present review.[69]

Thus, the goal with respect to these three factors is to assess and control their confounding influences. Otherwise, it may be impossible to unequivocally attribute significant or null clinical effects to the impact of the omega-3 fatty acids. Given how poorly the present collection of studies fared in achieving this goal, it is difficult to place much trust in the internal validity of many of the treatment studies in spite of their good Jadad-defined quality. One RCT selected only nonsmokers, yet failed to report whether they had also obtained information allowing them to rule out participants' smoking history.[67] Another factor worth noting for its possible influence as a confounder, yet for which there was a similar lack of appreciation in the present studies, is background diet. Very few investigators asked participants to maintain a constant background diet to assure that changes thereto would not bring additional variation to the task of explaining results.[57,70]

On the other hand, the primary prevention studies were far more likely to recognize the need to control for at least two of these confounders (i.e., factors influencing asthma control, and specifying exposures)[48] although these investigations were not conducted without limitations of their own. Most of the observational studies adopted a cross-sectional perspective whereby the timeframes associated with the assessment of the frequency of dietary fish intake were likely too short (e.g., the last month, current intake)[48,76] to reliably shed light on the possible influence of lifetime dietary intake patterns on the risk of developing asthma.[78] Moreover, in that interview questionnaires likely produce less misclassification of food-related information than is found in self-administered surveys, results using the former strategy might have been quite different.[48] Unfortunately, Huang et al.'s interview data regarding PUFA use were not broken down by type of PUFA.[48]

The primary prevention studies also investigated the possible impact of different definitions of fish. For example, some identified the types of (e.g., oily) fish rich in omega-3 fatty acids,[77] whereas at least one of the studies including adolescents did not make any distinctions regarding the type of fish.[76] This might account for the positive relationship between fish intake and asthma prevalence. Had only fish assumed to be rich in omega-3 fatty acids been investigated, the positive association might have disappeared. The other study with adolescents did differentiate by type of fish, yet their sample was small.[48] No studies directly assessed the possibility that the ways of preparing fish rich in omega-3 fatty acids (e.g., frying; salting) could influence results by altering their fatty acid content.[48] Finally, no study attempted a comprehensive analysis of the omega-3 fatty acid content of the fish participants had eaten, at best preferring to define "oily fish" as containing more than 2% fat, for example.[76,77] As with some of the treatment studies, the primary prevention RCT included, as part of its intervention, uncontrolled servings of margarine and oils.[51]

The Decision to Forego Meta-Analysis

A number of criteria required satisfaction before meta-analysis could be considered. First, only RCTs were eligible, because of their greater potential to control for certain biases in meaningfully elucidating questions about the efficacy of any intervention/exposure. Second, it was established that, given the differences in clinical picture associated with age, data from pediatric and adult studies should not be combined in qualitative or quantitative synthesis. At the same time there had to be at least two studies with data capturing the same outcome construct (e.g., asthma severity). Yet, it is likely the case that having data contributed by more than two studies is best, especially if the studies contain small samples. More reliable estimates of variation may be derived.

Regarding Questions 1 (improving respiratory outcomes), 2 (impact of effect modifiers), and 3 (influencing mediators of inflammation), there were only seven adult and two pediatric treatment trials; and, meta-analysis with data from children was impossible given that the RCTs neither employed the same clinical or intermediate (i.e., mediators of inflammation) outcomes. One RCT had to be excluded from consideration for quantitative synthesis since it did not provide demographic information sufficient to determine even the age of participants.[65]

The varying definitions of symptom scores observed in three RCTs ruled out any possibility of meta-analysis;[57,58,67] and, while there were four separate occasions when at least four RCTs employed the same clinical outcome (FEV_1, AM PEF, PM PEF, bronchodilator use), several important observations translated into a decision to forego meta-analysis.

First, to meaningfully compare, then combine, RCTs evaluating the possible impact of omega-3 fatty acids, the contrasts involving a treatment and comparator should be similar or the same. In five of seven RCTs, the contrast involved controlled dosing of fish oils (i.e., EPA/DHA) compared with similar olive oil capsules.[57,58,67-69] One other RCT compared high- versus low-dose EPA ethyl ester, while a seventh compared uncontrolled servings of perilla seed oil and corn oil.[66] The interpretability of a pooled estimate combining data from one of the latter two trials with any of the five studies comparing fish oil and an olive oil control would be limited. The contrasts are too dissimilar. This restricts the pool of studies.

Second, as discussed previously, there was too much missing, limited or contradictory information concerning both the adult study populations (e.g., asthma diagnosis details, including severity, duration, and concomitants/triggers) and study interventions (e.g., omega-3 fatty acid content).[66] Moreover, in studies of older adults, and for whom descriptions of current or past smoking were typically unavailable, there is little confidence that trialists reliably excluded adults with COPD.[54,58,66] The situation that these examples illustrate does not permit an unambiguous appreciation of the populations and interventions to whom any pooled results could be generalized. Combining studies whose specific potential for generalization is uniformly low, or that vary on this basis, would yield a single estimate without a well-defined target. In the present collection of studies, so many population and intervention data were missing, making it difficult to generalize any meta-analytic results.

Third, there were too many studies of adults with flawed or limited research designs and methodologies to be able to meaningfully determine the relative contributions of each of the wanted and unwanted influences (e.g., the above-noted confounders) on a pooled effect. Fourth, certain study populations were too different to consider combining data from them. For example, one adult trial randomized in-patients,[66] whereas all other samples included out-patients; and, one RCT studied allergic asthmatics during pollen season.[67] Also, there was likely

strong heterogeneity in the background diets given the countries in which the studies were conducted. Overall, while there were sufficient numbers of RCT to consider, a decision was made to forego any meta-analysis.

Regarding the primary outcome, FEV_1, three very different intervention-comparator contrasts were represented. They included: uncontrolled perilla seed oil supplementation compared with uncontrolled corn oil supplementation;[66] a high as opposed to a low dose EPA ethyl ester;[54] and, EPA/DHA from green-lipped mussel versus olive oil.[69] This lack of comparability in contrasts, combined with other key differences (e.g., in-patients in a very structured environment who received the uncontrolled supplementation;[66] very different background diets) made it inappropriate to pool their data. The situations with respect to the other three outcomes are somewhat more complicated.

Five studies reported having collected AM PEF data, yet one did not report data.[58] As well, Okamoto et al. gave uncontrolled servings of oil to in-patients,[66] while Stenius-Aarniala et al. used uncontrolled servings of oil in their 3-phase crossover RCT.[68] This intervention-related problem complicates the inclusion of these two studies in any synthesis. Stenius-Aarniala also failed to report inclusion criteria and, whether corticosteroid use was balanced across study arms.[68] They also did not employ a washout, and thus control for a possible carryover effect; and, they never established blinding given there was no attempt to conceal the taste of the dietary oil supplementation. Furthermore, Stenius-Aarniala et al. acknowledged having randomized three smokers and 12 ex-smokers, yet never made it clear that they had ruled out COPD, or that these participants were equally distributed across the study arms. Finally, seven participants withdrew due to problems with the taste of the oil, although there was no indication of the study arm from which they withdrew. This RCT was extremely flawed, and received the lowest Jadad total quality score of all trials. Their total quality score of 2 indicates low internal validity.

Also with respect to AM PEF, Thien et al.'s study on the one hand provided insufficient data regarding their population (e.g., asthma severity; diagnostic method), while at the same time suggesting that they had randomized a very unstable population (i.e., allergic asthmatics studied during and outside pollen season) which was very different from any other study population in the present review.[67] They also did not establish participants' smoker status, appeared only to begin to collect "pretreatment" data at the same time treatment began, and reported data only for completers. Almost a third of participants left the study due to nausea or vomiting, in addition to various difficulties swallowing the 18 capsules per day. They nevertheless received a Jadad total quality score of 4 on the strength of solid blinding, and a clear description of participants lost to followup.

Arm et al. failed to report inclusion or exclusion criteria, the method by which the diagnosis was determined, participants' smoker status, and whether the use of inhaled corticosteroids was balanced across the study arms.[57] They also reported three dropouts due to problems with the size and number of capsules. Finally, notwithstanding their use of a unique source of EPA/DHA (i.e., green-lipped mussel), Emelyanov et al.'s RCT was strong methodologically.[69] All studies that obtained AM PEF data were conducted in different countries, indicating a wide divergence in background diets.

Thus, on the basis of the aforementioned limitations and problems, as well as their lack of comparability, meta-analysis of AM PEF data was not considered appropriate. All of these same studies also provided either PM PEF[57,58,67-69] or bronchodilator use data,[57,58,67,69] thereby making inappropriate any quantitative pooling of these datasets. Three of these studies contributed data pertaining to the impact of omega-3 fatty acid supplementation on mediators of

inflammation.[54,57,66] On the basis of divergent intervention-comparator contrasts and the above-noted problems, meta-analysis was not conducted.

A recent Cochrane review exclusively of fish oils in asthma conducted a number of meta-analyses of respiratory outcomes.[35] As with the decision made in the present review, they did not pool studies with different intervention-comparator contrasts. On the other hand, they did enter the Dry and Vincent trial data[65] into meta-analysis in spite of a lack of population-related information that would have permitted this RCT's classification as an adult or pediatric investigation. Moreover, they pooled data from this trial with that from a pediatric RCT,[52] and failed to find a significant effect for FEV_1. While they performed numerous analyses for PEF (undefined), including for the beginning and the end of studies, their analysis of change from baseline data revealed a nonsignificant effect. PEF data from one pediatric trial[52] were pooled with those from three adult study reports.[56,57,67] In doing so, Woods et al.[35] likely entered duplicate data since the two Arm et al. trial reports included a large number of the same participants.[56,57] Analysis of asthma symptom scores included data from scales assessing varying constructs, and revealed no effect. Data from two pediatric studies[52,64] and three adult study reports[56,57,67] were pooled, including those from the Arm et al. publications.[56,57] Heterogeneously defined asthma medication data were then combined, again without finding a significant effect. One pediatric[52] and the two Arm et al. datasets[56,57] were included with results from Thien et al.[67] Data pertaining to varying definitions of bronchial hyper-responsiveness likewise failed to reveal a significant benefit. Results from two studies randomizing children,[52,64] the Thien et al. trial,[67] and from the Arm et al. publications[56,57] were combined. When bronchial hyper-responsiveness results from children and adults were meta-analyzed separately, no benefits were found for fish oil supplementation. Nonsignificant effects were also reported for asthma symptom score results when pediatric and adult data were analyzed independently.

Whether or not the Cochrane review's results suggest what the present review might have found had meta-analysis been conducted for respiratory outcomes, it is clear that the Cochrane undertaking failed to critically assess included studies so as to seriously consider foregoing meta-analysis, appeared to enter duplicate data, pooled results from children and adults, and included data from a trial without any specification of basic information such as age. Even so, they reported no benefit associated with fish oil supplementation.

Meta-analysis of primary prevention data was not considered, given the existence of one RCT.[51] Too few safety data were observed to consider their further synthesis. Overall, poor reporting practices, which led to an inability to know whether and how these or other confounders might have influenced individual treatment RCT results, together with the lack of comparability in many of the RCTs' parameters (e.g., intervention-comparator contrasts), led to the decision to forego meta-analysis. Any pooled estimates would have been derived within a context instilling as little confidence in the appropriateness of the extrapolations of results as in the validity of the results themselves.

Clinical Implications

For those participants entered into treatment (or primary prevention) studies there is no notable safety profile associated with the consumption of omega-3 fatty acid content. As well, there is no consistent evidence, or any evidence from well-designed and sufficiently powered

studies to recommend their use or avoidance to treat asthma in populations in North America, or in those countries in which their efficacy was tested. There is thus no way to conclude anything definitive about their therapeutic potential. Moreover, to which factors (e.g., type, source or dose of omega-3 fatty acids) their value as a therapy can be attributed cannot be established based on the present evidence. While some studies did investigate the impact of high doses,[54] it is clear that more studies of this sort, albeit with more than 12 participants, must be conducted. Various sources (e.g., marine, seed) and types of omega-3 fatty acid content (e.g., EPA, EPA/DHA, ALA) were also investigated, but they too require proper testing in trials that are larger and better-controlled. At present, from treatment studies, perhaps the only consistent observation regarding the short- or longterm use of omega-3 fatty acids with the types and doses herein evaluated is that it is unlikely to do notable harm.

While the results obtained by Emelyanov et al. are interesting because they gave a relatively large adult sample a low dose of a unique marine source (i.e., 200mg/d of extract of green-lipped mussel, with 400 mg/d olive oil vs 600mg/d olive oil), while also controlling several confounders (i.e., corticosteroid-naïve; no current or ex-smokers; controlled dosing; equal intake of calories across study arms), more research is required to establish that their four (of seven) significant clinical benefits did not occur because of some undetermined factors (e.g., blinding broken). Likewise, more work is required to understand how three studies of invariably limited intervention length ($\leq$4 weeks) failed to produce a nonsignificant clinical effect when uncontrolled doses of perilla seed oil, and thus undefined amounts of ALA, were given to adults.[59,66,71] Further testing might show that the observed clinical effects diminish over longer periods of time, the consumed doses of ALA were extremely high, or, in the case of two of these studies, the results were obtained because in-patients in controlled environments had been enrolled.[59,66] To better understand the possible utility of this type/source of omega-3 fatty acids, more research is needed.

One other factor that needs to be accounted for with respect to the perilla seed oil supplementation is that all three studies were conducted in Japan, where the omega-6/omega-3 fatty acid ratio in the typical diet (4:1) is much lower than in the United States (10-30:1), for example.[81-83] The lower ratio in Japan might make it more likely that this country's population can be affected by additional omega-3 fatty acid supplementation. With "less competition" from AA for the same metabolic pathways, EPA and DHA may be better able to affect the inflammation-based process by which the symptoms of asthma are produced. Also, it may explain why, in spite of poor air quality and higher rates of smoking,[84] for example, asthma is less prevalent in Japan (0.7%) than it is worldwide (5%).[85] As an aside, a crude assessment of the numbers of significant result relating to respiratory outcomes showed that clinical benefits accruing to omega-3 fatty acid supplementation were more likely in RCTs (6/6 in two trials[64,66] vs 6/38 in the remaining eight trials) and noncomparative case series investigated in Japan (13/15 in three noncomparative case series[59,62,71] vs 15/35 in the other 6 studies) than in all other countries combined.

At the same time, it may be the case that the continuing high consumption of omega-6 fatty acids in countries such as the United States can offset the possible asthma-related benefits from omega-3 fatty acid supplementation. Some have even speculated that a highly imbalanced omega-6/omega-3 intake ratio in favor of the omega-6 fatty acids predisposes individuals to asthma.[30] Correct or not, it is likely essential that background diet be accounted for in the interpretation of individual study results, as well as any between-study differences.[24] In trying to explain the impact of PUFA consumption in asthma, it is also likely important to take into

consideration the possibility that populations may vary in terms of the genetic factors influencing the expression of the asthma phenotype. It may also be best in planning treatment studies, as was seen in a few included studies[70,73] and the primary prevention RCT,[51] to try to modify these PUFAs simultaneously.

Broughton et al. have suggested that it is the ratio of omega-6 to omega-3 fatty acid consumption that inhibits or attenuates inflammatory activity, leading to reliable respiratory benefits.[73] They have noted that modifying this ratio is critical for altering eicosanoid biosynthesis in rats. One implication is that, while providing omega-3 fatty acid supplementation alone necessarily alters the intake ratio involving omega-3 and omega-6 fatty acids, it is the active, marked reduction in omega-6 fatty acid ingestion that should likely accompany omega-3 fatty acid supplementation. With so few studies in the present evidence collection measuring background diet, however, study participants' intake of all PUFAs largely remains unknown.

Determining whether, and how, the clinical benefits of omega-3 fatty acid supplementation are made possible by their influence on mediators of inflammation was not an objective of the present systematic review. Nonetheless, an informal assessment is likely appropriate. There were few studies that observed significant and consistent influences of omega-3 fatty acids on mediators of inflammation (i.e., any leukotriene series), as well as too few studies that found significant and consistent clinical benefits while also having collected data regarding their impact on mediators of inflammation. Possible reasons for both observations include poorly designed studies, varying populations, and, small sample sizes. Before these observations are scrutinized further, however, an even more basic question may be whether there is evidence from the present collection of treatment studies that the omega-3 fatty acid exposures were incorporated into the biosystems of participants receiving them. EPA content did typically increase significantly although a concomitant, significant decrease in the AA content of tissue/plasma was not reliably observed.[57,67,68,74] But, this picture did not correlate well with significant clinical effects. Three of four nonsignificant clinical effects for AM PEF were associated with increased fatty acid content in tissue/plasma,[57,67,68,74] and, an RCT reported increased fatty acid content yet nonsignificant clinical effects for FEV_1 as well as five other respiratory outcomes.[54]

Five studies were identified which employed one or more of the four respiratory outcomes (FEV_1, AM PEF, PM PEF, bronchodilator use) meeting the criteria to address Question 2 (i.e., at least two studies, with at least one demonstrating a significant clinical effect), while also reporting data with respect to the impact of omega-3 fatty acids on mediators of inflammation. Three were RCTs[54,57,66]) and two were noncomparative case series.[59,71] The only pattern highlighting a mediator of inflammation that was exclusively associated with a significant clinical effect involved the suppression of LTC_4. That is, when LTC_4 generation was significantly suppressed, two RCTs and one noncomparative case series reported a significant clinical effect (i.e., increase) for AM PEF.[59,66,71] Interestingly enough, all three studies had used uncontrolled perilla seed supplementation. Also, when perilla seed supplementation led to a significant suppression of both LTB_4 and LTC_4 produced by leukocytes, two of these same studies reported a significant increase in AM PEF,[59,66] and there was a significant effect for FEV_1 in one of these trials.[66] Yet, two RCTs observed no benefit from fish oil supplementation despite a substantial attenuation of neutrophil chemotactic responses to LTB_4, fMLP, and C5a.[54,57] Unfortunately, given the limitations of these studies (e.g., small samples), all that these observations can suggest are possible future directions for research.

With the present studies, it is thus impossible to adequately address the issue of the observed lack of "translation" into significant clinical effects of some of the observed changes in fatty acid content in tissue/plasma or the observed influences on mediators of inflammation. Future research with asthmatic participants may discover that the present servings/doses of omega-3 fatty acids had been too small, mediators associated with pathways other than the lipoxygenase and cyclooxygenase ones are actually more important to the pathogenesis or treatment of asthma,[78] or that without also intentionally altering the intake of omega-6 fatty acids, positive impacts on both the mediators of inflammation and respiratory outcomes may be unlikely. Of note, the small numbers of study identified by this review made it impossible to adequately assess the relationship between the less "potent" LTB_5, and clinical effects.[86] One small RCT (n = 12) in which a significant increase in LTB_5 was observed, produced a nonsignificant effect for FEV_1.[54] Finally, the lipid mediators of inflammation were primarily evaluated in the present evidence collection; and, nonsignificant results regarding TNF-a were obtained from a pediatric study.[52]

One of this report's peer reviewers highlighted a very recently published study that, because of its late arrival, could not be systematically reviewed in the present review. Nevertheless, it is summarized here because it identified another exposure that might prove interesting in future studies of the impact of omega-3 fatty acids on leukotriene biosynthesis. In a three arm trial, 43 adults with mild to moderate, atopic asthma were randomized to receive, for 4 weeks, either 10 g of an emulsion containing 0.75 GLA and 0.5 g EPA, 15 g of this emulsion (1.13 g GLA and 0.75 g EPA), or, an olive oil placebo.[87] Results indicated a significant increase in plasma levels of EPA, DHA, dihommogamma-linolenic acid, and GLA; and, relative to placebo, stimulated whole blood LTB_4 biosynthesis decreased significantly in both active study arms. What is interesting is that GLA and EPA derive from different "parent" PUFAs.

It may also be too soon to conclude with respect to asthma, that omega-3 fatty acid supplementation is a better primary prevention than a therapeutic. While the results exclusively with children suggest a protective role, the studies involving adolescents do not. However, the failure to distinguish consumption data by type of fish in one study,[76] and the very small sample in the other,[48] might account for the positive associations of fish intake and asthma prevalence for adolescents. The adult study[75] found no relationship, but this study also did not distinguish by fish type in the same way that one pediatric study had, for example.[77] Interestingly enough, the other study involving children likewise did not draw such distinctions, yet it still reported a significant negative correlation between fish intake and asthma prevalence.[78] The reason for this result is unknown. Unfortunately, none of the studies reported having guesstimated the omega-3 fatty acid content of their subjects' exposures. What remains to be seen is whether or not the speculation that the capacity to alter risk may be inversely related to age is supported by future research. What appears certain is that a strong assessment of the possible protective role of omega-3 fatty acids in early childhood is currently underway.[51]

Two additional, recently published studies were pointed out by the above-noted peer reviewer. While they also arrived too late to be systematically reviewed, their key observations are likely worth mentioning. Nafstad et al. prospectively evaluated a cohort of Norwegian children and found that an inverse relationship between the early dietary intake of (any) fish (i.e., in the first 12 months of life) and the risk of asthma at age 4 years (n = 2,531) was only statistically significant in the bivariate analysis.[88] Adjusting for many factors such as parental atopy and respiratory tract infections, multivariate analysis did not reveal a statistically significant association. This appears to confirm the collective observation from the

aforementioned primary prevention studies with children. Finally, Woods et al.'s adjusted and unadjusted analyses demonstrated a lack of association in young Australian adults (aged 20-44 years; n = 1,601) between fish intake (types undefined) and asthma risk.[89] This seems to confirm Troisi et al.'s finding from the Nurses study.[75] Since neither of these studies was systematically reviewed, their key findings must be taken with caution.

It may turn out that the most profound protective effect requires the incorporation of omega-3 fatty acids in one's weekly diet beginning early in life. It may also be found that the propensity for eating fish starting early in life is naturally associated with a lesser intake of foods rich in omega-6 fatty acids. Yet, as children age, and with the increasing influence of a less balanced intake of omega-3 and omega-6 fatty acids, the possibility for protection against asthma diminishes. Eventually, it may be observed that different ratios, or balances, of omega-6/omega-3 intake increase and decrease the risk of asthma.[84] The possible protective effect of non-marine sources (e.g., ALA) may be a question worth exploring as well.

Other studies have looked at the possible protective effects of dietary fish intake, yet each was excluded from the review because, instead of evaluating its relationship to asthma, it assessed possible associations with respiratory symptoms (wheeze, bronchitis)[90] or FEV_1 in adults over 29 years of age,[91] respiratory symptoms (e.g., wheeze) in children 7 to 11 years of age[92] or adults 20 to 44 years of age,[93] and, bronchial hyper-responsiveness in children and adults.[94] A final study was excluded because it did not specifically evaluate the possible impact of omega-3 fatty acids in their assessment of the relationship of dietary PUFA intake and asthma risk.[95]

Research Implications and Possibilities

The research implications of the present findings are likely singular in pointing out the need for more research to address the questions of treatment and prevention. It is unlikely that attempts to try and explain the inconsistent results concerning treatment will ever yield a definitive answer to the question of efficacy. Moreover, such an attempt may be irrelevant if one of the key concerns is finding out whether omega-3 fatty acid supplementation can serve as an efficacious therapeutic for North American children and adults. Almost none of the included studies involved such populations with asthma. Asthma is an important health care problem, and it might be wise to plan some next research steps.

That there are no studies of secondary prevention may say as much about the difficulties inherent in planning a longterm study to evaluate the impact of omega-3 fatty acid supplementation on the progression of asthma as in conducting it. Such an undertaking presupposes knowing the exact nature and timing of the milestones (e.g., fundamental changes in respiratory functioning) marking the "natural progression" of asthma, and whose trajectory might be altered by omega-3 fatty acid supplementation (with or without modification of omega-6 fatty acid intake). At this time, what is known about the natural progression of asthma needs to be fully appreciated to permit designing such a study. On the other hand, the best test to date with respect to primary prevention is ongoing,[51] and its results may be pivotal in identifying the dietary/lifestyle changes required to prevent the development of asthma in children at risk. Early intervention may turn out to be the most cost-effective strategy.

With respect to the subject of treatment, it may be useful to design a large, well-powered, multi-site RCT in North America comparing three study arms, and with stratification. The study

would follow the CONSORT guidelines for reporting so that study quality could be adequately appraised, and the results effectively compared with those highlighted by other studies. Equal numbers of adult males and females would be randomized to receive controlled dosing (i.e., capsules) of fish oil (i.e., EPA/DHA), perilla seed oil (i.e., ALA), or controls (likely olive oil). The goal would be to evaluate the absolute efficacy of each of the omega-3 fatty acid interventions (vs placebo), as well as their comparative efficacy.

Appropriate methods to randomize participants as well as conceal these allocations would be employed. Double-blinding may require strengthening by altering the taste of the oils (e.g., peppermint flavoring).[96] Capsules would be identical. The investigators would need to be mindful of another key issue. The identity of the exposure, including the exact types and amounts of omega-3 fatty acids, must be clearly known. Different fish oils, or even the "same" fish oil from a single manufacturer across or within batches, may contain different ratios of EPA and DHA; and, if these fish oils vary in terms of their ratios of EPA to DHA, this is a possible confounder when the dose of omega-3 fatty acids is calculated as "EPA plus DHA." This calls for an in-depth assessment of the composition and purity of each exposure. As well, the presence and nature of other active agents perhaps added to the oils would need to be established.

Stratification would be by dose (high vs low), with the number and contents of capsules taken by all participants used to control the amount of oil/calorie intake. Control oil would be added to active interventions, as needed, to produce the low dose. Pilot testing could establish reasonable definitions of high and low doses especially for the perilla seed oil intervention. Yet, whether the intervention contains perilla seed oil, or flaxseed oil, as others might recommend instead as a source of ALA, there remains an as yet unanswered question posed from the point of view of biology: given its status as a "parent" omega-3 fatty acid, and relative to EPA and DHA, could increased ALA intake possibly affect asthma?

Half of the participants randomized to each arm would also have their background diet adjusted based on an assessment of their lifetime (assessed by decade) intake of omega-6 fatty acids, including patterns of preparing all foods. The goal would be to establish a more balanced omega-6/omega-3 intake ratio. Monthly assessments of dietary intake would be conducted. The remaining half of participants would have their lifetime background diet assessed prior to the study and followed on a monthly basis. A request would be made of this second group of participants to maintain their prestudy diet across the study. A panel of experts could determine the appropriate definition of the modified omega-6/omega-3 intake ratio as well as the length of the intervention period needed to observe a meaningful clinical effect. Compliance for all participants would be monitored closely via monthly contacts. Stratification by dose and diet would allow secondary questions to be investigated.

Unfortunately, there is no shortage of candidate participants for inclusion in such a study. To qualify, each would have to receive a diagnosis of asthma following established professional criteria. Data would be obtained concerning concomitants/triggers with the potential to influence asthma control (e.g., allergies), as well as the duration and severity of asthma determined via pre-established professional criteria. The prestudy severity of each of the concomitants/triggers would be ascertained. A judgment regarding how well the prestudy asthma is being controlled by medication could be derived. Data concerning all prestudy asthma medications, and doses, would be collected and participants would be asked to maintain their prestudy regimen while on-study. They would also be asked to notify the appropriate study liaison should their on-study asthma status change or their medication require modification. A predetermined protocol would

guide all decisions. A clear indication of possible differences among study arms for asthma- and asthma medication-related variables would be established at baseline, although controlling experimentally for either of these variables might make the research design too complex.

It might also be easier to exclude adults who are current and ex-smokers, thereby excluding adults with possible COPD. Otherwise, this would constitute another variable requiring control. Excluded would be individuals exhibiting bleeding or clotting disorders. The inclusion of equal numbers of males and females is suggested by the possibility that hormonally mediated genetic processes may make the male lung more susceptible to exposures, result in lung immaturity in utero, and yield a different picture of asthma than is observed in females.[97] Any parallel study of children would require distinguishing asthma and disorders of wheezing as well as weight-adjusting treatment doses, for example.

While multiple respiratory outcomes could be used, it is important to employ an established standard to assess pulmonary function. FEV_1 is a likely candidate for primary outcome yet other objective measures (e.g., PEF; bronchodilator use; health care utilization), and even one subjective measure (e.g., functional status), might be appropriate. Changes produced by supplementation would turn out to be respiratory outcome/function-dependent. Modifications to medication use would also be measured, and this might indicate either worsening or improving asthma. A panel of experts could determine the most pertinent ways to assess fatty acid compositions in tissue/plasma, as well as those mediators of inflammation that may be impacted by supplementation. In the active treatment arms, identifying those who do and those who do not respond with the significantly increased suppression of LTC_4 by leukocytes in response to omega-3 fatty acid supplementation may help predict those for whom the treatment does and does not produce some clinical benefit.[71]

The details of this or any other proposed study require consultation and collaboration. Moreover, if there is a belief that there may be some asthma-related benefit associated with taking omega-3 fatty acid supplementation, then some might argue that only by randomizing North Americans will results be observed that exhibit the degree of applicability required to elucidate the treatment of asthma in this population. Others might suggest that research also needs to be done to clearly ascertain whether or not North Americans and other populations vary sufficiently on any bases, including or beyond their patterns of omega-6/omega-3 fatty acid intake (e.g., cultural; racial-ethnic; environmental; genetic), to justify the above-noted divide when it comes to generalizing results. And, if significant empirical differences are not observed, it may become untenable to suggest that results from studies of those living outside North America cannot be generalized to North Americans. Still others might argue that, given the methodologic problems observed with respect to the present evidence base, it is more important at this point in time to conduct small, inexpensive trials to further clarify the mechanisms responsible for the putative beneficial effect of omega-3 fatty acids in asthma while also determining key data such as "the appropriate dose" required to yield reliable effects.

Limitations of the Review

The assessment of RCT quality was conducted using validated instruments; and, notwithstanding the uniformly "unclear" status of studies' handling of the concealment of allocation, the grades indicated good quality. However, in exclusively utilizing the four

constructs provided by the Jadad and Schulz instruments, this review missed an opportunity to find that, using other constructs, the quality of the present collection of RCTs was actually low. If one were to measure quality in terms of each study's reporting of having controlled for confounders discussed previously (e.g., lack of cross-arm equivalence in asthma medication users and doses), most of the studies would have received a grade of "unclear" or "inadequate." A failure to explicitly address the issues raised by these possible threats to internal validity means their confounding influences in the studies cannot be ruled out.

A similarly restricted definition of study quality likely characterized assessments of studies using designs other than an RCT. While the Downs and Black instrument from which the five items were selected, is a validated instrument, the fact that these typically small studies with many methodological limitations received a mean score likely indicating good quality is misleading. As with the evaluation of RCTs, a more comprehensive quality assessment of these other study designs (e.g., inadequate reporting of how, and if, asthma medication changed in a cohort across a study) likely would have yielded a very different picture. That this tool was insensitive to certain key quality issues required that this review's authors discuss these issues in considerable detail.

It is conceivable that identifying the country in which a study was conducted may have been all that was needed to assign an applicability rating, and may account for the observation that, on only one of 26 occasions did the independent assessors disagree. Nevertheless, the two applicability tools developed for the purposes of this review were never validated. More work is required to validate the assessment of this construct in systematic reviews.

Finally, while one publication reporting data from the NHANES II survey was captured and excluded because asthma per se had not been investigated,[90] another publication referring to results of this same, large study was missed when electronic and manual searches were conducted for this review.[97] It was discovered only after the present qualitative synthesis had been completed. Considered evidence pertaining to primary prevention, this study revealed that, after adjusting for age, gender, and race, fish intake (undefined fish types) in proportions per week for American children ages six months to eleven years of age neither predicted asthma nor wheeze.[97] This finding contradicts the picture of a protective effect seen for Australian and Japanese children.[77,78] Yet, it is consistent with the findings from the other American primary prevention study, which likewise reported a nonsignificant association between fish intake (undefined fish types) and asthma prevalence in adult nurses. The difference between the findings of this pediatric study and the others reported earlier[77,78] may be related to sampling methods or the possibility that the American diet contains enough omega-6 fatty acid content to offset the benefits of eating fish, even in children.

Conclusion

The present findings suggest that, with omega-3 fatty acid supplementation intended to influence asthma, there is little probability of harm beyond occasional mild discomfort. The most frequent troublesome events were produced by the delivery of the oils by large numbers and sizes of capsule. On the other hand, the lack of sufficiently consistent evidence, as well as a paucity of evidence from well-designed, well-conducted and adequately powered studies, suggests that no definitive conclusion can yet be drawn regarding the efficacy of omega-3 fatty acid supplementation as a treatment for asthma in children or adults. Likewise, nothing specific

can be concluded regarding the role of specific sources, types or doses of omega-3 fatty acid content in producing significant clinical effects. One possible explanation for the inconsistent findings is the heterogeneity in definitions of settings, populations, interventions/exposures, and the types and doses of asthma medication. To afford generalizability to adult and pediatric populations of North American asthmatic, or to those at risk, some research may need to be conducted on this continent. The present review highlighted some of the methodological issues worth considering in treatment RCTs. An interesting hypothesis requiring investigation relates to the possible asthma-related benefits associated with actively decreasing levels of omega-6 fatty acid intake concurrent with increasing the intake of omega-3 fatty acids.

Having too few well-designed studies with which to adequately address this question means that nothing definitive can be said about the influence of omega-3 fatty acids on those mediators of inflammation thought to be implicated in the pathogenesis of asthma, or about the actual role played by these mediators in asthma. More research is required.

No studies were identified which investigated the potential of omega-3 fatty acids as secondary prevention. Primary prevention attempts were found, again without unanimity in their findings. While two studies of children outside North America noted a protective effect of dietary fish intake for asthma, one recently identified American study reported no benefit. Moreover, studies outside North America and primarily including adolescents found that dietary fish intake actually increased the risk of asthma. The only study involving adults found no relationship between these variables. However, these studies employed varying sampling methods and definitions of both the frequency of fish intake and, fish types. Likely the most promising attempt to use omega-3 fatty acids as primary prevention involves a large, ongoing RCT of expectant mothers whose children at risk for asthma are being followed for five years. To date, 18-month, interim analysis data are too unreliable given the difficulties in diagnosing asthma in children this young.

At this point in time, aside from an acceptable safety profile, it is impossible to definitively conclude anything with respect to the value of using omega-3 fatty acid supplementation in asthma for adults or children either in or beyond North America.

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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
COPD	Chronic obstructive pulmonary disease
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
FEF_{25-75}	Forced mid expiratory flow rate
FEV_1	Forced expiratory volume in one second
fMCP	Formyl-methionyl-leucyl-phenylalanine
FVC	Forced vital capacity
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
PEF	Peak expiratory flow
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
V_{25}	Maximal expiratory flow at 25% of the forced vital capacity
VLDL	Very low density lipoprotein

Appendix A. Search Strategies

Search Strategy 1

1. exp Asthma/
2. Bronchial hyperreactivity/
3. asthma$.mp.
4. wheez$.mp.
5. respiratory sounds/
6. exp LEUKOTRIENES/
7. leukotrien$.mp.
8. (lung$ or pulmon$ or respirat$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
9. exp INFLAMMATION/
10. exp Inflammation Mediators/
11. inflammat$.mp.
12. 8 and (or/9-11)
13. or/1-7,12
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. limit 46 to human

Search Strategy 2

#1 omega 3

#2 ("essential-fatty-acids" in SU) or ("linolenic-acid" in SU)

#3 ("docosahexaenoic-acid" in SU) or ("eicosapentaenoic-acid" in SU)

#4 explode "plant-oils" in SU

#5 explode "fish-oils" in SU

#6 "fish-consumption" in SU

#7 "polyenoic-fatty-acids" in SU

#8 "polyunsaturated-fats" in SU

#9 "dietary-fat" in SU

#10 (n 3 fatty acid* or omega 3) in ti,ab,id

#11 (docosahexanoic or docosahexaenoic) in ti,ab,id

#12 (eicosapentanoic or eicosapentaenoic) in ti,ab,id

#13 (alpha linolenic)in ti,ab,id

#14 (linolenate or cervonic or timnodonic) in ti,ab,id

#15 (mediterranean diet) in ti,ab,id

#16 ((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

#17 (walnut* or butternut* or soybean* or pumpkin seed*) in ti,ab,id

#18 (fish oil* or cod liver oil* or marine oil* or marine fat*) in ti,ab,id

#19 (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*) in ti,ab,id

#20 (fish consumption or fish intake) in ti,ab,id

#21 (diet* fatty acid*) in ti,ab,id

#22 (ropufa or maxepa or omacor or efamed or resq or epagis or almarin or coromega) in ti,ab,id

#23 ((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

#24 "long-chain-fatty-acids" in SU

#25 (fish and diet) in ti,ab,id

#26 ((fish and diet) in ti,ab,id) or ("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 ((docosahexanoic or docosahexaenoic) 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 ((diet* fatty acid*) in ti,ab,id) 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)

#27 Bronchial hyperreactiv*

#28 Asthma*

#29 Wheez*

#30 Leukotrien*238

#31 explode "leukotrienes-" in SU

#32 "respiratory-hypersensitivity" in SU

#33 explode "asthma-" in SU

#34 Lung* or pulmon* or respirat*

#35 explode "inflammation-" in SU

#36 Inflammat*

#37 #34 and (#35 or #36)

#38 (explode "leukotrienes-" in SU) or (Leukotrien*) or (Wheez*) or (Asthma*) or (#34 and (#35 or #36)) or (Bronchial hyperreactiv*) or (explode "asthma-" in SU) or ("respiratory-hypersensitivity" in SU)

#39 #26 and #38
#40 "man" in od
#41 #40 and #39

Appendix B. Letter to Industry Representatives

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

Appendix C. Data Assessment and Data Abstraction Forms

Relevance Assessment Form

Please respond to each of the first 7 questions. Comments typed into the box can identify duplicate reports, a key review whose references should be checked, anomalies, etc.

a. **Inclusion criteria**:
1.   Does this study involve human participants?
        YES   Can't Tell   NO
2.   Does this study employ (foods known to contain) omega-3 fatty acids (n-3) as an intervention/exposure?
        YES   Can't Tell   NO
3.   Is the purpose of the intervention/exposure: a. when used by individuals with asthma, to improve respiratory outcomes, or, influence mediators of inflammation; or, b. to prevent asthma?
        YES   Can't Tell   NO

b. **Exclusion criterion**:
4.   Is this a narrative or systematic review, opinion piece or editorial, letter, guideline or policy paper, etc. that, if it does so at all, only describes studies (and their results) reported elsewhere (i.e., it does not present evidence published for the first time)?
        YES   Can't Tell   NO

c. **Context**:
5.   The study appears to investigate (***select at least one option; click on all that apply***):
        __ n-3's potential impact on respiratory outcomes in individuals with asthma
        __ n-3's potential impact on mediators of inflammation (e.g., leukotrienes) in individuals with asthma
        __ n-3's potential to prevent asthma
        __ children or adolescents as the target population
        __ at least one control or comparator group
        __ US population dietary intake data regarding n-3 *or* n-6 fatty acids
        __ none of the above

6. The study appears to *also or instead* concern omega-3 fatty acids as an intervention/exposure for the following human health/disease domains (***select at least one option; click on all that apply***):
        __ cardiovascular (human *or* non-human/*in vitro* focus)
        __ gastrointestinal/renal   __ immune-mediated
        __ autoimmune   __ transplantation
        __ cancer   __ mental health
        __ neurology   __ none of the above
        __ child/maternal health   __ eye health

7.   Is this study written up in a language other than English?
        YES   NO

8.   Comments box

Data Abstraction Form

Instructions : *Please answer each question.* Selecting response options means clicking on them. A text box requires you to provide specific information. When it is not reported (= NR), the question does not apply (= N/A), you cannot tell what/where it is (= CT), or you have no comment to make (= NC), type the relevant code in the text box. If the research report describes more than one study, answer in this eForm all the questions for the *first reported study* while at the same time letting the review manager know that another data abstraction form is required.

1. Initials of reviewer: **COMMENTS BOX = BOX**
2. Reference identification # (Refid#): **BOX**
3. Author, Year: **BOX**
4. Unique identifier # (*type NR for now*): **BOX**
5. Number of unique, review-relevant studies that this report describes: **BOX**
6. Publication status (*select one*):
      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
      Other

7. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

8. If other review-relevant reports refer to this same study, provide their Refid #s: **BOX**

9. Country in which the study was conducted (*select all that apply*):
      Australia
      Canada
      United States
      Japan
      United Kingdom (*not* Ireland)
      France
      Germany
      Italy
      Finland
      Russia
      Other
      Not reported

10. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

11. Number of sites: **BOX**

12. Funding source type (*select all that apply*):
      Government
      Industry
      Private (non-industry)
      Hospital
      Other
      Not reported
      Can't tell

13. Specify the funding source(s): **BOX**

14. Study complexity (*select one*):
      Multiple study arms, cohorts, or phases (i.e., crossover)
      Single study arm/cohort

15. Study design (*select one*):

      RCT: parallel design
      RCT: cross-over design
      RCT: factorial design
      Controlled clinical trial (non-RCT)
      Multiple cohorts
      Single cohort
      Case-control
      Cross-sectional
      Case series
      Case study
      Other

16. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

17. Identify any notable details concerning (e.g., restricted randomization; blocking size), or problems with, the research design or its implementation (e.g., inappropriateness of: placebo/control(s), run-in and washout protocols/durations, etc.): **BOX**

18. Total # of individuals screened: **BOX**

19. # enrolled/randomized participants (hereafter, 'study participants'): **BOX**

20. # study participants completing the study: **BOX**

21. Study participants' percentage of males: **BOX**

22. Comments, including notable differences between study arms/cohorts re '% male participants': **BOX**

23. Mean age (SD/SE; range) of study participants: **BOX**

24. Comments, including notable differences between study arms/cohorts re age: **BOX**

25. Body weight of study participants (mean; range): **BOX**

26. Comments, including notable differences between study arms/cohorts re body weight: **BOX**

27. From which racial groups were study participants drawn (*select all that apply)?*
      Black/African ancestry
      Native American/Canadian
      Inuit/Eskimo
      Hispanic
      Asian
      Caucasian/European
      Other
      Not reported
      Can't tell

28. Specify each racial group's percentage/proportion of full sample: **BOX**

29. Comments, including notable differences between study arms/cohorts re racial composition**: BOX**

30. Concurrent conditions (*select all that apply*)?

      Diabetes
      Lipid-related problems (e.g., hypercholesterolemia)
      Allergic rhinitis
      Atopy (e.g., atopic dermatitis)
      Other allergies or sensitivities (e.g., aspirin/ASA)
      Other
      None reported

31. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

32. Specify the type and severity (mean; SD/SE; range: with units) of each concurrent condition, as well as how it was defined and diagnosed: **BOX**

33. Specify the percentage/proportion of the whole sample re each type of concurrent condition: **BOX**

34. Comments, including notable differences between study arms/cohorts re concurrent conditions: **BOX**

35. Specify pre-study medications or treatments for each concurrent condition, with dose/frequency: **BOX**

36. Comments, including notable differences between study arms/cohorts re pre-study medications/treatments: **BOX**

37. Describe any pre-study use of omega-3 fatty acid supplements (*may constitute a retrospective evaluation of dietary intake*): **BOX**

38. Comments, including notable differences between study arms/cohorts re the pre-study use of omega-3 fatty acid supplements: **BOX**

39. How was the dietary intake of omega-3 fatty acid usage evaluated (*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), yet no details provided
      Other
      Can't tell
      Not reported

40. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

41. Describe any pre-study use of other dietary supplements, including dose/frequency: **BOX**

42. Comments, including notable differences between study arms/cohorts re the pre-study use of other dietary supplements: **BOX**

43. Types of pre-study diet attributed to study participants (*select all that apply*):
      High fish diet
      Fish-vegetarian diet
      Low fish diet
      Low fat diet
      High fat diet
      Mediterranean diet
      Other
      Can't tell
      Not reported

44. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

45. Specify percentage/proportion of participants on each diet: **BOX**

46. Comments, including notable differences between study arms/cohorts re the type of baseline diet: **BOX**

47. Describe the full sample's *absolute* fatty acid content of the baseline diet: **BOX**

48. Comments, including notable differences between study arms/cohorts re the *absolute* fatty acid content of the baseline diet: **BOX**

49. Describe the full sample's *relative* fatty acid content of the baseline diet: **BOX**

50. Comments, including notable differences between study arms/cohorts re the *relative* fatty acid content of the baseline diet: **BOX**

51. Describe the full sample's baseline blood lipid biomarker levels, with units: **BOX**

52. Comments, including notable differences between study arms/cohorts re these blood lipid biomarker levels: **BOX**

53. Describe the full sample's baseline (serum, tissue, or cell membrane) levels of fatty acids: **BOX**

54. Describe the full sample's baseline omega-6/omega-3 tissue ratios of fatty acid: **BOX**

55. Describe any notable differences between the study arms/cohorts re their baseline fatty acids (serum, tissue, or cell membrane) or omega-6/omega-3 tissue ratios of fatty acid: **BOX**

56. What percentage/proportion of participants were diagnosed at study entry with asthma? **BOX**

57. Why were <100% of participants diagnosed with asthma at study entry (e.g., primary prevention study): **BOX**

58. Was asthma clearly defined? YES CT NO NR

59. How was asthma defined? **BOX**

60. How was asthma diagnosed? **BOX**

61. Identify the percentage/proportion of participants per asthma sub-type: **BOX**

62. According to the report, what was the likely cause(s) of the asthma (e.g., exercise- or aspirin-induced): **BOX**

63. Comments, including notable differences between study arms/cohorts re the definition, subtypes, or causes of asthma: **BOX**

64. What is the certainty of the asthma diagnosis? (*select one*)
     Not applicable
     No information reported
     Can't tell

Possible: compatible symptoms
Probable: MD clinical diagnosis
Definite: MD clinical diagnosis or compatible symptoms *PLUS* objective measure of airway reactivity (FEV_1 improves $\geq$ 15% post-bronchodilator; methacholine challenge test reveals PC20 <8mg/ml; diurnal variation in PEF or $FEV_1 >$ 15%)

65. Comments, including notable differences between study arms/cohorts re the certainty of the asthma diagnosis: **BOX**

66. Was asthma severity clearly defined? YES CT NO NR

67. How was asthma severity defined (e.g., daily symptoms of cough, wheeze, breathlessness; frequency of rescue inhaler use; nocturnal awakenings; exercise limitation; emergency visits and hospitalizations; recent use of systemic [oral; IV] corticosteroids; FEV_1, peak flow; peak flow variability; measured nonspecific airway reactivity [e.g., histamine or methacholine challenge testing])? **BOX**

68. Describe the full sample's baseline (mean; SD/SE; range) level of asthma severity: **BOX**

69. Comments, including notable differences between study arms/cohorts re participants' baseline severity of asthma: **BOX**

70. According to the authors, how well-controlled by medication(s) were participants' asthma? (*select one*)

    Well-controlled
    Symptomatic
    Not indicated
    Can't tell
    Not applicable

71. How did the authors define well-controlled *vs.* symptomatic? **BOX**

72. Comments, including notable differences between study arms/cohorts re baseline asthma control: **BOX**

73. Describe any notable differences at baseline between study arms/cohorts in terms of any indices of participants' asthma clinical status or pulmonary function: **BOX**

74. Participants' asthma duration (mean; SD/SE; range): **BOX**

75. Comments, including notable differences between study arms/cohorts re asthma duration: **BOX**

76. Describe atopy status of participants, including their family history: **BOX**

77. Comments, including notable differences between study arms/cohorts re history of atopy: **BOX**

78. Participants' family history of asthma: **BOX**

79. Comments, including notable differences between study arms/cohorts re family history of asthma: **BOX**

80. Specify presence of furry/feathered pets at home or work (e.g., % participants): **BOX**

81. Comments, including notable differences between study arms/cohorts re presence of furry/feathered pets at home or work: **BOX**

82. Specify socioeconomic status of participants: **BOX**

83. Comments, including notable differences between study arms/cohorts re socioeconomic status: **BOX**

84. Describe participants' family size and living conditions (e.g., crowdedness; cleanliness): **BOX**

85. Comments, including notable differences between study arms/cohorts re family size or living conditions: **BOX**

86. Identify location of participants' present residence (*select one*):
      100% Urban
      100% Rural
      Some from each

87. Comments, including notable differences between study arms/cohorts re residence location: **BOX**

88. # study participants (working) in daycare (for infections which exacerbate asthma): **BOX**

89. Comments, including notable differences between study arms/cohorts re study participants (working) in daycare: **BOX**

90. Describe participants' history of respiratory infections (e.g., bronchiolitis): **BOX**

91. Comments, including notable differences between study arms/cohorts re participants' history of respiratory infections: **BOX**

92. Describe participants' history of exposure to environmental tobacco smoke: **BOX**

93. Comments, including notable differences between study arms/cohorts re participants' history of exposure to environmental tobacco smoke: **BOX**

94. Describe participants' smoking history and present smoker status: **BOX**

95. Comments, including notable differences between study arms/cohorts re participants' smoking history and present smoker status: **BOX**

96. Other asthma risk factors, and percentage/proportion of participants re each (*specify*): **BOX**

97. Comments, including notable differences between study arms/cohorts re these risk factors: **BOX**

98. Other factors adversely affecting asthma control, and percentage/proportion of participants re each (*specify*): **BOX**

99. Comments, including notable differences between study arms/cohorts re these factors influencing asthma control: **BOX**

100. Describe pre-study asthma medication(s) or treatments, including dose/frequency: **BOX**

101. Comments, including notable differences between study arms/cohorts re pre-study asthma medication(s) or treatments, including dose/frequency: **BOX**

102. Comments re the appropriateness of pre-study asthma medications or treatments, including dose/frequency: **BOX**

103. Comments, including notable differences between study arms/cohorts re the appropriateness of the pre-study asthma medication(s) or treatments, including dose/frequency: **BOX**

104. Describe participants' pre-study exacerbation, emergency visit, or hospitalization rates: **BOX**

105. Comments, including notable differences between study arms/cohorts re the pre-study exacerbation, emergency visit, or hospitalization rates: **BOX**

106. Describe participants' pre-study rescue inhaler use: **BOX**

107. Comments, including notable differences between study arms/cohorts re the pre-study rescue inhaler use: **BOX**

108. Comments about any other asthma-related covariates (e.g., baseline serum IgE levels), including any notable differences between the study arms/cohorts in terms of these: **BOX**

109. Season the study was initiated: **BOX**

110. Season the study was completed: **BOX**

111. List the study's inclusion criteria: **BOX**

112. List the study's exclusion criteria: **BOX**

113. Intention of study (*select all that apply*)
      Treatment
      Primary prevention
      Secondary prevention
      Impact on mediators of inflammation
      Safety
      Other
      Unclear

114. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

115. Type of study (*select one*):
      Interventional
      Observational

116. 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 follow-up data)
      Can't tell
      Other

117. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

118. Study duration, including units (includes run-in period duration, washout duration, etc.):
BOX

119. Omega-3 fatty acid product name(s) (*select all that apply*):
      Almarin
      Coromega
      Eiconol
      Efamed
      Epagis
      MaxEPA
      Menhaden oil
      ResQ
      Omacor
      Ropufa
      Other
      Not reported
      Not applicable

120. If you answered 'Other' to the preceding question, specify what you mean: **BOX**

121. Name of manufacturer of the omega-3 fatty acid product(s): **BOX**

122. Reported information re the purity of the omega-3 fatty acid product: **BOX**

123. Reported information re the presence of other, potentially active agents in the omega-3 fatty acid product: **BOX**

124. Asthma medications allowed or mandated during the study, including dose and frequency: **BOX**

125. Comments, including notable differences between study arms/cohorts/phases re participants' asthma medications, including dose/frequency: **BOX**

126. Permitted or mandated medications or treatments for concurrent conditions during the study (specify type, dose/frequency, and for which concurrent condition): **BOX**

127. Comments, including notable differences between study arms/cohorts/phases re participants' permitted or required medications or treatments for concurrent conditions: **BOX**

128. Review-relevant outcomes assessed (e.g., efficacy; incidence; prevalence; mediators of inflammation): **BOX**

129. Timing of follow-up assessment(s) per outcome, relative to start of intervention (e.g., after 8 hours; at week 4): **BOX**

130. Total # of study arms or cohorts (note: in a crossover trial, each phase type is considered an exposure/intervention 'arm:' e.g., placebo vs. omega-3): **BOX**

131. # crossovers: **BOX**

132. Define only the study arms, cohorts, or phases of interest to the present review (*exclude others, for which data will not be extracted*): **BOX**

133. With a specific omega-3 fatty acid 'active' arm in mind, type ARM1 in the text box: **BOX**

134. Re this study arm, what is the sample size at study entry? **BOX**

135. Sample size of those completing the study: **BOX**

136. Intervention length (e.g., weeks, months): **BOX**

137. Arm type (active; placebo; control) **BOX**

138. Intervention/exposure type (e.g., marine diet; plant diet; marine-based supplement; plant-based supplement; nuts; nut oil): **BOX**

139. Define the intervention/exposure components (e.g., 'omega-3 rich diet;' anchovy serving; fish oil supplement; flaxseed/linseed; rapeseed/canola; walnut oil; softgel capsule): **BOX**

140. Specific source(s) of omega-3 fatty acids (i.e., type[s] of fish or plant): **BOX**

141. Per-dose/serving amount of omega-3 fatty acids (e.g., grams): **BOX**

142. Dose/serving frequency (e.g., once daily): **BOX**

143. Timing (e.g., with breakfast; any time): **BOX**

144. Route of administration: **BOX**

145. Total daily (mean; SD/SE; range) omega-3 fatty acid intake (e.g., grams): **BOX**

146. Type(s) of omega-3 fatty acid identified (i.e., DHA, EPA, DPA, ALA): **BOX**

147. Total daily amount/dose (mean; SD/SE; range) of *each* type of omega-3 fatty acid, or combination (e.g., EPA+DHA) (e.g., grams): **BOX**

148. Omega-3 fatty acid composition (%) of the exposure/intervention: **BOX**

149. Permitted or mandated amount/dose (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure) of omega-6 fatty acid intake (e.g., grams): **BOX**

150. Permitted or mandated omega-6/omega-3 ratio of the exposure/intervention: **BOX**

151. Other permitted or mandated type(s) of co-intervention (e.g., anti-oxidants such as Vitamin E; other dietary supplements; other foodstuff), including respective dose/servings (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure), with units: **BOX**

152. Total daily fat intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

153. Total daily caloric intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

154. Describe whether, and why, it was necessary or possible to change the standard asthma medications/treatments during the course of the study: **BOX**

155. If standard asthma medications/treatments were changed, then how? **BOX**

156. If there is a second omega-3 fatty acid 'active' arm or, if none, then a control arm (e.g., placebo), type ARM2 in the text box (however, click here if there are no more arms/cohorts; this links directly to question #252) **BOX**

157. Re this study arm, what is the sample size at study entry? **BOX**

158. Sample size of those completing the study: **BOX**

159. Intervention length (e.g., weeks, months): **BOX**

160. Arm type (active; placebo; control) **BOX**

161. Intervention/exposure type (e.g., marine diet; plant diet; marine-based supplement; plant-based supplement; nuts; nut oil): **BOX**

162. Define the intervention/exposure components (e.g., 'omega-3 rich diet;' anchovy serving; fish oil supplement; flaxseed/linseed; rapeseed/canola; walnut oil; softgel capsule): **BOX**

163. If control/placebo, describe it (e.g., 'omega-3 poor diet') or what was used (e.g., olive oil, safflower oil): **BOX**

164. Specific source(s) of omega-3 fatty acids (i.e., type[s] of fish or plant): **BOX**

165. Per-dose/serving amount of omega-3 fatty acids (e.g., grams): **BOX**

166. Dose/serving frequency (e.g., once daily): **BOX**

167. Timing (e.g., with breakfast; any time): **BOX**

168. Route of administration: **BOX**

169. Total daily (mean; SD/SE; range) omega-3 fatty acid intake (e.g., grams): **BOX**

170. Type(s) of omega-3 fatty acid identified (i.e., DHA, EPA, DPA, ALA): **BOX**

171. Total daily amount/dose (mean; SD/SE; range) of *each* type of omega-3 fatty acid, or combination (e.g., EPA+DHA) (e.g., grams): **BOX**

172. Omega-3 fatty acid composition (%) of the exposure/intervention: **BOX**

173. Permitted or mandated amount/dose (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure) of omega-6 fatty acid intake (e.g., grams): **BOX**

174. Permitted or mandated omega-6/omega-3 ratio of the exposure/intervention: **BOX**

175. Other permitted or mandated type(s) of co-intervention (e.g., anti-oxidants such as Vitamin E; other dietary supplements; other foodstuff), including respective dose/servings (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure), with units: **BOX**

176. Total daily fat intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

177. Total daily caloric intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

178. Describe whether, and why, it was necessary or possible to change the standard asthma medications/treatments during the course of the study: **BOX**

179. If standard asthma medications/treatments were changed, then how? **BOX**

180. If there is an additional omega-3 fatty acid 'active' arm or, if none, then a control arm (e.g., placebo), type ARM3 in the text box (however, click here if there are no more arms/cohorts; this links directly to question #252) **BOX**

181. Re this study arm, what is the sample size at study entry? **BOX**

182. Sample size of those completing the study: **BOX**

183. Intervention length (e.g., weeks, months): **BOX**

184. Arm type (active; placebo; control) **BOX**

185. Intervention/exposure type (e.g., marine diet; plant diet; marine-based supplement; plant-based supplement; nuts; nut oil): **BOX**

186. Define the intervention/exposure components (e.g., 'omega-3 rich diet;' anchovy serving; fish oil supplement; flaxseed/linseed; rapeseed/canola; walnut oil; softgel capsule): **BOX**

187. If control/placebo, describe it (e.g., 'omega-3 poor diet') or what was used (e.g., olive oil, safflower oil): **BOX**

188. Specific source(s) of omega-3 fatty acids (i.e., type[s] of fish or plant): **BOX**

189. Per-dose/serving amount of omega-3 fatty acids (e.g., grams): **BOX**

190. Dose/serving frequency (e.g., once daily): **BOX**

191. Timing (e.g., with breakfast; any time): **BOX**

192. Route of administration: **BOX**

193. Total daily (mean; SD/SE; range) omega-3 fatty acid intake (e.g., grams): **BOX**

194. Type(s) of omega-3 fatty acid identified (i.e., DHA, EPA, DPA, ALA): **BOX**

195. Total daily amount/dose (mean; SD/SE; range) of *each* type of omega-3 fatty acid, or combination (e.g., EPA+DHA) (e.g., grams): **BOX**

196. Omega-3 fatty acid composition (%) of the exposure/intervention: **BOX**

197. Permitted or mandated amount/dose (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure) of omega-6 fatty acid intake (e.g., grams): **BOX**

198. Permitted or mandated omega-6/omega-3 ratio of the exposure/intervention: **BOX**

199. Other permitted or mandated type(s) of co-intervention (e.g., anti-oxidants such as Vitamin E; other dietary supplements; other foodstuff), including respective dose/servings (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure), with units: **BOX**

200. Total daily fat intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

201. Total daily caloric intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

202. Describe whether, and why, it was necessary or possible to change the standard asthma medications/treatments during the course of the study: **BOX**

203. If standard asthma medications/treatments were changed, than how? **BOX**

204. If there is an additional omega-3 fatty acid 'active' arm or, if none, then a control arm (e.g., placebo), type ARM4 in the text box (however, click here if there are no more arms/cohorts; this links directly to question #252) **BOX**

205. Re this study arm, what is the sample size at study entry? **BOX**

206. Sample size of those completing the study: **BOX**

207. Intervention length (e.g., weeks, months): **BOX**

208. Arm type (active; placebo; control) **BOX**

209. Intervention/exposure type (e.g., marine diet; plant diet; marine-based supplement; plant-based supplement; nuts; nut oil): **BOX**

210. Define the intervention/exposure components (e.g., 'omega-3 rich diet;' anchovy serving; fish oil supplement; flaxseed/linseed; rapeseed/canola; walnut oil; softgel capsule): **BOX**

211. If control/placebo, describe it (e.g., 'omega-3 poor diet') or what was used (e.g., olive oil, safflower oil): **BOX**

212. Specific source(s) of omega-3 fatty acids (i.e., type[s] of fish or plant): **BOX**

213. Per-dose/serving amount of omega-3 fatty acids (e.g., grams): **BOX**

214. Dose/serving frequency (e.g., once daily): **BOX**

215. Timing (e.g., with breakfast; any time): **BOX**

216. Route of administration: **BOX**

217. Total daily (mean; SD/SE; range) omega-3 fatty acid intake (e.g., grams): **BOX**

218. Type(s) of omega-3 fatty acid identified (i.e., DHA, EPA, DPA, ALA): **BOX**

219. Total daily amount/dose (mean; SD/SE; range) of *each* type of omega-3 fatty acid, or combination (e.g., EPA+DHA) (e.g., grams): **BOX**

220. Omega-3 fatty acid composition (%) of the exposure/intervention: **BOX**

221. Permitted or mandated amount/dose (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure) of omega-6 fatty acid intake (e.g., grams): **BOX**

222. Permitted or mandated omega-6/omega-3 ratio of the exposure/intervention: **BOX**

223. Other permitted or mandated type(s) of co-intervention (e.g., anti-oxidants such as Vitamin E; other dietary supplements; other foodstuff), including respective dose/servings (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure), with units: **BOX**

224. Total daily fat intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

225. Total daily caloric intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

226. Describe whether, and why, it was necessary or possible to change the standard asthma medications/treatments during the course of the study: **BOX**

227. If standard asthma medications/treatments were changed, then how? **BOX**

228. If there is an additional omega-3 fatty acid 'active' arm or, if none, then a control arm (e.g., placebo), type ARM5 in the text box (however, click here if there are no more arms/cohorts; this links directly to question #252) **BOX**

229. Re this study arm, what is the sample size at study entry? **BOX**

230. Sample size of those completing the study: **BOX**

231. Intervention length (e.g., weeks, months): **BOX**

232. Arm type (active; placebo; control) **BOX**

233. Intervention/exposure type (e.g., marine diet; plant diet; marine-based supplement; plant-based supplement; nuts; nut oil): **BOX**

234. Define the intervention/exposure components (e.g., 'omega-3 rich diet;' anchovy serving; fish oil supplement; flaxseed/linseed; rapeseed/canola; walnut oil; softgel capsule): **BOX**

235. If control/placebo, describe it (e.g., 'omega-3 poor diet') or what was used (e.g., olive oil, safflower oil): **BOX**

236. Specific source(s) of omega-3 fatty acids (i.e., type[s] of fish or plant): **BOX**

237. Per-dose/serving amount of omega-3 fatty acids (e.g., grams): **BOX**

238. Dose/serving frequency (e.g., once daily): **BOX**

239. Timing (e.g., with breakfast; any time): **BOX**

240. Route of administration: **BOX**

241. Total daily (mean; SD/SE; range) omega-3 fatty acid intake (e.g., grams): **BOX**

242. Type(s) of omega-3 fatty acid identified (i.e., DHA, EPA, DPA, ALA): **BOX**

243. Total daily amount/dose (mean; SD/SE; range) of *each* type of omega-3 fatty acid, or combination (e.g., EPA+DHA) (e.g., grams): **BOX**

244. Omega-3 fatty acid composition (%) of the exposure/intervention: **BOX**

245. Permitted or mandated amount/dose (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure) of omega-6 fatty acid intake (e.g., grams): **BOX**

246. Permitted or mandated omega-6/omega-3 ratio of the exposure/intervention: **BOX**

247. Other permitted or mandated type(s) of co-intervention (e.g., anti-oxidants such as Vitamin E; other dietary supplements; other foodstuff), including respective dose/servings (mean; SD/SE; range), frequency, method of delivery, and timing (relative to the omega-3 fatty acid exposure), with units: **BOX**

248. Total daily fat intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

249. Total daily caloric intake (mean; SD/SE; range) of the exposure/intervention, with units: **BOX**

250. Describe whether, and why, it was necessary or possible to change the standard asthma medications/treatments during the course of the study: **BOX**

251. If standard asthma medications/treatments were changed, then how? **BOX**

252. Was there a clear difference in daily total-gram omega-3 fatty acid intake across the study arms/cohorts/phases? YES CT NO N/A

253. Was there a clear difference in the respective daily intake amounts for each of the different omega-3 fatty acids across the study arms/cohorts/phases? YES CT NO N/A

254. Was there a clear difference in the total daily omega-6 fatty acid intake across the study arms/cohorts/phases? YES CT NO N/A

255. Was there a clear difference in the omega-6/omega-3 ratio of the daily fatty acid intake across the study arms/cohorts/phases? YES CT NO N/A

256. Was the daily overall fat intake equivalent across study arms/cohorts/phases? YES CT NO N/A

257. Was the daily caloric intake equivalent across study arms/cohorts/phases? YES CT NO N/A

258. Did control participants appear to receive more than trace amounts of omega-3 fatty acid? YES CT NO N/A

259. Were the standard medications/treatments for asthma equivalent or comparable across the study arms/cohorts/phases? YES CT NO N/A

260. Were the standard medications/treatments for concurrent conditions equivalent or comparable across the study arms/cohorts/phases? YES CT NO N/A

261. Identify any factors intentionally kept constant across the study (e.g., background diet for those in a study of the impact of supplements): **BOX**

262. Additional comments re the possible non-comparability of populations or interventions/exposures, and, other possible sources of bias: **BOX**

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

264. Identify the question(s) this study addresses (*select all that apply*):

   What is the evidence for the efficacy of omega-3 fatty acids to improve respiratory outcomes among individuals with asthma?

   What is the evidence that the possible value (efficacy/association) of omega-3 fatty acids in improving respiratory outcomes is dependent on the: specific type of fatty acid (DHA, EPA, DPA, ALA, fish, fish oil); specific source (fish, plant, food, dietary supplement [fish oil, plant oil]); its serving size or dose (fish or dietary supplement); amount/dose of omega-6 fatty acids given as a co-intervention; ratio of omega-6/omega-3 fatty acids used; fatty acid content of blood lipid biomarkers; absolute fatty acid content of the baseline diet; relative fatty acid content of the baseline diet; tissue ratios of fatty acid (omega-6/omega-3) during the investigative period; intervention length; anti-oxidant use; and, the manufacturer and its product(s) (different purity; presence of other potentially active agents)?

   What is the evidence that, in individuals with asthma, omega-3 fatty acids influence mediators of inflammation which are thought to be related to the pathogenesis of asthma?

   Are omega-3 fatty acids effective in the primary prevention of asthma?

   Among individuals with asthma, do omega-3 fatty acids alter the progression of asthma (i.e., secondary prevention)?

   What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acid use to treat or prevent asthma (DHA, EPA, DPA, ALA, fish oil, fish)?

   What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations of asthmatic individual such as diabetics?

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*.

<p style="text-align:center">TOTAL POINTS: 0   1   2   <u>SCORE</u> = __</p>

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*.

<p style="text-align:center">TOTAL POINTS: 0   1   2   <u>SCORE</u> = __</p>

3. Withdrawals and dropouts: Was there a description of withdrawals and dropouts?
<p style="text-align:center">Yes = 1   No = 0   <u>SCORE</u> = __</p>

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*.

<p style="text-align:center"><u>JADAD TOTAL SCORE</u> = __</p>

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

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

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

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

Quality Assessment Form—All Other Study Designs

1. Is the hypothesis/aim/objective of the study clearly described?
     Yes= 1
     No= 0   SCORE: _____

2. Are the characteristics of the participants/patients included in the study clearly described?
     Yes= 1
     No= 0   SCORE: _____

3. Have the characteristics of participants/patients lost to follow-up been described?
     Yes= 1[1]
     No= 0   SCORE: _____

4. Were the outcome measures used accurate (valid and reliable)?
     Yes= 1
     No= 0
     Unable to determine= 0   SCORE: _____

5. Are the interventions/exposures of interest clearly described?
     Yes= 1
     No= 0   SCORE: _____

[1]Yes= also, if no losses, or, losses so small that findings would be unaffected by their inclusion

Applicability Indices

For studies of the treatment and secondary prevention (i.e., to alter the progression) of asthma:

Assign 'I' to a study population of otherwise 'healthy' asthmatic North American individuals, namely those representing a somewhat broad demographic picture (i.e., gender, race), possibly exhibiting 'typical' conditions concomitant to asthma (e.g., atopy), living a 'typical' North American lifestyle (e.g., background diet), receiving 'typical' types and doses of asthma treatment (e.g., medications), yet without significant comorbid health problems.

Assign 'II' to a study population of asthmatic individuals representing a more restricted North American demographic picture (e.g., a North American sub-population), exhibiting more severe forms of 'typical' condition concomitant to asthma, living a less 'typical' North American lifestyle, receiving less 'typical' types and doses of asthma treatment, or having significant comorbid health problems (e.g., diabetes).

Assign 'III' to a study population of asthmatic individuals representing a narrow demographic picture that is not a 'typical' North American one (e.g., a population living outside North America), living a lifestyle that is not a 'typical' North American one (e.g., different background diet), exhibiting more severe forms of 'typical' condition concomitant to asthma, receiving less 'typical' types and doses of asthma treatment, or having significant comorbid health problems.

Assign 'X' when applicability cannot be ascertained due to incomplete reporting, particularly of the details defining the study population of asthmatic individual, including demographics, the diagnostic criteria and method to identify asthma, comorbid health problems, and, asthma care.

For primary prevention studies:

Assign 'I' to a study population of typical 'healthy' North Americans across a broad demographic spectrum, or, those otherwise 'typical' North Americans (i.e., no other significant health problems) across a broad demographic spectrum yet at risk to develop asthma (e.g., family history; environmental exposure to smoke; early history of respiratory infections).
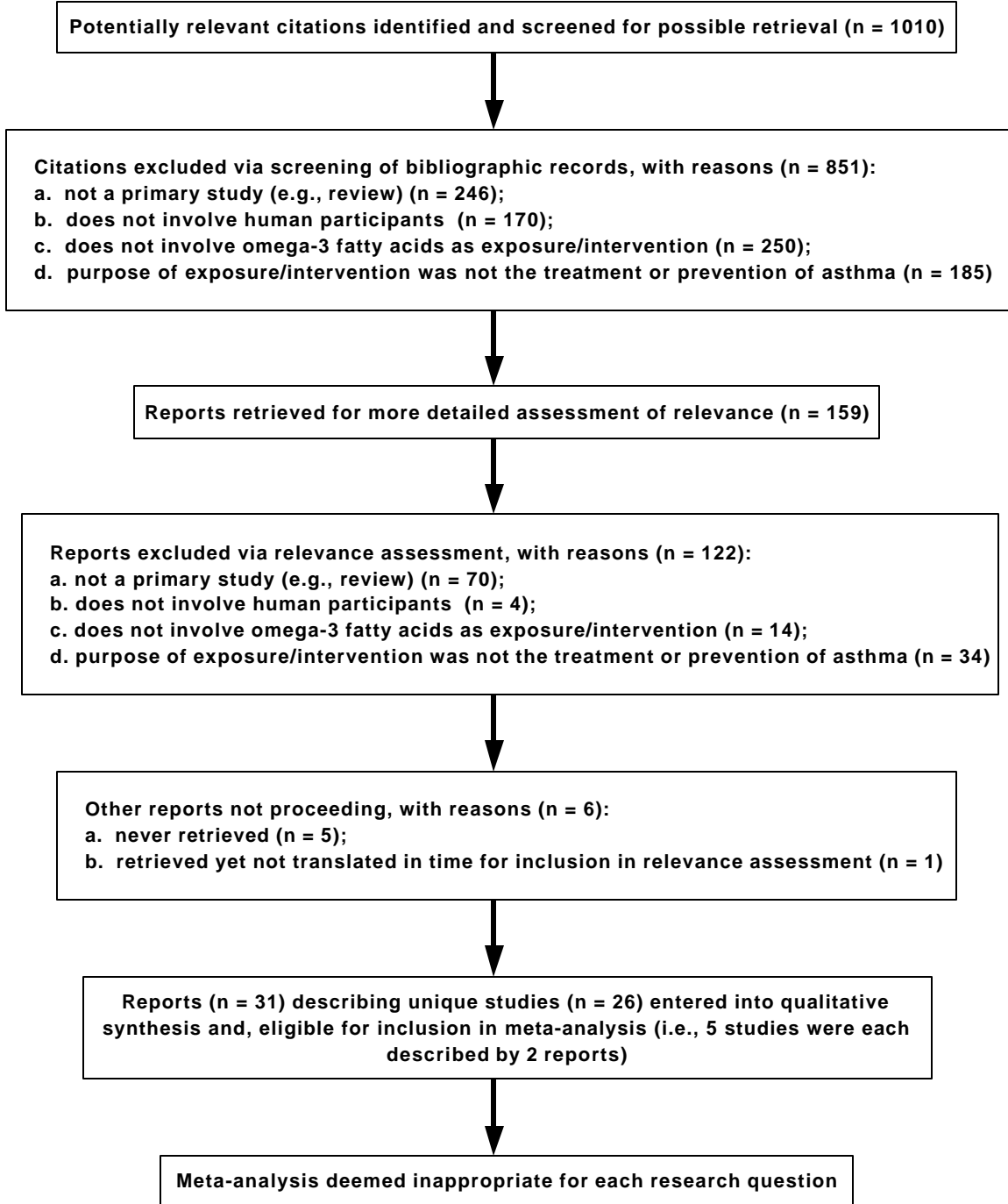
Assign 'II' to a study population of North Americans, with or without the risk of developing asthma, yet representing a restricted demographic picture (e.g., a sub-population), lifestyle (e.g., different background diet), or other significant health problems (e.g., diabetes).

Assign 'III' to a study population living outside North America, with or without the risk of developing asthma, and thus representing --relative to North Americans-- a different demographic picture or lifestyle, or, other significant health problems (e.g., diabetes).

Assign 'X' when applicability cannot be ascertained due to incomplete reporting, particularly of the details defining the study population.

Appendix D. Modified QUOROM Flow Chart

Modified QUOROM Flow Chart

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┌─────────────────────────────────────────────────────────────────────────────┐
│ Potentially relevant citations identified and screened for possible retrieval │
│ (n = 1010)                                                                    │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Citations excluded via screening of bibliographic records, with reasons       │
│ (n = 851):                                                                     │
│ a.  not a primary study (e.g., review) (n = 246);                             │
│ b.  does not involve human participants  (n = 170);                           │
│ c.  does not involve omega-3 fatty acids as exposure/intervention (n = 250);  │
│ d.  purpose of exposure/intervention was not the treatment or prevention of   │
│     asthma (n = 185)                                                           │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Reports retrieved for more detailed assessment of relevance (n = 159)         │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Reports excluded via relevance assessment, with reasons (n = 122):            │
│ a. not a primary study (e.g., review) (n = 70);                               │
│ b. does not involve human participants  (n = 4);                              │
│ c. does not involve omega-3 fatty acids as exposure/intervention (n = 14);    │
│ d. purpose of exposure/intervention was not the treatment or prevention of    │
│    asthma (n = 34)                                                             │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Other reports not proceeding, with reasons (n = 6):                           │
│ a.  never retrieved (n = 5);                                                   │
│ b.  retrieved yet not translated in time for inclusion in relevance           │
│     assessment (n = 1)                                                         │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Reports (n = 31) describing unique studies (n = 26) entered into qualitative  │
│ synthesis and, eligible for inclusion in meta-analysis (i.e., 5 studies were  │
│ each described by 2 reports)                                                   │
└─────────────────────────────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Meta-analysis deemed inappropriate for each research question                 │
└─────────────────────────────────────────────────────────────────────────────┘
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Appendix E. Evidence Tables

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Arm,[56,57] 1988, England	• Enrolled/evaluated: 25/20 • Age (mean & range): 27 (15-42) y • % Male: 40 • Race: NR, likely Caucasian/ European • Number of sites: 1	• Parallel RCT, double-blind • 12-14 wk (Run-in: 2-4 wk)	• Inclusion: NR • Exclusion: NR	• NR, mild asthma, 22 atopic, none aspirin-sensitive, some exercise-induced asthma (6/12 MaxEPA; 5/8 control) • Severity: mild (undefined) • Duration: NR • Method: NR • Pre-study: on regular inhaled corticosteroids (11/25); 1 on long-acting theophylline at night; all on inhaled beta-2 agonists as required; none on oral corticosteroids • Study: NR	• 5.4 g/d from fish oil capsules (3.2 g/d EPA + 2.2 g/d DHA) • 18 MaxEPA® (Seven Seas Ltd., Marfleet, Hull, UK) capsules/d • MaxEPA® contains mainly triglycerides, with 34% of the total fatty acids & 86% of the polyunsaturated fatty acids consisting of EPA + DHA • Usual diet unchanged • 10 wk intervention • n=NR/12 (6 males, 10 atopic)	• Identical capsules containing olive oil (Seven Seas Ltd., Marfleet, Hull, UK) • Capsules/d: NR, though likely matched • Usual diet unchanged • 10 wk intervention • n=NR/8 (4 males, all atopic)
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Arm,[56,57] 1988, England	• NS ? in AM PEF (L/min) in either study arm (*p* >.05)* or between study arms [mean difference: 5 (95% CI 26, -16)] • NS ? in PM PEF (L/min) in either study arm (*p*>.05)* or between study arms [mean difference: -2 (95% CI 16, -19)] • NS ? in PEF lability (AM-PM difference as % of higher figure) in either study arm (*p*>.05) or between study arms [mean difference: -0.1 (95% CI 2.36, -2.6)] • NS ? in total symptoms score (nocturnal cough & wheeze; daytime wheeze; 0= asymptomatic; 3= severe) in either study arm (*p* >.05)* or between study arms [mean difference: 3.2 (95% CI 13, -6.7)] • NS ? in bronchodilator use (total doses) in either study arm (*p*>.05)* or between study arms [mean difference: 7.8 (95% CI 20, -4.4)] • NS ? in airways histamine responsiveness (specific airways conductance: sGAW) in either study arm (*p*>.05)* • NS ? in maximal % decreases in sGAW as airways response to exercise challenge in either study arm (*p*>.05)* • NS ? in acute airways response to allergen challenge (sGAW) in either arm (*p*>.05)* • S suppression at 2 (*p*=.006)* & 3-7 h (*p*<.005)* on late airways response to allergen challenge (sGAW) only in omega-3 fatty acid arm • NS suppression in calcium ionophore induced generation of LTB_4 (ng/2 x 10^6 PMN) in either study arm (*p*>.05)* • no calcium ionophore induced generation of LTB_5 (ng/2 x 10^6 PMN) before either intervention or after control intervention; some generated after omega-3 fatty acid intervention (NR)* • S suppression of total LTB compounds generation (ng/2 x 10^6 PMN) by ionophore stimulated neutrophils only in omega-3 fatty acid arm (*p*<.01)* • S suppression of neutrophil chemotaxis (# neutrophils per 5 high power fields) to fMLP (M) (*p*=.01)* & LTB_4 (*p*=.04)* only in omega-3 fatty acid arm	NR	•n=5, with no data regarding from which study arm 4 left •after 3 wk of MaxEPA®, hospitalized for acute asthma, took oral corticosteroids & stopped MaxEPA® (n=1) •found number & size of capsules unmanageable (n=3) •personal reasons (n=1)	•Randomization: 1 •Blinding: 2 •Withdrawals/ dropouts: 1 •Jadad total score: 4 (Grade: A) •Allocation concealment: unclear •Applicability: III	Asthma Research Council (UK) & International Association of Fish Meal Manufacturers

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Dry, 1991, France[65]	• Enrolled/ evaluated: 12/12 • Age (mean & range): NR (NR) • % Male: NR • Race: NR, but likely Caucasian/ European • Number of sites: NR	• Parallel RCT, double-blind • 12 mo (Run-in: NR)	• Inclusion: NR • Exclusion: NR	• NR, allergic asthmatics (definition: reversible airway obstruction & bronchopulmonary hyper-reactivity, likely due to airway inflammation via chemical mediators) • Severity: NR • Duration: NR • Method: NR • Pre-study: routinely used salbutamol, inhaled corticosteroids & sodium nedocromil (no data) • Study: NR	• Low dose omega-3 fatty acids • 1 g/d EPA+DHA (relative amounts undefined; delivery method undefined, likely capsule); Liparmonyl® (Ponroy Laboratories, France) • 12 mo intervention • n=NR/100%	• 'Placebo' (undefined) • 12 mos intervention • n=NR/100%

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Dry, 1991, France[65]	• At 9 mo, S greater increase in FEV_1 (% predicted) in the omega-3 fatty acid arm (p<.005) • NB: no statistical test conducted at final follow-up at 12 mo, with FEV_1 (% predicted) results continuing to diverge	NR	n=0	• Randomization: 1 • Blinding: 1 • Withdrawals/ dropouts: 0 • Jadad total score: 2 (Grade: C) • Allocation concealment: unclear • Applicability: X	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/Severity/Duration/ Diagnostic Method/Pre-study Medication/Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Emelyanov, 2002, Russia[69]	• Enrolled/ evaluated: 46/46 • Age (mean & range): 39.1 (18-56) y • % Male: 26.1 • Race: NR, likely Caucasian/ European • Number of sites: 1	• Parallel RCT, double-blind • 10 wk (Run-in: 2 wk; regular treatment stopped, only short-acting beta-2 agonists allowed: salbutamol, terbutaline)	• Inclusion: NR, volunteers; recruited in outpatient hospital department • Exclusion: use of inhaled corticosteroids within prior 4 wk, oral corticosteroid use within last 3 mo; current or ex-smoker; clinically S heart, renal, liver & intestinal disorders, women of childbearing potential not using adequate contraception; receiving inhaled corticosteroids or hospitalized for asthma during run-in period	• Atopic asthma, all house-dust mite sensitive; • Severity: mild-to-moderate via NIH/WHO criteria (1995); mild (n=36) = symptoms $\leq$ twice a wk, $FEV_1 \geq 80\%$ of predicted, using inhaled short-acting beta-2 agonists; moderate (n=10) = daily symptoms & FEV_1 60%-80% of predicted & used inhaled short-acting beta-2 agonists daily; • Duration: 5.9 y • Method: clinical history, reversibility of FEV1 of >15% & diurnal PEF variability of >20%; American Thoracic Society (1987) criteria; atopy via positive skin-prick test to common inhalant allergens (house-dust mite; animal; pollen); • Pre-study: NR • Study: only short-acting beta-2 agonists allowed (rescue)	• Extract of New Zealand green-lipped mussel (Perna Canaliculus) • 4 capsules (2 capsules, twice daily) of liquid extract Lyprinol® (Mac Lab, Melbourne, Australia), each containing 50 mg omega-3 fatty acids (EPA+DHA: undefined) & 100 mg olive oil), for total of 600 mg/d of oil, including 200 mg EPA+DHA/d & 400 mg/d olive oil/d • 8 wk intervention • n=23/23	• 2 matching capsules (2 capsules, twice daily) each containing 150 mg of olive oil, for a total of 600 mg/d olive oil (manufacturer: NR) • 8 wk intervention • n=23/23

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Emelyanov, 2002, Russia[69]	• S greater decrease in daytime wheeze in omega-3 fatty acid arm (p=.026) • NS between-arm difference in ? in night-time awakenings (p=.085) • S greater decrease in use of inhaled beta-2 agonists (puffs/d) in omega-3 fatty acid arm (p=.022) • NS between-arm difference in ? in FEV$_1$ (% predicted) (p=.708) • S greater increase in AM PEF (L/min) in omega-3 fatty acid arm (p=.00001) • NS between-arm difference in ? in PM PEF (L/min) (p=.136) • S greater decrease in the concentration of exhaled hydrogen peroxide (H_2O_2) in expired breath condensate (marker of airway inflammation) in the omega-3 fatty acid arm (p=.0001)	NR	• n=0 • 60 volunteers, 46 of which were randomized: 14 withdrew before randomization due to deterioration in asthma control (lower FEV1 than those randomized: p<.001) = more severe asthmatics withdrew before randomization • Compliance (self-recorded): 95% & 93% for omega-3 fatty acids & control group, respectively)	• Randomization: 2 • Blinding: 2 • Withdrawals/ dropouts: 1 • Jadad total score: 5 (Grade: A) • Allocation concealment: unclear • Applicability: III	**NR**

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Hodge, 1998,[52,53] Australia	• Enrolled/ evaluated: 45/39 • Age (mean & range): 10.25 (8-12) y • % Male: 43.6 • Race: NR, but likely Caucasian/ European • Number of sites: 1	• Parallel RCT, double-blind • 26 wk (Run-in: 2 wk)	• Inclusion: episodic wheeze in last 12 mo & airways hyper-responsiveness (no mention of how recruited) • Exclusion: other significant diseases; taking regular oral corticosteroids; known aspirin or dietary salicylate sensitivity	• NR, with 19/20 & 17/19 atopic in omega-3 & omega-6 fatty acid groups, respectively • Severity: NR (baseline scores reported per study arm, yet no interpretation of severity) • Duration: NR • Method: episodic wheeze in last 12 mo & airways hyper-responsiveness & FEV_1 & FVC & allergen skin prick tests • Pre-study: numbers of pts using inhaled corticosteroids, beta-2 agonist use & disodium cromoglycate similar across study arms (13/20 & 13/19 & used inhaled corticosteroids in omega-3 & omega-6 fatty acids groups, respectively) • Study: medication use did not change significantly throughout the study (no data)	• Omega-3 fatty acid group: 1.22 g/d from fish oil capsules, *plus* omega-3 fatty acid diet (use only provided canola oils & margarines & salad dressings, from unmarked containers; plus, instructed to have a fish meal at least once per month) (diet manufacturer: Meadowlea Pty Ltd.) • 0.3 g MaxEPA® (RP Scherer, Melbourne, Australia) capsules (0.18 g EPA & 0.12 g DHA per capsule): 4 per day (total: 0.72 EPA g/d, 0.48 DHA g/d); ALA undefined • 6 mo intervention • n=NR/20	• Omega-6 fatty acid group: matched capsules plus omega-6 fatty acid diet (use only provided sunflower oils & margarines & salad dressings & oils, from unmarked containers; plus, asked to refrain from eating fish) (diet manufacturer: Meadowlea Pty Ltd.) • Control capsules (0.45 g safflower oil, 0.45 g palm oil, & 0.1 g olive oil; no EPA or DHA): 4 per day, of safflower/palm/olive oil • 6 mo intervention • n=NR/19
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Hodge, 1998,[52,53] Australia	• NS ? in FEV$_1$ (% predicted) in either study arm (p=NR)* • NS ? in asthma severity score (parental diary card: composite of daily diary data re AM expiratory flow rate, day & night symptoms, & medication use) in either study arm (p=NR)* • NS ? in dose response ratio to histamine challenge in either study arm (p=.10)* • NS between-arm difference in ? in TNF-alpha production (p=.075)	NR	• n=6 (dropped out at baseline; no reasons reported, or which study arm they left)	• Randomization: 1 • Blinding: 1 • Withdrawals/ dropouts: 1 • Jadad total score: 3 (Grade: B) • Allocation concealment: unclear • Applicability: III	Fisheries Research and Development Corporation of Australia, &, Asthma Foundation of New South Wales

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery /Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Kirsch, 1988, USA[54,55]	• Enrolled/ evaluated: 12/12 • Age (mean & range): 58.2 (42-73) y • % Male: 25 • Race: NR • Number of sites: 1	• Parallel RCT, double-blind (maintained via restricted discussion of side effects, adjusted steroid doses, & treatment of minor complications) • 16 wk (Run-in: 6 wk; 2 wk close-out)	• Inclusion: asthma $\geq$3 y duration; reversible airway obstruction $\geq$50% of d in past y (no description of recruitment process) • Exclusion: status asthmaticus, pneumonitis, pneumothorax or other major lung disease in past year.	• Asthmatic, 9/12 allergic rhinitis via history & pin-prick test (5 & 4 in Low & High dos e groups, respectively); • Severity: moderate (self-reported, & physician/observer, ratings): similar across study arms • Duration: 26.08 y • Method: standard clinical evaluations & pulmonary function tests • Pre-study: NR • Study: types & doses of all on-study medication, except for oral corticosteroids, kept constant; therapist allowed to adjust oral predisone dose $\leq$ 5 mg/wk; 10/12, including 6/6 in High dose group, got predisone; 1 on inhaled corticosteroids in Low dose group; 2/6 not on oral predisone in Low dose group, neither of whom on inhaled corticosteroids as well; similar oral predisone doses across study arms; 6/6 and 4/6 of same participants in Low & High dose groups, respectively, on both theophylline-like drug & beta-2 agonists; 3/6 & 2/6 in Low & High dose groups on cromolyn.	• High dose omega-3 fatty acids group: 4 total g/d EPA ethyl ester via gelatine capsules (92% pure; contained <2.5% DHA: Maruyasu Ltd, Osaka, Japan; checked by gas chromatography & high performance liquid chromatography): 2 capsules, 4 times/d, each capsule with 0.5 g & each dose with 1g • 8 wk intervention • n=6/6	• Low dose omega-3 fatty acids group: 0.1 total g/d EPA via gelatine capsules (same assessment of purity): 2 capsules, 4 times/d, each capsule with 0.0125 g & each dose with 0.025 g • 8 wk intervention • n=6/6

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Kirsch, 1988, USA[54,55]	• NS ? in total lung capacity in either study arm (p>.18)* • NS ? in airflow resistance in either study arm (p>.18)* • NS ? in FEV_1 in either study arm (p>.18)* • NS ? in FEF_{25-75} in either study arm (p>.18)* • NS ? in self-reported asthma severity ratings in either study arm (p>.10)* • NS ? in observer-reported asthma severity ratings in either study arm (p>.10)* • NS ? in generation of PGE by 10^6 PMN leukocytes in either study arm (p>0.5)* • NS ? in generation of PGE by mononuclear leukocytes in either study arm (p>.05)* • S decrease in generation of LTB_4 by 10^6 PMN leukocytes only in High dose study arm (p<.01)* • S increase in generation of LTB_5 by 10^6 PMN leukocytes in High dose (p<.01)* & Low dose study arms (p<.001)* • NS ? in generation of PGE by mononuclear leukocytes in either study arm (p>.05)* • S decrease in generation of LTB_4 by mononuclear leukocytes only in the High dose arm (p<.01)* • S increase in generation of LTB_5 by mononuclear leukocytes in High (p<.001)* and Low dose arms (p<.05)* • S suppression of PMN leukocyte chemotaxis to C5a, LTB_4 (3ng/ml), LTB_4 (30ng/mL), 10^{-7} fMLP (M), & 10^{-6} fMLP (M) only in High dose study arm (all: p<.01)* • NS ? in suppression of mononuclear leukocyte chemotaxis to C5a, LTB_4 (3ng/ml), LTB_4 (30ng/ml), 10^{-7} fMLP (M), & 10^{-6} fMLP (M) (all: p>.01)*	NR	n=0	• Randomization: 1 • Blinding: 1 • Withdrawals/ dropouts: 1 • Jadad total score: 3 (Grade: B) • Allocation concealment: unclear • Applicability: I	NIH Grants AI-19784, HL-31809, & HL-24136, &, the Veteran's Administration

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
McDonald, 1991, Australia[58]	• Enrolled/ evaluated: 15/NR • Age (mean & range): NR (28-72) y • % Male: 13.3 • Race: NR, likely Caucasian/ European • Number of Sites: NR	• RCT, 2-phase crossover (no phase orders reported); • 28 wk (Run-in: 2 wk; washout: 6 wk)	• Inclusion: NR (recruited from a Chest Clinic at hospital) • Exclusion: peptic ulcers, cardiovascular disease, other potential bleeding disorders	• NR, non-smoking asthmatics (at least 7 were ex-smokers: stopped 1-31 y before study, & smoked 3-50 y prior to cessation); • Severity: moderately severe (undefined) • Duration: NR • Method: recurrent reversible symptoms • Pre-study: NR • Study: NR	• Omega-3 fatty acid supplementation via fish oil (manufacturer: NR) • 15 Lipitac capsules/day: total of 2.7 g/d EPA & 1.8 g/d DHA • On-study dietary fish intake to be kept constant • 10 wk intervention • n=15/≤10	• Control supplementation via 15 control capsules (undefined), containing a total of 15 g/d of olive oil (manufacturer: NR) • On-study dietary fish intake to be kept constant • 10 wk intervention • n=see omega-3 fatty acids description

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = *n* completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
McDonald, 1991, Australia[58]	• NS between-arm difference in ? in AM PEF[†] • NS between-arm difference in ? in PM PEF[†] • NS between-arm difference in ? in bronchodilator use[†] • NS between-arm difference in ? in asthma symptom scores (cough, wheeze, dyspnoea, night-time asthma)[†] [†]no data or tests of significance reported	NR	• n=NR ($\geq$5) • Problems swallowing capsules (n=2) • Unrelated medical problem (n=3)	• Randomization: 1 • Blinding: 1 • Withdrawals/ dropouts: 1 • Jadad total score: 3 (Grade: B) • Allocation concealment: unclear • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Nagakura, 2000, Japan[64]	• Enrolled/ evaluated: 30/29 • Age (mean & range): 11.02 (4-17) y • % Male: 51.7 • Race: NR, but likely Asian • Number of sites: 1	• Parallel RCT, double-blind (stratified for weight, with block size of 4) • 12 mo (Run-in: 2 mo)	• Inclusion: NR (in-patients 85% of the time due to asthma) • Exclusion: NR	• NR • Severity: NR • Duration: mean = 10.1 y • Method: NR • Pre-study: oral corticosteroids; undefined numbers on daily doses (no data) of theophylline, salbutamol, disodium cromoglycate, & beclomethasone diproprionate (inhaled corticosteroids: 3 users/study arm; mean dose in fish oil group: 166.7 mg/d; mean dose in controls: 183.3 mg/d); rescue = inhaled beta-2 agonists with intravenous theophylline, with or without hydrocortisone. • Study: study arms "differed significantly" in amount of medication for acute asthma attacks (no data)	• EPA+DHA from fish oil • Capsule: 300 mg, including 84 mg EPA & 36 mg DHA (Nippon Suisan Kaisha Ltd., Tokyo, Japan) • 6-12 capsules/d based on body weight (17-26.8 mg/kg/d EPA & 7.3-11.5 mg/kg/d DHA); 18.8-24.2 kg = 6 capsules/d, (2, three times daily); 24.8-32.6 kg = 8/d (3/2/3); 34.0-41.1 kg = 10/d (3/3/4); 45.3-59.2 kg = 12/d (4, three times daily) • 10 mo intervention • n=15/11	• Visually identical olive oil capsules • Capsule: 300 mg olive oil (Nippon Suisan Kaisha Ltd., Tokyo, Japan) • 6-12 capsules/d based on body weight (see fish oil arm for regimen) • 10 mo intervention • n=15/12

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity))	Funding Source
Nagakura, 2000, Japan[64]	• S decrease in observer-evaluated asthma symptom scores only in omega-3 fatty acid arm (p=.01)* • S decrease in bronchial hyper-responsiveness to acetylcholine challenge only in the omega-3 fatty acid arm (p=.001)*	NR	• n=7 (23.3%: 3 were controls) • unable to swallow capsules (n=1/control); • after asthma improved at 6 mo, discharged at request of parents (n=2); • no reasons given for discharge (n=4)	• Randomization: 1 • Blinding: 2 • Withdrawals/ dropouts: 1 • Jadad total score: 4 (Grade: A) • Allocation concealment: unclear • Applicability: III	NR

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Okamoto, 2000a, Japan[66]	• Enrolled/ evaluated: 14/14 • Age (mean & range): 58.9 (22-84) y • % Male: 42.9 • Race: NR, but likely Asian • Number of sites: 1	• Parallel RCT, blinding (NR) • 4 wk (Run-in: NR)	• Inclusion: NR (admitted to hospital for treatment of asthma) • Exclusion: NR	• NR, although 7 atopic (baseline serum IgE observed) • Severity: moderate (undefined) • Duration: mean = 15 y • Method: post-bronchodilator FEV_1 & response to methacholine challenge & diurnal PEF variation & clinical diagnosis via International Consensus of Diagnosis and Management of Asthma criteria (airways inflammation, bronchial hyper-responsiveness to non-specific stimuli, episodic & reversible airflow obstruction) • Pre-study: all regularly using long-acting oral theophylline, inhaled beta-2 agonists, &, beclomethasone dipropionate (inhaled corticosteroid; mean dose: 196.4±173.7 mg/d) • Study: NR	• ALA from perilla seed oil-rich supplementation (manufacturer: NR) • Replacing other oils, used as salad dressing &/or mayonnaise: 10-20 g/d • Other dietary components unchanged • 4 wk intervention • n=7/7	• Corn oil-rich supplementation (self-identified as source of omega-6 fatty acids) (manufacturer: NR) • Replacing other oils, used as salad dressing &/or mayonnaise: 10-20 g/d • Other dietary components unchanged • 4 wk intervention • n=7/7

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Okamoto, 2000a, Japan[66]	• S greater increase in FEV_1 in the omega-3 fatty acid arm ($p<.05$) • S increase in AM PEF only in the omega-3 fatty acid arm ($p<.05$)* • S greater increase in FVC in the omega-3 fatty acid arm ($p<.05$) • S increase in V_{25} only in the omega-3 fatty acid arm ($p<.05$)* • S greater decrease in generation of LTB_4 by peripheral leukocytes in the omega-3 fatty acid arm ($p<.05$)[†] • S greater decrease in generation of LTC_4 by peripheral leukocytes in the omega-3 fatty acid arm ($p<.05$)[†] [†]no assessment of results at final 4-wk followup, with decreasing LTB_4 & LTC_4 generation in the control arm	NR	n=0	• Randomization: 1 • Blinding: 0 • Withdrawals/ dropouts: 1 • Jadad total score: 2 (Grade: C) • Allocation concealment: unclear • Applicability: III	NR

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Stenius - Aarniala, 1989, Finland[68]	• Enrolled/evaluated: 36/29 • Age (mean & range): 40 (19-61) y • % Male: 52.6 • Race: NR, but likely Scandinavian • Number of sites: 1	• RCT, 3-phase crossover (6 possible phase orders); double-blind • 32 wk (Run-in: 2 wk); no washout	• Inclusion: NR • Exclusion: fish allergy, diabetes, or coagulation disorders NB: Excluded during run-in period because variations (undefined) in their diurnal PEF were too small (n=4)	• Relatively stable asthma: 4 aspirin-sensitive; 4 skin-test positive; • Severity: moderate (= PEF variability >15%); 3/29 smokers; 12/29 ex-smokers (not in last 2 y); • Duration: NR • Method: MD clinical diagnosis: all fulfilled American College of Chest Physicians & American Thoracic Society (1975) criteria; • Pre-study: 29/29 on inhaled beta-2 agonists, 24 inhaled corticosteroids, 8 long-term oral corticosteroids, 2 disodium cromoglycate, 3 ipratropium bromide, 26 oral theophylline, 1 oral beta-2 agonists. • Study: drug use unchanged during all phases (no data re how may have changed from pre-study)	• 20 mL daily of MaxEPA® fish oil (Seven Seas Health Care Ltd., Hull, UK): bottles concealed yet no attempt to conceal taste • 18% EPA + 12% DHA (dose not given in g) • Self-delivery by 10 mL spoon • 10 wk intervention (per phase) • n=36/29	• Control phase: 20 mL daily of olive oil (bottles concealed yet no attempt to conceal taste): 77% monoenoic acids (mainly oleic acid) (Seven Seas Health Care Ltd., Hull, UK) • Phase 3: 20 mL daily of Evening primrose oil: Naudicelle®: Bio-Oil Research Ltd., Crewe, UK) phase (bottles concealed yet no attempt to conceal taste): 72% cis-linoleic acid & 9% gammalinolenic acid (source of omega-6 fatty acids) • Each preparation self-delivered by 10 mL spoon • 10 wk intervention (per phase) • n=see omega-3 fatty acids description

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Stenius - Aarniala, 1989, Finland[68]	• NS differences between the 3 phases for AM PEF (% predicted) [†]* • NS differences between the 3 phases for PM PEF (% predicted) [†]* • S higher plasma PGE_2 levels in the fish oil phase than the other 2 phases ($p<.05$)* • S lower plasma $PGF_{2-alpha}$ levels in the control (olive oil) phase than the other 2 phases ($p<.05$)* • NS between-phase differences in plasma levels of TxB_2 ($p>.05$)* • NS between-phase differences in plasma levels of 6-keto-$PGF_{1-alpha}$ ($p>.05$)* • NS between-phase differences in urine levels of PGE_2 ($p>.05$)* • NS between-phase differences in urine levels of $PGF_{2-alpha}$ ($p>.05$)* • NS between-phase differences in urine levels of TxB_2 ($p>.05$)* • NS between-phase differences in urine levels of 6-keto-$PGF_{1-alpha}$ ($p>.05$)* [†]no tests of significance reported	NR	• n=7 (could not tolerate taste of the oil, or difficulty keeping asthma diary: no breakdown for study phases by problem)	• Randomization: 1 • Blinding: 0 • Withdrawals/ dropouts: 1 • Jadad total score: 2 (Grade: C) • Allocation concealment: unclear • Applicability: III	NR, with MaxEPA® provided by Orion Pharmaceuticals

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-phase difference in (%) ? in the outcome

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Thien, 1993, Engand[67]	• Enrolled/ evaluated: 37/25 • Age (mean & range): NR (19-42) y (completers only) • % Male: 52 (completers only) • Race: NR, but likely Caucasian/ European • Number of sites: 1	• Parallel RCT, double-blind (evaluated in and out of pollen season) • 26 wk (Run-in: 2 wk)	• Inclusion: grass pollen sensitive; hay fever symptoms associated with asthma during pollen season; (recruited from Hospital Allergy Clinic) • Exclusion: NR	• NR, no aspirin sensitivity; all pollen-sensitive (positive skin-prick test) & hay fever; some sensitive to fungal spores yet assumed that equally distributed via randomization • Severity: NR • Duration: NR • Method: NR (only histamine bronchial challenge) • Pre-study: no oral corticosteroids, sodium cromoglycate, nedocromil sodium, or theophylline; • Study: asked to maintain constant inhaled corticosteroid dose (confirmed; no data), & 8/25 completers regularly used them ($\leq$200 µg/d, 1 used 400 µg/d; 13/25 completers on salbutamol inhaler (EPA: 8; control: 5); 7 regular salbutamol (EPA: 3; control: 4); 5 regular salbutamol & beclomethasone dipropionate (inhaled corticosteroid) via inhaler (EPA: 4; control: 1); chlorpheniramine or terfenadine permitted for symptom relief; longer-acting anti-histamines (e.g., cetirizine, astemiozole) not permitted	• 5.4 g/d from fish oil capsules • MaxEPA® (Seven Seas, Ltd., Marfleet, Hull, UK) capsule (total: 3.2 g/d EPA + 2.2 g/d DHA): 18 capsules/d • 6 mo intervention • n=NR/15	• Visually identical olive oil capsules (no amount of oil reported) (Seven Seas Ltd, Marfleet, Hull, UK) • 6 mo intervention • n=NR/10

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 1: Randomized controlled trial evidence of health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Thien, 1993, England[67]	• NS between-arm difference in respiratory symptom score (diary card) in pollen season[†*] • NS between-arm difference in total bronchodilator use (diary card) in pollen season[†*] • NS between-arm difference in AM PEF (% predicted) in pollen season[†*] • NS between-arm difference in PM PEF (% predicted) in pollen season[†*] • NS between-arm difference in diurnal PEF variability (% maximum) in pollen season[†*] • NS between-arm difference in histamine responsiveness (airways conductance: sGAW) in pollen season[†*] [†]intervention began when started recording data using diary cards, suggesting that 'pre-intervention' data were influenced by intervention.	NR	• n=12 (32%): (no indication of study arms from which 11/12 participants left): • withdrew from EPA study arm in first wk when developed nausea & vomiting after taking capsules (n=1) • size & number of capsules found to be unmanageable, withdrew after first wk (n=2) • size & number of capsules found to be unmanageable, withdrew in first 2 wk (n=4) • withdrew in first month when unable to perform daily peak flows & complete diary cards (n=2) • difficulty taking capsules & recording daily peak flows & diary cards (n= 2) • withdrew for personal reasons (n=1)	• Randomization: 1 • Blinding: 2 • Withdrawals/ dropouts: 1 • Jadad total score: 4 (Grade: A) • Allocation concealment: unclear • Applicability: III	British United Provident Association Medical Foundation (independent medical research charity), National Asthma Campaign (UK), &, Seven Seas, Marfleet, Hull (UK) for MaxEPA® & matched control capsules

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Ashida, 1997, Japan[59]	• Enrolled/evaluated: 5/5 • Age (mean & range): 60.2 (51-72) y • % Male: 0 • Race: NR, likely Asian • Number of sites: 1	• Non-comparative case series • 2 wk (Run-in: NR)	• Inclusion: pts with asthma admitted to hospital for treatment • Exclusion: NR	• Bronchial asthma (n=4), cough variant asthma (n=1) • Severity: NR • Duration: mean = 10.6 (4-19) y • Method: NR • Pre-study: all on oral long-acting theophylline (200-400 mg/d); inhaled beta-2 agonists; inhaled beclomethasone dipropionate (400-1200 μg/d), prednisolone 5 mg/d (n=2) • Study: same as prestudy (doses of inhaled corticosteroid & oral theophylline constant during study)	• Perilla seed oil supplementation (ALA: undefined amount) • 15 g/d Perilla seed oil as replacement salad dressing &/or mayonnaise • 2 wk exposure • Other diet unchanged • n=5/5	NA
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Ashida, 1997, Japan[59]	• S decrease in asthma symptoms score (cough, wheeze, daytime activity, sputum volume, dyspnoea) ($p<.05$) • S increase in AM PEF ($p<.05$) • S increase in PM PEF ($p<.05$) • S decrease in generation of LTB_4 by peripheral leukocytes ($p<.05$) • S decrease in generation of LTC_4 by peripheral leukocytes ($p<.05$)	NR	n=0	• Total quality score: 3 (Grade: B) • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Broughton, 1997, USA[73]	• Enrolled/evaluated: 26/19 • Age (mean & range): 22 (19-25) y • % Male: NR • Race: NR • Number of sites: 1	• Non-comparative case series (2-phase): High ratio always followed by Low ratio exposure • 8 wk (Run-in: NR; no washout)	• Inclusion: non-specific bronchial responsiveness to methacholine with FEV_1>70%; non-smoking atopic asthmatic pts • Exclusion: use of fish oil supplements; >1 fish meal/wk; history of bleeding disorder or delayed clotting time	• Non-smoking, atopic asthmatics; no upper respiratory tract infections or asthma exacerbations 6 wk prior to study • Severity: NR • Duration: NR • Method: air flow obstruction; FEV_1>70% of predicted with methacholine test • Pre-study: salbutamol, oral corticosteroids, oral theophylline, (doses: NR) • Study: NR, no nonsteroidal anti-inflammatory drugs	• Low fish oil supplementation[†] • Average dose: ~0.7 g/d EPA+DHA • Omega-6/omega-3 fatty acid ratio = 1:0.1 • Capsules of fish oil (Dose: NR; Shaklee Corporation) • 4 wk exposure (average increase in energy was <1.5%) • n=26/19	• High fish oil supplementation[†] • Average dose: ~3.3 g/d EPA+DHA • Omega-6/omega-3 fatty acid ratio = 1:0.5 • Capsules of fish oil (Dose: NR; Shaklee Corporation) • 4 wk exposure (average increase in energy was <1.5%) • n=26/19

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
[†]Fish oil regimes individualized based on analysis of pre-study omega-6 fatty acid intake

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Broughton, 1997, USA[73]	- With low ratio exposure: S reduction from baseline of 51%, 89%, 65% & 92% in provocative methacholine dose to cause a 20% fall in FVC_1, FEV_1, PEF, FEF_{25-75}, respectively ($p<.05$)* - With high ratio exposure: NS difference ($p>.05$)* from baseline in provocative methacholine dose to cause a 20% fall in each of FVC_1, FEV_1, PEF, FEF_{25-75} - With high ratio exposure: responders' (NS fall in respiratory measures with increased challenge) respiratory responses were never reduced by 20%, regardless of the methacholine dose (no data) - With high ratio exposure: nonresponders (respiratory reductions with increased challenge) had significantly greater difficulty breathing at 1.375 units methacholine, & respiratory capacity hindered by high omega-3 fatty acid ratio for 3 of 4 respiratory outcomes (no data), with only FEF_{25-75} improved (no data) - S increase in urinary total LTE_4 excretion associated with low ratio ($p<.05$)* - NS Δ in urinary LTE_5 excretion associated with low ratio ($p>.05$) - NS Δ in urinary LTE_4 excretion with high ratio for responders or nonresponders ($p>.05$)* - Significantly lower urinary LTE_4 excretion with high ratio ($p<.05$)* - S increase in urinary LTE_5 excretion with high ratio for responders & nonresponders ($p<0.5$)* - NS Δ in urinary LTE_4 excretion in responders & nonresponders combined ($p>.05$)* - Significantly higher urinary LTE_5 excretion for responders with high ratio ($p<.05$)*	NR	7 (27%) dropouts; Reasons: NR	- Total quality score: 3 (Grade: B) - Applicability: I	University of Wyoming Biomedical Research Support & Shaklee Corporation (Hayward, CA)

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Gorelova, 1998, Russia[70]	• Enrolled/ evaluated: 33/NR • Age (mean & range): NR (1-12) y • % Male: NR • Race: NR • Number of sites: 1	• Non-randomized controlled trial: matched for age, diagnosis & treatment (no data) • NR (Run-in: NR)	• Inclusion: NR • Exclusion: NR	• Asthmatic pts with atopic dermatitis • Severity: NR • Duration: NR • Method: NR • Pre-study: broncholytics, antihistamines and corticosteroids (undefined) • Study: same drugs	• 'Polyen' supplementation & hypoallergenic diet (poorly defined) • Fish oil capsules from seafish bodies; 1 capsule = 0.3 g fish oil: total 4.5 g/d fish oil (omega-3 fatty acid content not <25%) (types & amounts not defined) • Omega-6/omega-3 fatty acid ratio data contradictory • Length: NR • n=23/NR	• Hypoallergenic diet (poorly defined) • Control (NR) • Omega-6/omega-3 fatty acid ratio data contradictory • Length: NR • n=10/NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Gorelova, 1998, Russia[70]	• Significantly lower bronchodilator use in the omega-3 fatty acids arm ($p<.05$)*	• Atopic dermatitis & NR	NR	• Total quality score: 2 (Grade: C) • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Hashimoto, 1997, Japan[62]	• Enrolled/ evaluated: 8/8 • Age (mean & range): 61.6 (38-78) y • % Male: 12.5 • Race: NR, likely Asian • Number of sites: 1	• Non-comparative case series • 10 wk (Run-in: 2 wk)	• Inclusion: ambulatory pts with Total Cholesterol >220 mg/dL or triglycerides >170 mg/dL with pre-existing hyperlipidemia and mild to moderate asthma • Exclusion: antihistamine <2 wk prior to study; >5 mg/d oral prednisone; long-term steroids (undefined) started <1 mo before study	• Mild to moderate asthmatic pts, allergic dermatitis (n=4), hyperlipidemia (n=8) • Duration: NR • Severity: mild to moderate • Method: NR • Pre-study: NR • Study: NR	• EPA • 1800 mg/d EPA • 8 wk exposure • n=8/8	NA

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Hashimoto, 1997, Japan[62]	• S decrease in symptom score (undefined) ($p<.05$) • S decrease in asthma score (undefined) ($p<.05$) • S decrease in therapeutic score (undefined) ($p<.05$) • NS Δ in sleep score (undefined) ($p>.05$) • NS Δ in daily life score (undefined) ($p>.05$) • S % increase in AM PEF ($p<.05$) • S % increase in PM PEF ($p<.05$) • NS Δ in urinary LTB_4 excretion ($p>.05$) • NS Δ in urinary LTE_4 excretion ($p>.05$)	• Allergic dermatitis (n=4); Hyperlipidemia (n=8)	n=0	• Total quality score: 3 (Grade: B) • Applicability = III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts= participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Machura, 1996, Poland[63]	• Enrolled/ evaluated: 60/60 • Age (mean & range): NR (7-17) y • % Male: NR • Race: NR, likely Caucasian/ European • Number of sites: NR	• Non-randomized controlled trial • 12 wk (Run-in: NR)	• Inclusion: NR • Exclusion: NR	• Bronchial asthma: mild (n=21; 76% atopic); severe (n=16; 56% allergic asthma); controls (75% atopic) • Severity: NR • Duration: mild (mean = 7.6 y); severe (mean = 9.25 y); controls (mean = 7.36 y) • Method: NR • Pre-study: routine asthma treatment • Study: NR	• Fish oil supplementation • 5 mL oil at each of 3 main meals: total 15 mL fish oil/d, 3 g/d EPA • 12 wk exposure • n=37/37	• Control: sunflower oil • 5 mL oil at each of 3 main meals: total 15 mL sunflower oil/d • 12 wk exposure • n=23/23
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Machura, 1996, Poland[63]	• NS difference between mild asthma subgroup and controls in number of days with increased severity of asthma symptoms ($p>.05$)* & S difference between severe asthma subgroup and controls in number of days with increased severity of asthma symptoms ($p=.05$)* • NS difference between either subgroup and controls in loss of asthma control ($p>.05$)* • NS difference between either asthma subgroup and controls in PEF ($p>.05$)* • Significantly higher FEF_{25-75} only in mild asthma subgroup relative to controls ($p<.05$)* • NS difference between either asthma subgroup and controls in FEV_1 ($p>.05$)*	NR	NR	• Total quality score: 3 (Grade: B) • Applicability: III	NR

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Source/Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Masuev, 1997a, Russia[60]	• Enrolled/ evaluated: 34/NR • Age (mean & range): 50.2 (NR) y • % Male: NR • Race: NR • Number of sites: NR	• Non-randomized controlled trial: matched for age, sex & asthma severity • 2 mo (Run-in: NR)	• Inclusion: NR • Exclusion: NR	• Bronchial asthma atopic (n=17); infection-dependent asthma (n=10) • Severity: NR • Duration: NR • Method: NR • Pre-study: NR • Study: NR	• EPA+DHA (undefined amount) & vitamin E (undefined amount) • 'Eiconol' capsules: 6 g/d • 2 mo exposure • n=27/NR	• Olive oil capsules: 6 g/d • 2 mo exposure • n=7/NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report							

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Masuev, 1997a, Russia[60]	• S decrease in 5-hydroxyeicosatetraenoic acid (5-HETE) production with omega-3 fatty acids exposure ($p<.05$)* • ? in 5-hydroxyeicosapentaenoic acid (5-HEPE) with omega-3 fatty acids exposure (statistical test: NR)*	NR	NR	• Total quality score: 2 (Grade: C) • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Masuev, 1997b, Russia[61]	• Enrolled/evaluated: 8/8 • Age (mean & range): NR (17-40) y • % Male: NR • Race: NR, likely Caucasian/ European • Number of sites: NR	• Non-randomized controlled trial: identified those with both acute & late asthma reaction to allergen inhalation challenge, then divided them into 2 subgroups matched for age, sex, & duration of asthma • 8 wk (Run-in: NR)	• Inclusion: selected on basis of positive skin prick test to house dust, & late asthmatic reaction to allergen inhalation challenge; test was positive if, after 4-8 h, PEF decreased by ≤35% • Exclusion: NR	• Bronchial asthma (relative remission), & hyper-sensitive to house dust • Severity: NR • Duration: mean = 3-12 y • Method: NR • Pre-study: not taking steroids (undefined) • Study: NR	• 6 g/d EPA+DHA • 'Eiconol' capsules • 8 wk exposure • n=5/5	• Capsules of olive oil (6 g/d) not containing omega-3 fatty acids • 8 wk exposure • n=3/3

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Masuev, 1997b, Russia[61]	• S increase in PEF (relative to pre-exposure) 4-8 h after allergen challenge (late response period) only in the omega-3 fatty acids subgroup ($p<.05$)*	NR	n=0	• Total quality score: 4 (Grade: A) • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Okamoto, 2000b, Japan[71]	• Enrolled/evaluated: 26/26 • Age (mean & range): 61 (30-84) y • % Male: 38.5 • Race: NR, likely Asian • Number of sites: 1	• Non-comparative case series • 4 wk (Run-in: NR)	• Inclusion: mild asthmatic pts • Exclusion: NR	• Mild asthmatic pts: atopic (n=13) • Duration: mean = 8.7 y • Severity: mild • Method: according to criteria of the International Consensus on Diagnosis and Treatment of Asthma: symptoms, FEV_1, PEF variability, or methacholine test • Pre-study: long-acting oral theophylline, inhaled beta-2 agonists, inhaled corticosteroids (mean dose = 305.8 µg/d) • Study: NR	• Perilla seed oil supplementation (ALA: undefined amount) • 10-20 g/d as replacement salad dressing &/or mayonnaise (mean dose = 14.65 g/d) • 4 wk exposure • Diet unchanged • n=26/26	NA

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant;; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Okamoto, 2000b, Japan[71]	• Identified responders (vs nonresponders) as participants with significantly decreased LTC_4 generation by peripheral leukocytes (see below) • While S increase in AM PEF for responders & nonresponders ($p<.05$), values significantly lower for responders during study ($p<.05$) • Significantly lower baseline FVC, FEV_1 & V_{25} values for responders ($p<.05$) • S increases in FVC & FEV_1 from exposure only for responders ($p<.05$) • S differences between responders & nonresponders in FVC & FEV_1 at final follow-up ($p<.05$) • LTC_4 generation by peripheral leukocytes decreased and increased significantly for responders & nonresponders, respectively ($p<.05$) • At final follow-up, LTC_4 levels differed significantly for responders & nonresponders ($p<.05$)	NR	n=0	• Total quality score: 4 (Grade: A) • Applicability: III	NR
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report *No reported statistical test of the between-arm difference in (%) ? in the outcome					

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Picado, 1988, Spain[74]	• Enrolled/evaluated: 10/10 • Age (mean & range): 52 (31-65) y • % Male: 30 • Race: likely Caucasian/ European • Number of sites: 1	• Non-comparative case series (2-phase): first placebo, then fish oil • 14 wk (single blind) (Run-in: 2 wk; no washout)	• Inclusion: aspirin-intolerant asthmatic pts • Exclusion: NR	• Aspirin-intolerant asthmatic pts, nasal polyps (n=5) • Severity: NR • Duration: mean = 24.7 (4-56) y • Method: bronchial reaction to aspirin challenge • Pre-study: steroid dependent (oral prednisone & inhaled beclomethasone dipropionate) (n=7) • Study: oral prednisone (n=7), fixed dose inhaled beclomethasone dipropionate and fixed dose salbutamol (2 puffs every 6 h); prednisone 30 mg/d if acute attack	• Experimental diet: MaxEPA® & sardine oil • 18.4% EPA + 10.5% DHA • 3 g/d of omega-3 fatty acids (150 mg sardine oil & 12 MaxEPA® fish oil capsules) & eucaloric diet (including 32% fat) • 6 wk exposure • n=10/10	• Placebo (lactose) • 12 capsules/d & eucaloric diet (including 32% fat) • 6 wk exposure • n=10/10

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study;* Note: superscripts refer to reference list in main report

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Picado, 1988, Spain[74]	• NS ? in pulmonary symptom score (cough/dyspnoea) with either exposure ($p>0.05$)* • S decrease in PEF only with fish oil exposure ($p<.05$)* & S difference in PEF between fish oil and control at final followup ($p<.05$)* • NS between-exposure difference in oral corticosteroid use over the study ($p>.05$)* • S increase in bronchodilator use only during the last 2 wk of fish oil exposure ($p<.05$)* & S between-exposure difference in bronchodilator use in last 2 wk, with greater use in fish oil exposure ($p<.05$)* • S decrease in concentration of TxB_2 only with fish oil exposure ($p<.001$)*	NR	n=0	• Total quality score: 5 (Grade: A) • Applicability: III	Sociedad Española Patologia Respiratoria

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-study Medication/ Study Medication	Intervention/Exposure Definition (Omega-3 Fatty AcidTypes(s)/Source/Delivery/ Serving Size or Dose/ Length) & Number of Pts Enrolled/Completed	Comparator Definition (Control or Background Diet/Source/ Delivery/Serving Size or Dose/Length) & Number of Pts Enrolled/Completed
Villani, 1998, Italy[72]	• Enrolled/evaluated: 7/7 • Age (mean & range): 31 (20-49) y • % Male: 57 • Race: NR, likely Caucasian/European • Number of sites: 1	• Non-comparative case series • 30 d (Run-in: NR)	• Inclusion: asthmatic participants in clinical remission & FEV_1>80% predicted, & positive skin prick test to $\geq$2 aero-allergens • Exclusion: receiving asthma medication	• Atopic pts with mild seasonal asthma due to airborne allergens, in clinical remission; no respiratory infections <8 wk prior to enrollment; assessed outside pollen season • Duration: NR • Severity: mild • Method: positive skin prick test to $\geq$2 aero-allergens, FEV_1 >80% • Pre-study: none • Study: none	• EPA+DHA • 1 g/gel capsule = 3 g/d with EPA & DHA in 1:1 ratio • 30 d exposure • Free diet • n=7/7	NA

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants: n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 2: Evidence from other study designs regarding health effects of omega-3 fatty acids on asthma (Part B continued)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Villani, 1998, Italy[72]	• S reduction in maximum fall in FEV_1 in response to bronchial challenge ($p<.05$) • S reduction in airways responsiveness to bronchial challenge ($p<.05$) • S decrease in residual volume after 30 d ($p<.05$) • NS ? in TLC ($p>.05$) • NS ? in FEF_{25-75} ($p>.05$) • NS ? in PEF ($p>.05$) • NS ? in slow vital capacity ($p>.05$)	NR	n = 0	• Total quality score: 4 (Grade: A) • Applicability: III	NR

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; pts = participants; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report
*No reported statistical test of the between-arm difference in (%) ? in the outcome

Evidence Table 3: Randomized controlled trial evidence of omega-3 fatty acids to prevent asthma (Part A)

Author, Year, Location	Study Characteristics	Study Design & Duration	Eligibility Criteria	Asthma Description/ Severity/Duration/ Diagnostic Method/ Pre-Study Medication/ Study Medication	Intervention/Exposure Definitions (number Randomized) (Omega-3 Fatty Acid Type(s)/Source/Delivery/ Serving Size or Dose Intervention Length)	Comparator Definitions (number Randomized) (Control or Background Diet/Source/Delivery/ Serving Size or Dose/ Intervention Length)
Mihrshahi, 2003,[50,51] Australia	• Enrolled/ evaluated: 616/554 • Age (mean & range): 18 mo • % Male: 50 • Race: NR, likely European/ Caucasian; some of Aboriginal/ Torres Strait Islander descent (3%) • Number of Sites: 6	• Factorial RCT • 18 mo interim analysis in 60 mo study (Run-in: NR)	• Inclusion: pregnant women (36 wk gestation) with unborn children at high risk for asthma ($\geq$1 parent or sibling with asthma or asthma symptoms), reasonable fluency in English, telephone at home, reside within 30 km of recruitment center • Exclusion: pet cat at home, families on strict vegetarian diet, multiple births, born <36 wk gestation	• Possible asthma & symptoms in 18 mo-old children: MD diagnosis & use of asthma medication <6 mo • Severity: American Thoracic Society definition (mild, moderate, severe) • Duration: NR • Method: positive skin prick test, symptoms assessed by nurse & questionnaire. • Pre-study: NA • Study: inhaled bronchodilators (albuterol, terbutaline &/or ipratropium bromide), cromoglycate or nedocromil, inhaled corticosteroids (beclomethasone, budesonide, or fluticasone), oral antihistamines, nasal steroids, oral prednisone	• Arm C (n=159): active diet (see below) & no house dust mite reduction (advice on cleaning & ventilation; no placebo mattress covers) • Arm D (n=153): active diet & active house dust mite reduction • Active diet: one 500 mg capsule/d tuna fish oil (0.8 mg EPA + 3.6 mg DHA per kg body weight; 37% omega-3 fatty acids & 6% omega-6 fatty acids: Clover Corporation, Sydney, Australia) given to child in favorite foods/drinks from age 6 mo; if breast fed pre-6 mo, no supplement used (omega-3 fatty acids in breast milk equals supplement); if bottle fed, fish oil added to formula; dose standardized for fluid intake & child's age; pre-birth onwards, family given canola oil & margarine (6% omega-3 fatty acids & 16% omega-6 fatty acids) (ALA: NR) • Target omega-6/omega–3 fatty acid ratio = 5:1 • 18 mo intervention	• Arm A (n=149): placebo diet & no house dust mite reduction • Arm B (n=155): placebo diet & active house dust mite reduction (impermeable mattress covers; washable play mat; bedding & mat washed in acaricidal detergent prior to birth & every 3 mo) • Placebo diet: one 500 mg/d Sunola oil capsule (0.3% omega-3 fatty acids, 7% omega-6 fatty acids, 82% monounsaturated fatty acids: Clover Corporation, Sydney, Australia) delivered as per active diet; pre-birth onwards, family given polyunsaturated oils & margarines (1.2% omega-3 fatty acids, 40% omega-6 fatty acids) • Target omega-6/omega–3 fatty acid ratio = 15-20:1 • 18 mo intervention
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report						

Evidence Table 3: Randomized controlled trial evidence of omega-3 fatty acids to prevent asthma (Part B)

Author, Year, Location	Results	Concurrent Conditions & Medications	Number (%) of & Reasons for Dropouts/ Withdrawals (Per Study Arm)	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Mihrshahi, 2003,[50,51] Australia	• NS difference in diagnosed prevalence of asthma (14.7% vs 12.5% in active vs control diet groups): -2.2% [95% CI -7.9% to 3.5%]) or for any medication use, including inhaled corticosteroids (1.3 [-3.2 to 5.8]) • Significantly lower number of episodes of wheeze 'ever' (9.8% [1.5%-18.1%]; p=.02) & of wheeze >1 wk (7.8% [0.5-15.1; p=.04) in active (vs control) diet arm • NS differences in number of: episodes of wheeze >1 wk unassociated with a cold (p=.34), episodes of wheeze with difficulty breathing (p=.82), visits to doctor for wheeze (p=.09), visits to emergency for wheeze (p=.30), hospital admissions for wheeze (p=.54), &, episodes of cough for >1 wk unassociated with a cold (p=.76) • NS effect for house dust mite intervention for any of above-noted outcomes (p>.05) • NS interactions between active diet and house dust mite avoidance interventions in effect on any outcomes (p>.05) • Significantly higher proportion of omega-3 fatty acids in active diet than control arms (p<.001), &, of omega-6 fatty acids in control arm than in active diet arm (p<.0001) • Significantly different ratio of omega-6/omega-3 fatty acids in active (5:1) & control arm plasma (7.14: 1: p<.0001) • NB: Confounders equally distributed across arms (environmental smoke exposure; being male; maternal asthma history; breast-fed; low birth weight; young mothers)	• Smoking in pregnancy (24%) • Mothers with eczema (26.9% control, 22.6% diet) • Family history asthma: mother (55%), father (40%) • Medications (NR)	• Withdrew immediately after birth (n=6) & prior to 12 mo visit: birth weight <2.5 kg; major surgery or hospitalization for >1 wk; congenital malformations or other significant disease • Withdrew before 12 mo visit (n=56; reasons: NR) • Withdrew before 18-mo assessment • (n=6; reasons: NR) • Characteristics associated with withdrawals: parents younger, mothers less likely to be tertiary-educated, & fathers less likely to be employed full-time • No data per study arm.	• Randomization: 1 • Blinding: 0 • Withdrawals/ dropouts: 1 • Jadad total score: 2 (Grade: C) • Allocation concealment: adequate • Applicability: III	• National Health and Medical Research Council of Australia, New South Wales Health Department; The Children's Hospital at Westmead; & Cooperative Research Centre for Asthma • Goods & services from Allergopharma Joachim Ganzer KG Germany, John Sands Australia, Hasbro, Refrigerated Roadways, & AstraZeneca • Reduced cost goods from Auspharm, Allersearch, Meadow Lea Foods, & Clover Corporation

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part A)

Author, Year, Location	Study Characteristics	Study Design/ Selection Criteria/ Selection Method/ Study Duration	Asthma (sub-) Population Description/ Severity/Duration/ Diagnostic Method/ Medications	Other (Sub-) Population(s): Description	Factors Distinguishing (Sub-) Populations	Exposure(s)	Dietary Intake Data Collection Method/ Timeframe/ Informant-Administrator
Hodge, 1996,[77] Australia	• Enrolled/ evaluated: 584/468 • Age (mean & range): 9.5 (9.4-9.6) y • % Male: 50.2 • Race: NR, likely Caucasian/ European • Number of Sites: NR (all schools)	• Stratified case-control design • Inclusion: Cross-section of 808 children aged 8-11 y from schools randomly selected within 10 km radius of Sydney landmark. With airways hyper-responsiveness (AHR) to exercise, wheeze in last 12 mo, & 3-in-5 sample of normal airways (no AHR, no wheeze) by excluding 2 after every 3 from numerically ordered list • Exclusion: non-responders • Duration: June 1993: respiratory questionnaire. Oct 1993: dietary questionnaire	• Current asthma: wheeze & AHR (n=71): Age (mean & range): 9.6 (9.4-9.8) y; % male: 56.3; weight (mean & range): 34.0 (32.3-35.7) kg • Severity: NR • Duration: NR • Method: AHR = ≥15% fall in FEV_1 after 6-min run on flat surface; & wheeze in the past 12 mo with or without exercise. • Medication: NR	• Normal airways (neither wheeze nor AHR: n=263): Age (mean & range): 9.5 (9.4-9.6) y; % male: 56.3; weight (mean & range): 32.8 (32-33.6) kg • Airways hyper-responsiveness only (n=55): Age (mean & range): 9.3 (NR) yrs; % male: 63.6; weight (mean & range): 33 (NR) kg • Wheeze only (n=79): Age (mean & range): 9.3 (NR) yrs; % male: 57; weight (mean & range): 32.9 (NR) kg	• Current asthmatics vs AHR only vs wheeze only vs normal airways: atopy (93% vs 65.5% vs 48.1% 27.8%); early respiratory infection (22.5% vs 10.9% vs 22.8% vs 11.4%); parental asthma (40.9% vs 20.0% vs 41.8% vs 21.3%); Australian born (81.7% vs 81.8% vs 89.9% vs 82.5%)	• Consumption of fish over the last year (fresh fish, non-oily fish, oily fish) • Oily fish: >2% fat (e.g., blue-eyed cod; blue mackerel) • Non-oily fish: ≤2% fat	• Dietary questionnaire (consumption patterns for >200 foods [& sodium intake] common in Australia, including fish): daily, weekly, monthly, rarely, never (Common-wealth Scientific & Industrial Research Organization; Division of Human Nutrition, South Australia) • Time: last 12 mo • Parental questionnaire (collected by blinded study coordinator)

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part B)

Author, Year, Location	Results	Number (%) of & Reasons for Exclusion	Quality Internal Validity & Applicability (External Validity)	Funding Source
Hodge, 1996,[77] Australia	• When results unadjusted, risk of current asthma significantly lower in consumers of any fresh fish [OR 0.50 (0.27-0.92); $p<.05$)] or oily fresh fish [OR 0.29 (0.13-0.67); $p<.01$); current asthma found in only 8.8% of children who ate oily fish but in 15.6% of those who ate non-oily fish only, & 23% of those who never ate fresh fish (p-values: NR) • When results adjusted for risk factors (atopy, parental asthma, parental smoking, ethnicity, country of birth, early respiratory illness, & gender), only children who ate oily fresh fish had a S reduced risk of current asthma [OR 0.26 (0.09-0.72); $p<.01$)]; in these children, the risk was 1/4 that of those who did not eat oily fish • Significantly fewer children with current asthma included oily fish in their diet than did children with normal airways ($p<.05$); NS difference in proportion of children with current asthma & normal airways who ate exclusively non-oily fish ($p>.05$); NS difference between the 4 groups in total fish intake (servings) per wk ($p>.05$) • Consumption of fresh fish of any kind did not significantly reduce the risk of AHR only or wheeze only either before or after adjusting for risk factors ($p>.05$) • NS associations of both fresh fish consumption & respiratory disease with: socioeconomic status (father's occupation) or consumption of vitamins, minerals or other dietary supplements (p>.05)	• Did not receive questionnaire (n=10; reasons: NR) • Non-responders: 106 (18.5%); NS difference between responders & non-responders in prevalence of AHR (26.0% vs 27.1%) or fish consumption (46.2% vs 52.1%)	• Total quality score: 2 (Grade: C) • Applicability: III	• Fisheries Research and Development Corporation, Australia
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report				

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design/ Selection Criteria/ Selection Method/ Study Duration	Asthma (Sub-) Population Description/Severity/ Duration/Diagnostic Method/Medications	Other (Sub-) Population(s): Description	Factors Distinguishing (Sub-) Populations	Exposure(s)	Dietary Intake Data Collection Method/Timeframe/ Informant-Administrator
Huang, 2001,[48,49] Taiwan	• Enrolled/ evaluated: 1166/1055 • Age (mean & range): 14.7 (13-17) y • % Male: 50 • Race: NR, likely Asian • Number of sites: 5 strata, including 3 districts within each	• Cross-sectional study • Inclusion: all aged 13-17 y in study areas • Exclusion: living on offshore islands & in mountain areas (unusual diets), & those reporting asthmatic symptoms but without MD asthma diagnosis • Method: stratified, multiple-staged, probability sampling (proportional to size): 3 (of 365 total) townships/districts in each of 7 strata (by dietary habit, degree of urbanization [high, intermediate, low], & geographical region) • Duration: 3 y (1993-1996)	• Asthmatic adolescents (35/36 evaluated) • Severity: NR • Duration: NR • Method: Health status questionnaire included in NAHSIT (Nutrition and Health Survey in Taiwan), addressing 19 major diseases in youth (4-17 y), including MD diagnosis of asthma • Medications: NR	• Adolescents with MD-diagnosed allergic rhinitis (n=115): nose stuffiness, running nose, or sneezing either during morning or upon exposure to dust, pollen or chemicals; • Adolescents with wheeze (n=11) • Control participants without diagnosis of asthma or allergic rhinitis (n=1,030)	NR	•Polyunsaturated fatty acids in 24-hr food intake (seafish 1.8% of total diet): oily fish rich in omega-3 fatty acids, seafish, shellfish	• NAHSIT directed at ≥4 y olds • 2 methods: food-frequency questionnaire, &, 24-hr recall (e.g., ingredients, sizes, cooking method, etc.) • Time: in the past month for food frequency questionnaire • In 3 strata: door-to-door visits to interview adolescents (response rate: 86%)

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part B continued)

Author, Year, Location	Results	Number (%) of & Reasons for Exclusion	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Huang, 2001,[48,49] Taiwan	• In univariate analysis of food frequency data, with intake categorized by quartiles of intake frequency, higher frequencies of oily fish intake were S associated with asthma prevalence (*p*<.01); NS association for 'all fish' & shellfish with asthma (*p*>.05) • Multivariate logistic regression of food frequency data before and after adjusting for levels of urbanization revealed that oily fish consumption was not associated with asthma prevalence (*p*=.65) • 24-h dietary recall data did not distinguish omega-3 & omega-6 polyunsaturated fatty acids, and so, data cannot be used here • NB: prevalence of MD-diagnosed asthma S higher in males than females (*p*-value: NR); S trend in association of asthma prevalence and urbanization in males (*p*=.001) but not females (*p*=.10)	• NR, but likely due to lack of response	• Total quality score: 3 (Grade: B) • Applicability: III	• Department of Health, Executive Yuan, Republic of China
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report				

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design/ Selection Criteria/ Selection Method/ Study Duration	Asthma (Sub-) Population Description/Severity/ Duration/Diagnostic Method/Medications	Other (Sub-) Population(s): Description	Factors Distinguishing (Sub-) Populations	Exposure(s)	Dietary Intake Data Collection Method/Timeframe/ Informant-Administrator
Satomi, 1994, Japan[78]	• Enrolled/ evaluated: 7,742/7,588 • Age (mean & range): NR (6-11) y • % Male: 49.3 • Race: NR, likely Asian • Number of sites: 43 schools (coastal areas: 25; inland areas: 18)	• Cross sectional study • Inclusion: children in grades 1, 3 & 5 (gender not identified: n=153) in: coastal (high fish consumption from the Annual Statistics of Fishery Products Marketing) & inland areas • Exclusion: NR • Method: NR (25 coastal & 18 inland schools) • Duration: 1 mo (Oct 1985)	• Asthmatic children (n=706; % male: 62.5%) • Severity: NR • Duration: NR • Method: NR, likely by MD (as asked via questionnaire) • Medication: NR	• Children without asthma (n=6,882)	• NR • Coastal area children only: food allergy (n=158); eczema, hives (n=385); eczema or pimple-like growths during weaning (n=1,037); pneumonia (n=230)	• Fish classified as reddish (sardine, mackerel, pike: high EPA or DHA), pale (flatfish, sea bream, turbot: low EPA & DHA) & other marine products (shellfish, seaweed, dried fish, & fish paste)	• Frequency of consumption via Cochrane-Armitage test: >4-5 meals/wk; 2-3/wk; 1/wk; 1-2/mo & <1/mo • Time: current diet • Parental questionnaire

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part B continued)

Author, Year, Location	Results	Number (%) of & Reasons for Exclusion	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Satomi, 1994, Japan[78]	• Overall: S negative correlation between asthma prevalence & frequency of fish consumption (*p*<.05) [NS difference between asthma prevalence at coastal (9.5%) & inland (9.1%) areas (NR)] • Overall: asthma prevalence lower in those eating fish ≥4 times/wk (7.3%) as compared with <1/mo (11.1%) (*p*-value: NR) • Only in coastal areas, significantly lower frequency of asthma history in those eating reddish fish >4-5/wk vs eating it <1/mo (*p*<.01) • Inland areas: significantly higher asthma prevalence in those eating pale fish or seaweed >4-5/wk vs eating it <1/mo (*p*<.01) • Asthma prevalence significantly higher in those with pneumonia, eczema during weaning, general eczema, urticaria, or food allergy than in those without these (*p*<.05), with S negative correlation between asthma prevalence & reddish fish intake maintained in latter group (*p*<.05) • After excluding the effects of multiple confounders positively correlated with asthma prevalence (air conditioning in home; dusty home; temperature difference between day & night; ≥1 parental smoker; maternal intake of fermented beans & mushrooms while pregnant; live near pasture), asthma prevalence decreased as reddish fish intake increased (*p*<.05) • Asthmatic children only in coastal areas showed S negative relationship between reddish fish intake & asthma prevalence (*p*<.05) but those with asthma complicated by allergic manifestations (rhinitis; atopic dermatitis) did not (p>.05)	• Overall: 154 (2%) non-responders	• Total quality score: 4 (Grade: A) • Applicability: III	NR

NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design/ Selection Criteria/ Selection Method/ Study Duration	Asthma (Sub-) Population Description/ Severity/Duration/ Diagnostic Method/ Medications	Other (Sub-) Population(s): Description	Factors Distinguishing (Sub-) Populations	Exposure(s)	Dietary Intake Data Collection Method/ Timeframe/ Informant-Administrator
Takemura, 2002, Japan[76]	• Enrolled/ evaluated 25,767/23,782 • Age (mean & range): NR (6-15) y • % Male: 50.4 • Race: NR • Number of Sites: 48 schools	• Cross-sectional study • Inclusion: all 33 public elementary schools & 15 junior high schools in Tokorozawa • Exclusion: insufficient answers on questionnaire; participants having experienced an asthma attack but not currently asthmatic • Method: NR • Duration: 15 days (2/2/98-17/2/98)	• MD-identified & -treated asthma (n=1,673) in past 2 y (episodes of cough or sputum, wheezy or whistling sound while breathing, shortness of breath precluding lying down): • Age (mean & range) = 10.41+/-2.41 y; % Male= 61.8% • Severity: NR • Duration: NR • Method: Japanese version of American Thoracic Society & Division of Lung Diseases -National Heart, Lung & Blood Institute questionnaire, & items about job history, dust exposure, ocular symptoms, family member smoking status, exposure to other indoor pollution, & parental history of asthma • Medications: NR	• Participants without current asthma (n=22,109) • Age (mean & range): 10.78±2.54 y; • % Male: 49.6	• Compared to control group, asthmatics more likely to be younger ($p<.0001$), male ($p<.001$) & have parental history of asthma ($p<.001$) • Asthma vs control groups: maternal smoker (15.2% vs 14.6%)	• Fish intake on a regular diet	• Validated, quantitative food frequency questionnaire: frequency of fish intake (almost none, 1-2 meals/mo, 1-2/wk, ≥3-4/wk) • Time: current • Parental questionnaire
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report							

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part B continued)

Author, Year, Location	Results	Number (%) of & Reasons for Exclusion	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Takemura, 2002,[76] Japan	• With 1-2 meals/mo as reference standard (mode), & after adjusting for age, gender, & parental history of asthma, a significantly higher asthma prevalence observed for those eating fish 1-2 meals/wk than those eating fish 1-2/mo [OR: 1.133 (95% CI 1.021-1.258)]; & the risk increased gradually with increasing frequency of fish intake, with a S positive trend (p=.0078) • With 1-2 meals/mo as reference standard (mode), & after adjusting for age, gender, parental history of asthma, vegetable & fruit intake, a significantly higher prevalence observed for those eating fish 1-2 meals/wk than those eating fish 1-2/mo [OR: 1.117 (95% CI 1.005-1.241)]; & the risk increased gradually with increasing frequency of fish intake, with a significantly positive trend (p=.0349) • S trend relating to increasing fish intake & asthma prevalence in males (p=.049) but not females (p=.36)	• Overall = 1,290 non-responders • n=695 had previously experienced an asthma attack but not currently asthmatic	• Total quality score: 3 (Grade: B) • Applicability: III	• Tokorozawa Medical Association, Saitama, Japan
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report				

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part A continued)

Author, Year, Location	Study Characteristics	Study Design/ Selection Criteria/ Selection Method/ Study Duration	Asthma (Sub-) Population Description/Severity/ Duration/Diagnostic Method/Medications	Other (Sub-) Population(s): Description	Factors Distinguishing (Sub-) Populations	Exposure(s)	Dietary Intake Data Collection Method/ Time Frame/ Informant-Administrator
Troisi, 1995, USA[75]	• Enrolled/ • evaluated: 121,700/77,866 (93,184 before exclusion criteria applied) • Age (mean & range): NR (34-68) y • % Male: 0 • Race: NR • Number of sites: 11	• Prospective cohort study • Inclusion: a Nurses' Health Study (NHS) supplemental questionnaire report of MD-diagnosed asthma & asthma medication use since diagnosis (1988-1990) • Exclusion: asthma, cardiovascular disease, diabetes, emphysema, chronic bronchitis or cancer on or before 1980 (n=760); non-responders & those denying asthma diagnosis on questionnaire • Method: see above • Duration: 10 y period	• Adult onset asthma (n=1,206 with confirmed diagnosis, from 1,446 with positive response in 1988-1990 & 1,400 via supplementary asthma questionnaire) • Severity: NR • Duration: NR • Method: NR • Medications: beta-2 agonists, oral theophylline, steroids (inhaled, oral or intravenous), cromolyn sodium	NR	NR	• Dark meat fish, along with tuna fish, & shrimp	• Semi-quantitative food frequency questionnaire about food intake over the past year in 1980 & every 2 years up to 1990 (1984 & 1986 versions: differentiated dark meat fish, higher in EPA, from other types of fish) • Self-administered
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report							

Evidence Table 4: Observational study evidence of omega-3 fatty acids to prevent asthma (Part B continued)

Author, Year, Location	Results	Number (%) of & Reasons for Exclusion	Quality (Internal Validity) & Applicability (External Validity)	Funding Source
Troisi, 1995, USA[75]	• 6-y risk of asthma was unrelated to frequency of intake of dark meat fish (χ^2 = -0.13; p=.90), tuna fish (χ^2= 0.19; p=.85), & shrimp (χ^2= -.21; p=.83) measured in 1984 • Adjusting for age & smoking status, a NS risk reduction of asthma for each quintile of energy-adjusted omega-3 fatty acid intake (assessed in 1984 & 1986) [e.g., fifth quintile: RR= 0.88 (95% CI 0.65-1.12)]; & NS test for trend (p=.87) • Adjusting for age, smoking status, body mass index, area of residence, number of physician visits, & quintiles of energy intake, a NS risk reduction of asthma for each quintile of energy-adjusted omega-3 fatty acid intake (assessed in 1984 & 1986) [e.g., fifth quintile: RR=0.85 (95% CI 0.65-1.12)]; & NS test for trend (p=.37)	• n=446 (63%) exclusions after censoring for cancer, cardiovascular, diabetes, etc. after 1980 & before date of asthma diagnosis	• Total quality score: 4 (Grade: A) • Applicability: II	• NIH grant CA 40356
NR = not reported; NA = not applicable; ? = change; S = significant; NS = nonsignificant; n = number of participants; enrolled = n qualified; evaluated = n analyzed; completed = n completing the study; Note: superscripts refer to reference list in main report			

Listing of Included Studies*

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Appendix F. Additional Acknowledgements