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
   __ autoimmune
   __ cancer
   __ neurology
   __ child / maternal health
   __ immune-mediated
   __ transplantation
   __ mental health
   __ none of the above
   __ 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*.

TOTAL POINTS: 0 1 2 SCORE = ___

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

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

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

TOTAL POINTS: 0 1 2 SCORE = ___

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

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

JADAD TOTAL SCORE = ___

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

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

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

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

Quality Assessment Form—All Other Study Designs

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

Potentially relevant citations identified and screened for possible retrieval (n = 1010)

↓

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)

↓

Reports retrieved for more detailed assessment of relevance (n = 159)

↓

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)

↓

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)

↓

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)

↓

Meta-analysis deemed inappropriate for each research question

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 ≥3 y duration; reversible airway obstruction ≥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 ≤ 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 (≥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 $\pm$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 $PGF_{2\text{-alpha}}$ 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-$PGF_{1\text{-alpha}}$ (p>.05)* • NS between-phase differences in urine levels of PGE_2 (p>.05)* • NS between-phase differences in urine levels of $PGF_{2\text{-alpha}}$ (p>.05)* • NS between-phase differences in urine levels of TxB_2 (p>.05)* • NS between-phase differences in urine levels of 6-keto-$PGF_{1\text{-alpha}}$ (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 (≤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 ≥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 ≥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 (≥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, Japan[76]	• 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

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