Chapter 3. Results

Results of Literature Search

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

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

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

Report and Study Design Characteristics of Included Studies

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

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

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

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

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

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

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

Overview of Relevant RCTs

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

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

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

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

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

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

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

Qualitative Synthesis of RCT Evidence Regarding Respiratory Outcomes

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Qualitative Synthesis of Individual RCT Results

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

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

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

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

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

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

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

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

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

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

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

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

Overview of Relevant Studies With Designs Other Than an RCT

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

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

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

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

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

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

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

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

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

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

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

Author, Year, Location	Omega-3 Fatty Acid Cohort/Phase		Comparator Cohort/Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Total Quality (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Ashida, 1997, Japan[59†]	5	15 g perilla seed oil (ALA: NR)	NA	NA	3/3	3 (Grade: B)	III
Broughton, 1997, USA[73†]	26	"Low" EPA + DHA intake: ~0.7 g (mean)	26	"High" EPA + DHA intake: ~3.3 g (mean)	5/16	3 (Grade: B)	I
Hashimoto, 1997, Japan[62†]	8	1.8 g EPA	NA	NA	5/7	3 (Grade: B)	III
Masuev, 1997b, Russia[61††]	5	6.0 g EPA+DHA	3	6.0 g olive oil	1/1	4 (Grade: A)	III
Okamoto, 2000b, Japan[71†]	26	10-20 g of perilla seed oil (ALA: NR)	NA	NA	5/5	4 (Grade: A)	III
Picado, 1988, Spain[74†]	10	3.0 g EPA+DHA + eucaloric diet	10	3.0 g lactose + eucaloric diet	3/4	5 (Grade: A)	III
Villani, 1998, Italy[72†]	7	3.0 g EPA+DHA (1:1 ratio)	NA	NA	3/7	4 (Grade: A)	III
CHILDREN							
Gorelova, 1998, Russia[70††]	23	4.5 g fish oil (NR) + hypo-allergenic diet	10	Control (NR) + hypo-allergenic diet	1/1	2 (Grade: C)	III
Machura, 1996, Poland[63††]	37	3.0 g EPA+DHA (15 mL fish oil)	23	15 mL sunflower oil	2/6	3 (Grade: B)	III

n = number of enrolled participants; NR = not reported; NA = not applicable; S = significant; †Noncomparative case series; ††non-RCT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N = number of randomized participants; *Pediatric trial

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

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

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

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

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

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

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

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

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

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

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

Qualitative Synthesis of Evidence Regarding the Assessment of Effect Modifiers

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

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

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

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

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

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

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		Results Favoring Omega-3 Fatty Acids	Research Design	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Arm, 1988, England[56,57]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	NS: AM PEF NS: PM PEF NS: BDU	RCT	III
Dry, 1991, France[65*]	NR	1.0 g EPA+DHA	NR	"Placebo" (NR)	S: FEV_1	RCT	X
Emelyanov, 2002, Russia[69]	23	200 mg EPA+DHA + 400 mg olive oil	23	600 mg olive oil	S: AM PEF S: BDU NS: FEV_1 NS: PM PEF	RCT	III
Kirsch, 1988, USA[54,55]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA ethyl ester (trace DHA)	NS: FEV_1	RCT	I
McDonald, 1991, Australia[58]	15	2.7 g EPA + 1.8 g DHA	15	15 g olive oil	NS: AM PEF NS: PM PEF NS: BDU	RCT, 2-phase crossover	III
Okamoto, 2000a, Japan[66]	7	10-20 g perilla seed oil (ALA: NR)	7	10-20 g corn oil	S: FEV_1 S: AM PEF	RCT	III
Stenius-Aarniala, 1989, Finland[68]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	NS: AM PEF NS: PM PEF	RCT, 3-phase crossover	III
Thien, 1993, England[67]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	NS: AM PEF NS: PM PEF NS: BDU	RCT	III
Ashida, 1997, Japan[59]	5	15 g perilla seed oil (ALA: NR)	NA	NA	S: AM PEF S: PM PEF	Non-comparative case series	III
Hashimoto, 1997, Japan[62]	8	1.8 g EPA	NA	NA	S: AM PEF	Non-comparative case series	III
Picado, 1988, Spain[74]	10	3.0 g EPA+DHA + eucaloric diet	10	3.0 g lactose + eucaloric diet	S: AM PEF NS: BDU[†]	Non-comparative case series (placebo, then fish oil)	III
Villani, 1998, Italy[72]	7	3.0 g EPA+DHA (1:1 ratio)	NA	NA	NS: AM PEF	Non-comparative case series	III

n = number of enrolled/randomized participants; NR = not reported; NA = not applicable; S = significant; NS = nonsignificant; BDU = bronchodilator use; [*]Age not reported [†]S greater BDU in last 2 weeks within the omega-3 fatty acids phase

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Overview of Relevant RCTs

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

Qualitative Synthesis of RCT Evidence Regarding Mediators of Inflammation

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

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

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

Author, Year, Location	Omega-3 Fatty Acid Arm/Phase		Comparator Arm/Phase		# of S Unique Results Favoring Omega-3 Fatty Acids	Jadad Total Quality / Allocation Concealment (Internal Validity)	Applicability (External Validity)
	n	Type & Dose/Day	n	Type & Dose/Day			
ADULTS							
Arm, 1988, England[56,57]	NR	3.2 g EPA + 2.2 g DHA	NR	Olive oil (NR)	3/5	4 (Grade: A)/ unclear	III
Kirsch, 1988, USA[54,55]	6	4.0 g EPA ethyl ester (trace DHA)	6	0.1 g EPA EPA ethyl ester (trace DHA)	9/17	3 (Grade: B)/ unclear	I
Okamoto, 2000a, Japan[66]	7	10-20 g perilla seed oil (ALA: NR)	7	10-20 g corn oil	2/2	2 (Grade: C)/ unclear	III
Stenius-Aarniala, 1989, Finland[68*]	36	20 mL fish oil (EPA+DHA: NR)	36	(1) 20 mL olive oil (2) 20 mL evening primrose oil	2/8	2 (Grade: C)/ unclear	III
CHILDREN							
Hodge, 1998, Australia[52]	NR	0.72 g EPA 0.48 g DHA + ALA (NR) via canola diet	NR	Omega-6 fatty acids: 1.8 g safflower oil + 1.8 g palm oil + 0.4 g olive oil + sunflower oil diet (NR)	0/1	3 (Grade: B)/ unclear	III

N = number of randomized participants; NR = not reported; S = significant; *Crossover trial

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

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

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

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

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

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

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

		Quality								
		A			B			C		
Applicability	I				Author	Year	N			
					Kirsch	1988	12			
	II									
	III	Author	Year	N	Author	Year	N	Author	Year	N
		Arm	1988	25	Hodge*	1998	45	Okamoto	2000a	14
								Stenius-Aarniala	1989	36

N = number of randomized participants; *Pediatric trial

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

Qualitative Synthesis of Individual RCT Results

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

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

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

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

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

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

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

Overview of Relevant Studies With Designs Other Than an RCT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

N = number of randomized participants

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

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

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

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

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

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

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

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

Qualitative Synthesis of RCT Evidence Regarding Primary Prevention

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

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

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

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

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

Overview of Relevant Observational Studies

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

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

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

Qualitative Synthesis of Observational Study Evidence Regarding Primary Prevention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Qualitative Synthesis of Individual Observational Study Results

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

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

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

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

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

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

There were no studies found that investigated this question.

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

Qualitative Synthesis of Safety Data for All Research Designs

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

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

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

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

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

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

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

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

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

There were no studies found that investigated this question.