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

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

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

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

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