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

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

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

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

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

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

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.