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The role of fish intake on asthma in children: A meta-analysis of observational studies

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Abstract

Background: The evidence is mixed on the use of long chain Omega-3 fatty acids in the prevention and management of childhood asthma.

Methods: We conducted a systematic search and meta-analysis investigating the role of fish intake, the main dietary source of long chain omega-3 fatty acids, on asthma in children.

Results: A total of 1119 publications were identified. Twenty-three studies on fish intake in association with childhood asthma were included in the final review. In 15 of 23 studies, early introduction of fish (6-9 months) and regular consumption (at least once a week) improved asthma symptoms and reduced risk in children 0-14 years as compared to no fish consumption; 6 of 23 showed no effect and 2 of 23 studies suggest adverse effects. Meta-analysis revealed an overall "beneficial effect" for "all fish" intake on "current asthma" [OR: 0.75; 95%CI: 0.60-0.95] and "current wheeze" [OR: 0.62; 95%CI: 0.48-0.80] in children up to 4.5 years old. An overall protective effect of "fatty fish" intake as compared to "no fish" intake in children 8-14 years old was also observed [OR: 0.35; 95%CI: 0.18-0.67].

Conclusion: This meta-analysis suggests that introduction of fish early in life (6-9 months) and regular consumption of all fish (at least once a week) reduces asthma and wheeze in children up to 4.5 years old, while fatty fish intake may be beneficial in older children. Future well-designed clinical trials are recommended to confirm the promising findings documented in this literature analysis.

KEYWORDS

asthma, children, fish, nutrition, oily fish, Omega-3 fatty acids

1 | INTRODUCTION

Despite advances in pharmacotherapy, globally, the asthma epidemic in children is a major public health problem as it continues to rise. Asthma is associated with morbidity, substantial healthcare costs and decreased quality of life.^{1,2} There is no cure for asthma; symptoms can only be controlled by medication which on a long-term basis may cause side effects. Therefore, identifying potential non-pharmacological interventions which improve management of asthma is of great public health significance.

The modern diet is low in fruits, vegetables, fish and high in refined grains, red meat and fast food³ which may have contributed to the high prevalence of asthma in Westernized countries.¹ As a result today's diet is deficient in anti-inflammatory nutrients (from fruit/vegetables) and long-chain Omega-3 fatty acids (LC n-3 PUFA) (obtained from fish) and high in Omega-6 fatty acids mainly from processed fats and oils such as margarine and vegetable oils.^{3,4} It is believed that the change in anti-inflammatory status, fatty acid composition, increase in Omega-6: Omega-3 fatty acid ratio is associated with an increase in oxidative stress

and airway inflammation promoting the development and symptoms of asthma.^{5,6}

There has been considerable interest in the potential therapeutic and protective properties of Omega-3 fatty acids (EPA/DHA) in the pathogenesis of asthma due to anti-inflammatory and immune-modulating properties.^{4,7} To date, the evidence for the beneficial effects of Omega-3 fatty acid intake in asthma is controversial and intervention trials investigating the impact of fish or fish oil supplementation in children are lacking.⁸ Most of the epidemiological evidence which gave rise to the hypothesis that marine Omega-3 fatty acids may have a protective effect is based on studies documenting that regular consumption of fish has a prophylactic effect.⁹⁻¹¹ In addition, many systematic reviews have investigated the impact of Omega-3 fatty acid intake during pregnancy on allergy outcome in offspring suggesting a beneficial effect.¹²⁻¹⁴ Little is known about fish intake on asthma during childhood (post-infancy) and this warrants further investigation.

The purpose of this study is to conduct an up-to-date systematic search, qualitatively synthesize the available evidence and perform a meta-analysis to determine the role of fish (lean and fatty) on childhood asthma. The impact of fish intake during pregnancy is beyond the scope of this review.

2 | METHODS

This review was conducted according to PRISMA guidelines¹⁵ (Data S4).

2.1 | Literature search strategy

We conducted a comprehensive literature search of publications up to July 2017 using the following bibliographic databases: Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, CINAHL (EBSCO), SCOPUS and EMBASE. No restrictions were applied on language or publication dates. Supplementary studies were sought from conference proceedings as well as clinical trials registries (International, European, Australia and New Zealand) in order to identify published/unpublished trials. Other potential relevant citations were identified by hand search of the reference lists of relevant articles, reviews, systematic reviews and meta-analysis. Databases were searched for relevant publications, by a two-step search strategy using the following search terms:

Search 1: ["fish OR fatty fish OR oily fish OR omega 3 fatty acids OR n-3 long chain polyunsaturated fatty acids AND "childhood asthma"]

Search 2: ["fish OR fatty fish OR oily fish OR omega 3 fatty acids OR n-3 long chain polyunsaturated fatty acids AND "children" AND "asthma"].

The final search was a combination of both searches using the term "OR." The full search strategy is provided in (Box S1).

2.2 | Study eligibility criteria

2.2.1 | Inclusion criteria

Inclusion criteria was based on Participants, Intervention, Comparator and Outcomes (PICO).¹⁶

2.2.2 | Type of participants

This systematic review considered publications that included children younger than 18 years old.

2.2.3 | Type of intervention

Publications reporting the effect of fish as the primary exposure measurement.

2.3 | Outcome measures

Primary outcomes of interest were all asthma symptoms (wheeze, dyspnoea, shortness of breath) and prevalence or incidence of asthma.

A publication was considered when exposures were measured and the presence of asthma was based on the manifestation of symptoms, pulmonary tests, or doctor-diagnosis.¹⁷ In addition, studies examining the effect of Omega-3 fatty acid intake on atopy in children were considered relevant when results on fish intake and asthma outcome in children could be separated.

2.4 | Type of studies

We considered experimental and epidemiological study designs including randomized controlled trials (RCTs), non-randomized controlled trials, before and after intervention studies, cohort, case-control and cross-sectional studies.

2.5 | Exclusion criteria

Exclusion criteria were based on PICO characteristics and reasons for exclusion are summarized in (Figure 1). Publications not included were as follows: reviews, systematic reviews, editorials, comments, letters, case studies, animal studies and those with no abstract, full text or English translation available. Interventions or risk factors other than fish consumption such as: formula supplementation, dietary patterns, food groups, individual nutrients, fish oil, obesity, dust mites, as well as studies focusing on maternal diet or asthma genotypes, were considered to be irrelevant.

2.6 | Selection of studies

MP and CI initially screened the titles, abstracts, or descriptors of all publications retrieved by the search and duplicates removed.

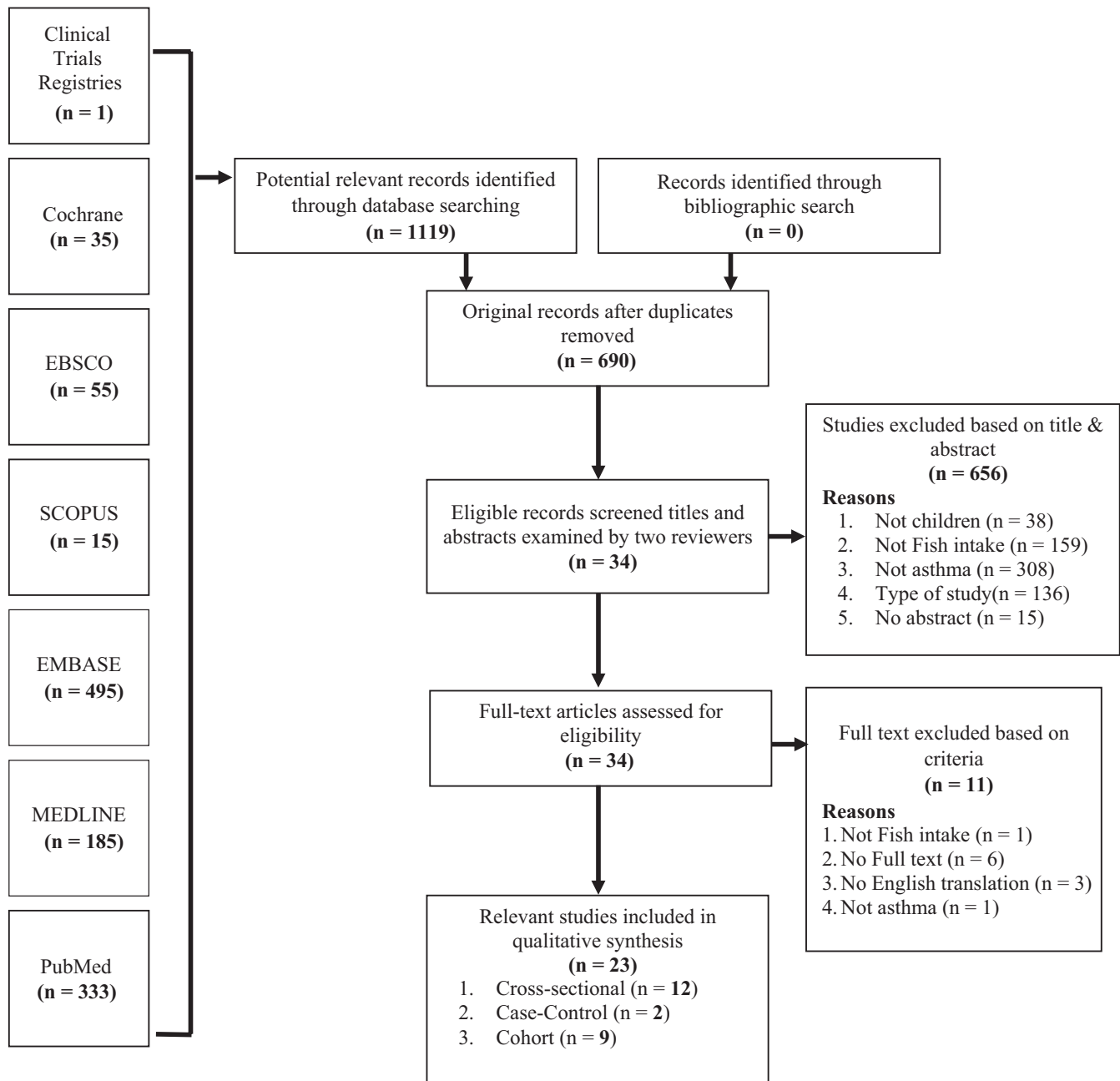


FIGURE 1 Flow chart of search details

When there was insufficient information in the abstract to warrant exclusion of the article, the full text of the article was retrieved. Full-text papers were then independently appraised by both reviewers for inclusion and details extracted. Discrepancies were resolved by discussion and consensus that led to agreement. The search was supplemented by cross-checking reference and bibliographies of relevant publications, systematic reviews and reviews.

2.7 | Quality assessment and risk of bias

SKS and MP independently rated all publications included in the meta-analysis using a validated quality assessment tool

according to Zaza et al¹⁸ (Data S2). The scientific soundness was rated using 24 validity questions with possible responses of “yes” or “no.” A value of one was assigned to “yes” and zero to “no.” The final score was presented as the percentage of total (maximum) probable scores for each study. Any discrepancies were addressed with mutual agreement between the authors or with a third reviewer (BE). Finally, the scores from both evaluators were averaged and presented as the final score. The observed median study quality score was used as the dividing point between low quality and high quality.¹⁹ We set the benchmark of 70% and above as a high-quality study while below 70% as low quality.

2.8 | Data extraction

Data extracted included authors, year of publication, study name, study design, geographic location, sample size, age range of target population, follow-up, dietary exposure, outcome measures, dietary and respiratory assessment tools, confounders, main findings (risk estimates along with 95% CI and *P*-values).

2.9 | Data synthesis and statistical analysis

Study outcomes were synthesized and categorized into two groups based on the effect on asthma symptoms (improvement or no improvement). Quantitative data were pooled in statistical meta-analysis software using STATA software version 14.1 (Stata Corp, Texas). For the purpose of the meta-analyses, publications assessing "all" types of fish and "fatty fish" as the exposures and regular fish intake, at least once a week were deemed appropriate. Studies were included in the meta-analysis when effect size was expressed as odds ratio (OR) and their 95% confidence intervals (95%CI) were reported or could be calculated. Eligible publications were categorized into two groups based on the common outcome of interest "current asthma" or "current wheeze" as defined by ISAAC.²⁰

For the purpose of the meta-analysis and due to heterogeneity among study designs, subgroup analyses were conducted based on study design, age range, follow-up and type of fish consumed. Cut-offs for age were defined based on children's age range in publications.

Two assessments were conducted for each outcome. One was a combination of all study designs with "all fish or 'fatty fish' exposure" and the other according to study design and similar age group. Heterogeneity was assessed using the standard Chi-square test and I^2 statistic.²¹ Considerable heterogeneity was considered to be an I^2 value >75%²¹ and statistical significance at the 5% level.²² We applied the random-effects model to estimate the pooled ORs and 95% CIs for "current asthma and 'current wheeze'."

3 | RESULTS

3.1 | Electronic search

The literature search identified a total of 1119 potential publications of which 690 remained, after removal of duplicates (Figure 1). No additional citations were found by cross-checking of reference lists. Only one ongoing RCT was identified from international clinical trial registries. Two reviewers (MP, CI) independently screened the 690 eligible papers by scanning titles and abstracts. A total of 656 were excluded based on publication type (136), no abstract (15) or on PICO criteria as they did not examine the effect of fish intake (160) in association with asthma symptoms (308) in children, (37) leaving 34 full-text articles to be assessed for eligibility. Of the remaining 34 potential studies, 11 full texts were deemed to be inappropriate (1 not intervention, 1 not asthma, 6 no full text available and 3 no English translation), leaving a total of 23 relevant studies.

Specifically, 12 cross-sectional,^{10,23-33} 2 case-control^{34,35} and 9 cohort studies^{11,36-43} examining the effect of fish consumption on asthma symptoms in children.

3.2 | Study characteristics

The database search identified 23 studies conducted from 1992 to July 2017 examining the effect of fish consumption on asthma in children. Two were undertaken in Australia,^{33,34} Japan,^{28,32} Spain^{10,25} and Finland^{35,41}; three in Norway^{38,40,42} and the Netherlands^{31,37,43}; four in Sweden^{11,27,36,39}; one in China,³⁰ Italy,²⁶ France,²³ Central Europe²⁹ and the ISAAC study which involved 20 countries globally.²⁴ Collectively, 163 744 children and adolescents up to 15 years old were investigated with sample sizes ranging from 138 to 50 004. A variety of assessment methods were used to assess dietary intake in children. Twenty studies evaluated fish intake using a number of different questionnaires^{10,11,23,24,26,27,29-34,36-43} ranging from one question to questionnaires consisting of limited food groups/items and detailed Food Frequency questionnaires (FFQ) comprising of a wide variety of foods that capture the entire dietary pattern, while two studies used a 3-day food record^{25,35} and one, a diet history questionnaire.²⁸

In all studies, consumption of "all types" of fish (lean and fatty) were investigated, while in six studies the effect of fatty fish intake on asthma symptoms was measured.^{28,34,36-38,42} Asthma was diagnosed using a questionnaire,^{10,23-32,34-39,41,43} parent-report,⁴² doctor-diagnosed^{11,37,40} and in one study by bronchial hyperresponsiveness (BHR).³³ The characteristics of included studies are shown in (Table S1). Overview of the literature search will be presented based on study design and age group.

3.2.1 | Cohort studies: 0-12 years of age

The nine cohort studies identified, investigated the effect of early fish intake on asthma in 33, 673 children from birth until 12 years of age.^{11,36-43} Seven studies revealed that early introduction and regular consumption of "all fish" were associated with a reduction in asthma symptoms up to 12 years of age^{11,36-41} and two showed no effect.^{42,43}

Two studies reported that early introduction of "all fish" (at 6-9 months of age) and regular consumption (≥ 1 /week) of "all fish"³⁷ and "fatty fish"³⁸ reduced asthma incidence (OR: 0.72; 95%CI: 0.55-0.93),³⁸ prevalence of wheeze (OR: 0.64; 95% CI: 0.43-0.94)³⁷ and use of medication (OR: 0.75; 95%CI: 0.58-0.96)³⁸ in children up to 4 years of age.^{37,38} Conversely, Kiefte-de-Jong et al noted that no fish during the first 12 months of life and introduction of "all fish" between 0 and 6 months was associated with an increase in prevalence of wheezing [(OR: 1.57; 95%CI: 1.07-2.31), (OR:1.53; 95%CI: 1.07-2.19)], respectively, at 48 months as compared to a reduction in the prevalence of wheezing with fish introduction at age 6-12 months (OR: 0.64; 95% CI: 0.43-0.94).

Beneficial effects of "all fish" intake were also documented in children during the first 5 years of life. Fish consumption

before 9 months had a protective effect for recurrent wheezing (OR: 0.6; 95% CI 0.4-0.8),³⁹ multiple trigger wheeze (OR: 0.6; 95%CI:0.3-0.99),³⁹ episodic viral wheeze (OR:0.6; 95%CI:0.4-0.99),³⁹ asthma risk (OR: 0.73; 95%CI: 0.55-0.97),¹¹ (OR: 0.84; 95% CI = 0.57-1.22),⁴⁰ all asthma ($P < .001$)⁴¹ and atopic asthma ($P < .05$)⁴¹ up to 5 years as fish intake increased from two to three times per month ($OR_{adj} = 0.82$ 95% CI: 0.54-1.29) to once a week ($OR_{adj} = 0.66$, 95% CI: 0.43-1.01) and at least once a week ($OR_{adj} = 0.55$; 95% CI 0.34-0.87; p trend = 0.003)¹¹ a dose response was observed.

A Swedish cohort which involved 3285 children with follow-up till 12 years of age, regular "all fish" intake ($\geq 2-3$ times/month) at age of 1 year was associated with reduced risk of prevalence (OR_{adj} : 0.71; 95%CI: 0.57-0.87) and incidence (OR_{adj} : 0.80; 95%CI: 0.65-0.98) of asthma up to age 12 years, after adjusting for confounders of parental history of allergic disease, sex, maternal smoking during pregnancy.³⁶ However, no significant association was observed between fish intake at age 8 years and incidence of asthma at 12 years (p trend = 0.303).³⁶ This finding is in agreement with two other cohorts that documented no relationship among early, late or long-term intake of any kind of fish on asthma in children at ages 2⁴² ($P = .16$) and 8 years.⁴³ However, Willers et al⁴³ did report that early fish intake was inversely associated with BHR in children at age 8 years old.

3.2.2 | Case-control studies: 5-15 years of age

A beneficial effect of fish intake on asthma in children was observed in 2 case-control studies.^{34,35} In a nested-cohort study which was a subgroup of the Finnish DIPP study, 182 children with asthma and 728 controls participated and were observed at 3, 6, 12 months and thereby annually up to 6 years.³⁵ Overall, early introduction of "all fish" and fish products (6-8 months) was associated with a reduction in "all asthma" risk (OR_{adj} : 0.87; 95%CI: 0.77-0.98) in children at 6 years adjusting for confounders. Another case-control study investigating the impact of fish intake on asthma symptoms in 584 children aged 8-11 years also reported a protective effect.³⁴ After adjusting for confounders, children who ate fresh, "fatty fish" at least once a week had a significantly reduced risk of current asthma (OR_{adj} : 0.26; 95%CI: 0.09-0.72) as compared to "any fresh" fish (OR_{adj} : 0.52; 95% CI: 0.24-1.15) and "non-fatty" fish (OR_{adj} : 0.68; 95% CI: 0.3-1.54) consumers. No reduction in asthma risk was observed with canned fish consumption.

3.2.3 | Cross-sectional studies: 0-15 years

The literature search retrieved 12 cross-sectional studies undertaken in 128 577 children aged 0-15 years.^{10,23-33} Five studies observed that regular "all fish" intake (>1 /week) was associated with a reduction in lifetime prevalence of asthma (OR_{adj} : 0.92; 95%CI: 0.78-1.08),²⁴ current wheeze [$(OR_{adj}: 0.85$; 95%CI:0.74-0.97)²⁴; (OR: 0.44; 95%CI: 0.21-0.93)],³¹ current wheeze with atopy positive (OR_{adj} : 0.51; 95%CI: 0.32-0.81),²⁴ doctor-diagnosed asthma

(OR: 0.54; 95%CI: 0.35-0.84),²⁷ night-time breathlessness (OR: 0.36; 95%CI:0.17-0.78),²⁷ current asthma (OR: 0.51; 95%CI: 0.31-0.84),²⁷ (OR: 0.34; 95%CI: 0.13-0.85),³¹ past-year wheeze (OR adj: 0.75; 95%CI: 0.53-0.93),²³ past-year wheeze and atopy negative (OR: 0.61; 95%CI: 0.43-0.87),²³ atopic asthma with BHR (OR:0.12; 95%CI: 0.02-0.66),³¹ atopic wheeze with BHR (OR: 0.15; 95%CI: 0.03-0.63)³¹ and BHR (OR:0.35; 95%CI: 0.1-0.9).³³ While one study²⁹ reported that irregular fish intake (<1 /month) was associated with an increase in "persistent cough" (OR: 1.18; 95%CI:1.04-1.34), "wheeze ever" (OR: 1.14; 95%CI:1.03-1.25) and "current wheeze" (OR: 1.21; 95%CI: 1.06-1.39). A recent study undertaken by Xu et al,³⁰ including 13, 877 children, 0-14 years old, observed that fish and shrimp intake triggered asthma episodes by 14% ($P < .05$), although estimated effect size was lacking. Adverse effects of "all fish" intake were also reported in a Japanese study of 1673 asthmatic children and 22 109 controls aged 6-15 years.³² After adjustment for confounders (age, gender, parental asthma), a statistically significant higher prevalence of asthma was observed in children consuming fish 1-2 times/week (OR_{adj} : 1.117; 95%CI: 1.005-1.241) and more than or equal to 3-4 times/week (OR_{adj} : 1.319; 95%CI: 0.896-1.943) than among those who consumed no fish (OR_{adj} : 1.039; 95%CI: 0.785-1.376).

3.2.4 | Quality assessment

Twenty-one of 23 studies were rated as "high quality." The average quality score was 82.1% with the highest score 100% and the lowest score 64% (Table 1). Most of the cohort studies included in the meta-analysis were of high quality, 8 of 9 studies scored above 90%. The studies that were rated lower quality were due to their failure to control for potential confounders and address possible biases. Using t test, we checked if there were any differences in the quality score for the selected studies between two reviewers and found no major difference in average score (P -value = .33).

3.3 | Meta-analysis

A total of nineteen studies were used in the meta-analysis.^{10,11,23-29,31,32,34-37,39,40,42,43}

3.3.1 | Current asthma

Assessment of cohort studies alone^{11,40,42} revealed a statistical significant effect²¹ of "all fish" intake on "current asthma" in children 0-4 years ($I^2 = 11.5\%$; $P = .32$; (OR: 0.75; 95% CI: 0.60-0.95). Overall, a 25% reduction in "current asthma" was observed with "all fish" intake in children up to 4 years old (Figure 2).

3.3.2 | Current wheeze

A pooled effect for current wheeze and "All fish" intake was found in cohort studies regarding children up to 4.5 years [$I^2 = 0\%$, $P = .809$; (OR: 0.62; 95%CI: 0.48-0.80)] (Figure 3). A 38% reduction in

TABLE 1 Summary table of Quality Assessment of relevant studies in this systematic review (Zaza)¹⁸

Study	Reviewers	Study design	Population Density	Population Description	Time points	Entire sampling or Probability sampling	Eligibility Criteria			Exposure Measures			Outcome Measures			Statistical Test Suitable	Adjustment For Confounders	Bias Discussed	Bias not covered	Overall Average Score (%)
							Validity	Reliability	Validity	Reliability	Validity	Reliability	Validity	Reliability	Validity					
Peat et al ³³	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	67.5%
Hodge et al ³⁴	SKS/MP	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	70.5%
Takemura et al ³²	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	83.0%
Farchi et al ²⁶	SKS/MP	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	73.0%
Nafstad et al ⁴⁰	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	91.0%
Kim et al ²⁷	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	79.5%
Kull et al ¹¹	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	95.0%
Tabak et al ³¹	SKS/MP	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	75.0%
Chatzi et al ¹⁰	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	82.0%
Antova et al ²⁹	SKS/MP	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	75.0%
Nagel et al ²⁴	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	83.0%
Oien et al ⁴²	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	95.0%
Rodriguez et al ⁴⁵	SKS/MP	✓	×	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	73.0%
Goksoy et al ³⁹	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	91.0%
Willers et al ⁴³	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	93.0%
Kunitsugu et al ²⁸	SKS/MP	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	73.0%
Kiefe de Jong et al ³⁷	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	95.0%
Dotterund et al ³⁸	SKS/MP	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	80.5%
Magnusson et al ³⁶	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	91.0%
Nwaru et al ⁴¹	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	97.5%
Lumia et al ³⁵	SKS/MP	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	78.0%
Saadeh et al ²³	SKS/MP	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	82.0%
Xu et al ³⁰	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	64.0%

Key: ✓, criteria satisfied; ×, criteria not satisfied.

"current wheeze" was observed with "All fish" intake in children up to 4.5 years old.

3.3.3 | Fatty fish versus No fatty fish

When analysing the effect of "Fatty fish" intake in children aged 8-14 years^{28,34} for "current asthma" in the combined subanalysis, an overall effect was observed [$I^2 = 0\%$, P -value = .481; (OR: 0.35; 95%CI: 0.18-0.67] (Figure 4). Fatty fish intake reduced "current asthma" in children aged 8-14 years by 65% as compared to "no fish" intake.

In contrast, no association was observed for "all fish" intake on "current asthma" in children aged (2-15 years) when combining all study designs^{11,24,25,27,28,31,32,34-36,40,42,43} (Figure S1) or in subanalysis based on study designs separately (Figure S2). No pooled age-specific effects were also found for "current wheeze" and "All fish" intake in children (0-13 years) irrespective of study design (Figures S3-S5). The same trend was established for "Fatty fish" intake vs "current asthma" in children (0-14 years) in the combined subanalysis (Figure S6).

4 | DISCUSSION

The aim of this qualitative synthesis and meta-analysis was to clarify the role of fish intake on different asthma outcomes in children. Although the meta-analysis produced mixed results, three important findings were highlighted. Firstly, early introduction of "all fish" intake during infancy (6-9 months of age) and regular consumption (at least once/week) of "all fish" reduced "current asthma" by 25% and "current wheeze" by 38% in children up to 4.5 years old.^{11,37,39,40,42} While "fatty fish" intake seems to confer an overall "prophylactic effect" in older children 8-14 years and reduced "current asthma" by 65%.^{28,34}

Summarizing the results of the database search, in 15/23 studies a protective effect was observed between fish consumption on asthma symptoms in children,^{11,23,24,27,29,31,33-41} 6/23 no effect^{10,25,26,28,42,43} and 2/23 an adverse effect.^{30,32} Two important results were highlighted in these observational studies. Early introduction during the first year of life (between 6 and 9 months) and regular consumption of fish (at least once a week) decreased risk, prevalence and asthma symptoms in children up to 14 years of age. This finding is in accordance with other observational studies that have found early introduction and frequent consumption of fish were associated with decreased asthma symptoms and improvement in pulmonary function in children and adolescents.^{9,44-46}

Our meta-analysis of nineteen¹⁹ publications showed an overall beneficial effect of "all fish" intake on "current asthma" and "current wheeze" in children up to 4.5 years old in five cohort studies alone^{11,37,39,40,42} and of "fatty fish" intake on "current asthma" in 8-14 year olds.^{28,34} The prophylactic effects documented in the cohort studies for young children up to 4.5 years old may be explained from research on biological mechanisms that have shown

that, the development and maturation of the immune system starts early in foetal life continue through infancy and early childhood.^{47,48} Infancy is a period in which the immune cells have an increased vulnerability and susceptibility to environmental exposures such as diet. A diet rich in Omega-3 fatty acids and lower Omega-6: Omega-3 fatty acid ratio may result in an increased incorporation of EPA and DHA into cell membranes at the expense of arachidonic acid. More EPA and DHA in the cell membrane result in decreased production of arachidonic acid-derived pro-inflammatory eicosanoids. EPA and DHA act as substrates for COX and LOX enzymes producing anti-inflammatory eicosanoids, protectins, resolvins and maresins that appears to exert anti-inflammatory and inflammatory resolving actions.⁴⁹ Apart from anti-inflammatory properties, Omega-3 fatty acids are able to modulate immune responses by promoting Th 1 cell generation, thereby reducing airway inflammation, improving pulmonary function and decreasing asthma symptoms.¹³

Additional protective effects on asthma symptoms were observed in two studies examining the effect of "fatty fish" as opposed to "all fish" in children aged 8-11 years old.^{34,38} Hodge et al³⁴ reported a 25% reduction in "current asthma" when fatty fish was consumed as compared to lean or no fish in children. Furthermore, no reduction in asthma risk was observed with the consumption of canned and processed fish. Perhaps, processing and food additives may alter the biological activity of Omega-3 fatty acids in fish oils. Dotterud et al³⁸ reported a 32% reduction in incidence of asthma with fatty fish consumption in infants at 2 years old, after adjusting for confounders. A beneficial effect of fatty fish intake was also noted in the studies undertaken by Kunitsugu and Oien, although results were not statistically significant, most probably explained by heterogeneity between study designs and small sample size.^{28,42} Our meta-analysis confirmed an overall "prophylactic" effect of fatty fish intake in older children.^{28,34} A 65% reduction in "current asthma" was observed in children aged 8-14 years.^{28,34}

The findings of this meta-analysis highlight that the type of fish consumed whether fatty or lean may matter. Fatty fish as compared to lean fish is a rich source of Omega-3 fatty acids which are able to counteract the action of Omega-6 fatty acids metabolites by down-regulating pro-inflammatory and immunological pathways, thereby preventing asthma development.^{50,51} Another possible explanation why fish consumption reduced asthma risk in children as compared to null effects reported from fish oil supplementation during childhood⁵² is that regular fish consumption may be a proxy for other healthy lifestyle habits that might promote the beneficial effect. In addition, fresh fish might have better bioavailability and absorption rate as opposed to fish oil. And apart from EPA/DHA, fresh fish contains other bioactive molecules such as selenium, iodine, vitamin D, potassium and B-vitamins that might interact synergistically providing these prophylactic properties.⁵³

On the other hand, our meta-analysis showed no statistical significant results for 14 studies (10 cross-sectional, 2 cohorts and 2 case-controls) on "current asthma" or "current wheeze" in children 6-15 years old.^{10,23-29,31,32,34,35,42,43} A possible reason for

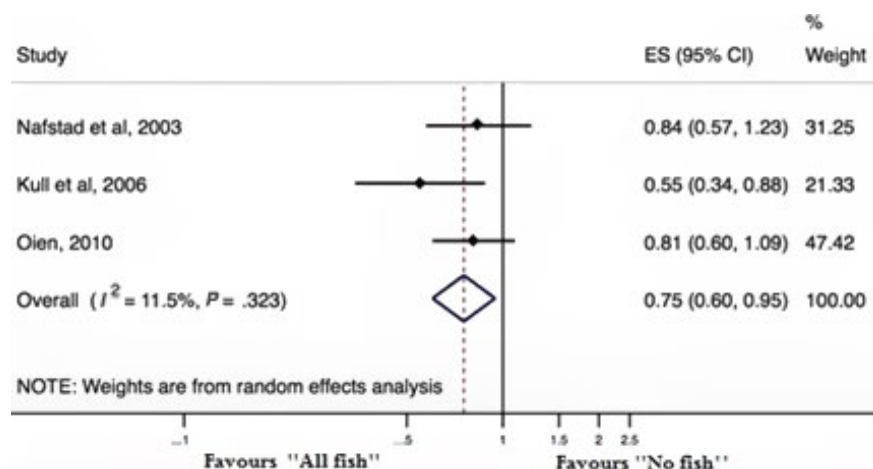


FIGURE 2 Forest plot of cohort studies children (0-4 years old) for "All fish" intake versus "No fish" and outcome "current asthma" [Colour figure can be viewed at wileyonlinelibrary.com]

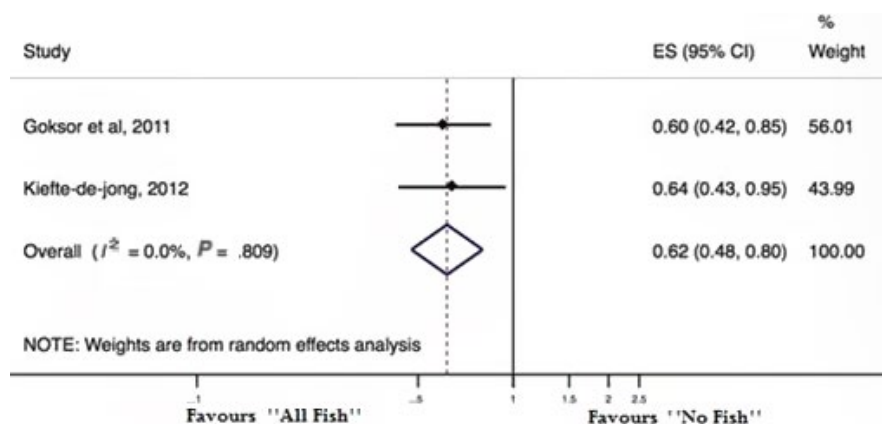


FIGURE 3 Forest plot of cohorts comparing the effect of "All fish" intake versus "No fish" on "current wheeze" in children aged 0-4.5 years [Colour figure can be viewed at wileyonlinelibrary.com]

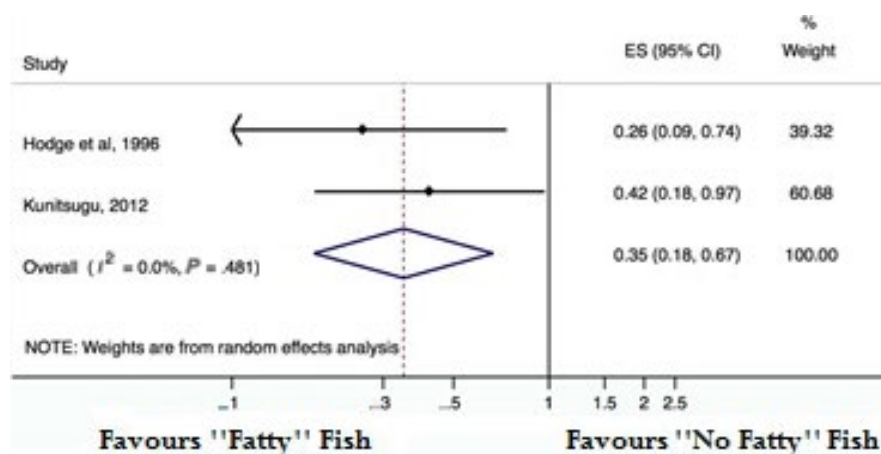


FIGURE 4 Forest plot in the combined analysis comparing "Fatty Fish" intake versus "No Fatty Fish" in children (8-14 years) for "current asthma" [Colour figure can be viewed at wileyonlinelibrary.com]

the null effects observed might be due to heterogeneity among study methodologies which included: population differences, sample size, children's age, gender, asthma definition, exposure and outcome measures, possible confounders, design of dietary questionnaires and food frequency categories, amount or type of fish consumed (fatty versus lean), quantity EPA/DHA, fish consumption patterns since nutritional guidelines may vary in

each country and food preparation methods. Use of invalidated and self-administered food frequency questionnaires, 3-day diet history for the recording of dietary intake require education and expertise are prone to information bias and response errors.^{43,28} Even though data on habitual diet were collected retrospectively from parents, in young children, it is well-established that parents provide reliable information on children's diet.⁵⁴ Misclassification

of asthma may have occurred in young children, since the diagnosis of asthma is uncertain in children younger than 5 years and wheezing is often the result of respiratory infection.^{55,56} Furthermore, spirometry which is considered to be the "gold standard" of pulmonary function testing in the diagnosis of asthma, cannot be performed efficiently in children younger than 5 years and diagnosis of asthma in young children is based on parents' report of symptoms.⁵⁵ In addition, parental allergic disease and early onset of allergic disease in children may cause parents to delay introduction or to avoid fish in the child's diet, thus influencing asthma outcome.

Two cross-sectional studies documented increased risk of asthma prevalence in children consuming fish in Japan and China.^{30,32} Today, the eating patterns of Japanese and Chinese children have changed to a more Westernized diet.^{57,58} Processed^{23,59} and pickled foods⁶⁰ as well as a high salt intake^{61,62} have been associated with an increase in bronchial hyperresponsiveness and asthma symptoms in children. In both studies confounding factors such as overweight, socio-economic level, maternal education, type of fish consumed (lean vs fatty), poor adherence to asthma therapy were not included in regression models and may have contributed to the adverse effects.

One of the strengths of this systematic review is the extensive literature search and large number of recent high-quality publications included which increases the power of the analysis. There are very few meta-analysis in the literature that examine fish intake and asthma in children (Yang, 2013; Zhang, 2017)^{14,63} and recent reviews (Best, 2016; Miles, 2017)^{12,13} address Omega-3 fatty acid intake during pregnancy. Our meta-analysis focuses exclusively on children and adolescents and adds to the existing evidence. Another strong point is the inclusion of cohort studies in the meta-analysis which are considered robust and provide strong scientific evidence because they measure events in temporal sequence thereby distinguishing causes from effects.⁶⁴ Another drawback might be publication bias where studies reporting no association between fish intake and asthma may not be published by periodicals.

5 | CONCLUSION

We conducted an up-to-date systematic search to determine the impact of fish intake in childhood asthma. This meta-analysis suggests that introduction of fish early in life (6-9 months) and regular consumption of all fish (at least once a week) reduces asthma and wheeze in children up to 4.5 years old, while fatty fish intake may be beneficial in older children. Future well-designed clinical trials are recommended to confirm the promising findings documented in this literature analysis.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTION

MP and CI jointly conducted searches, assessed inclusion, extracted data and assessed validity. MP drafted the manuscript and conducted the meta-analysis. BE and SKS made substantial contributions to analysis and interpretation of data quality. All authors critically reviewed the manuscript and approved the final version as submitted.

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Australian and New Zealand Clinical trial registry: <http://www.anzctr.org.au/trialSearch.aspx>
International Clinical trials registry: <http://www.clinicaltrials.gov>
European Union clinical trials registry: <http://www.clinicaltrialsregister.eu>

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Exposure- 'All fish'; Outcome- 'current asthma'

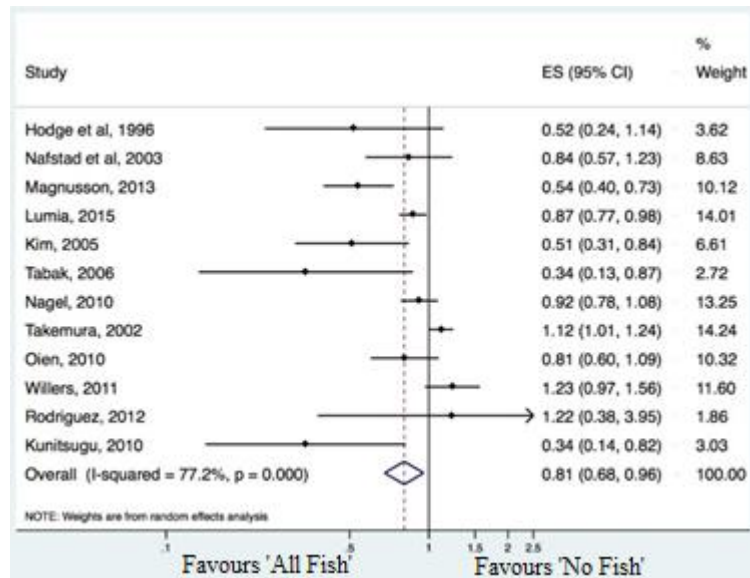


Fig S1. Forest plot of 'all study designs' and 'All Fish' intake versus 'No Fish' for 'current asthma' in children aged 2-15 y.o.

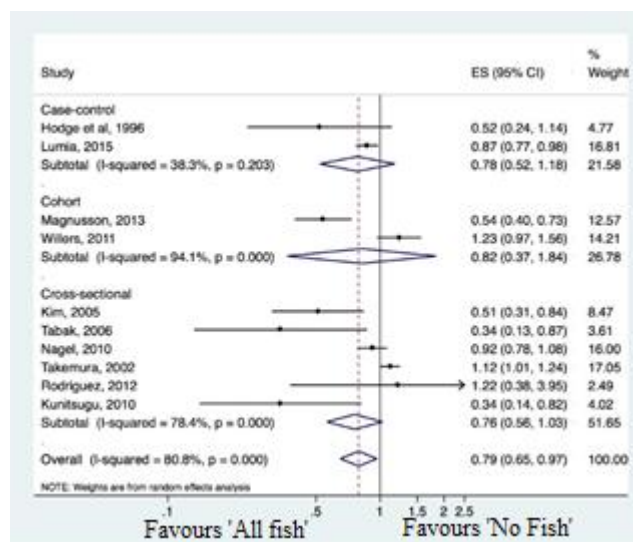


Fig S2. Forest plot of case-control trials in children (6-11 years), cohorts (8-12 years) and cross-sectional studies (5-15 years) for 'All Fish' intake versus 'No fish' and 'current asthma'

Exposure- 'All fish'; Outcome- 'current wheeze'

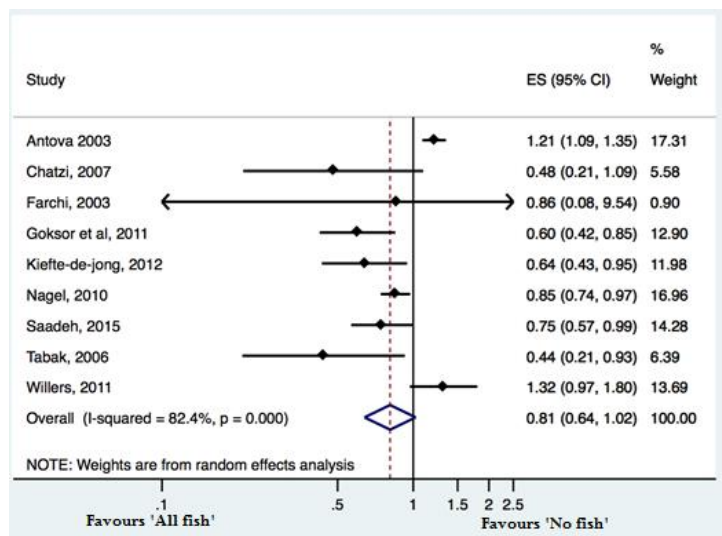


Fig S3. Forest plot of all study designs combined, children (0-13 years old) for 'All Fish' intake versus 'No Fish' and outcome 'current wheeze'.

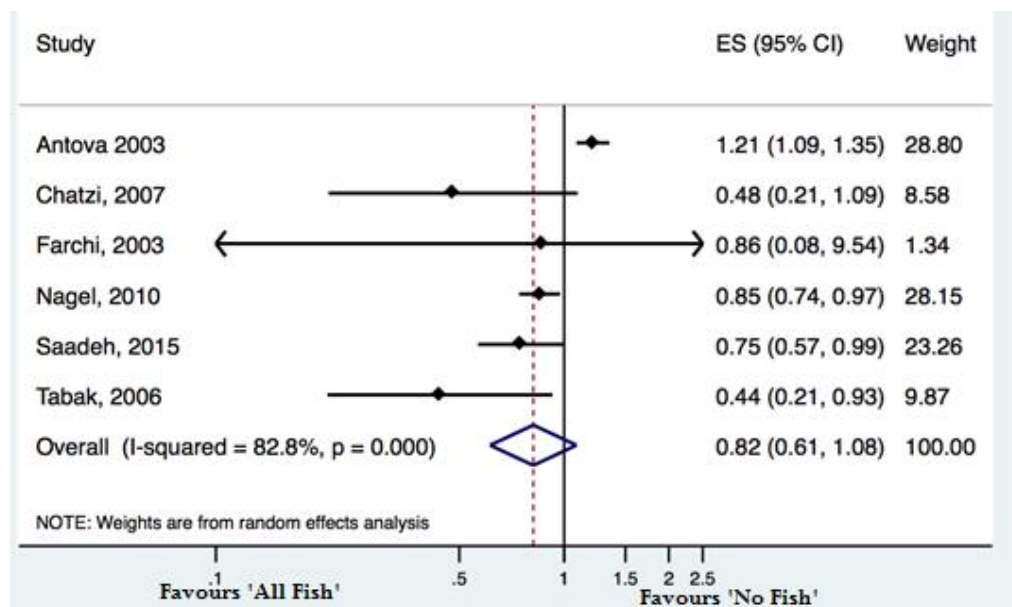


Fig S4. Forest plot of cross-sectional studies including children (6-13 years old) for 'All Fish' intake versus 'No Fish' and outcome 'current wheeze'.

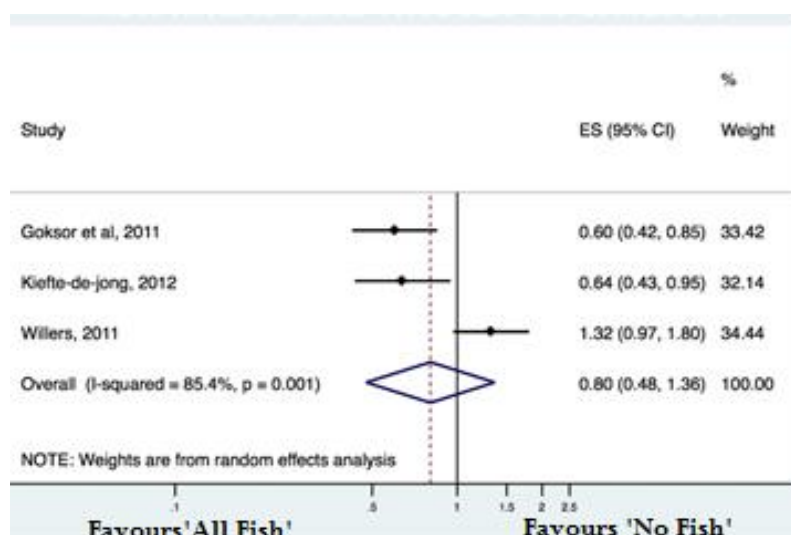


Fig S5. Forest plot of cohort studies children (0-8 years old) for 'All' Fish intake versus 'No Fish' and outcome 'current wheeze'.

Exposure-'Fatty fish'; Outcome-'current asthma'

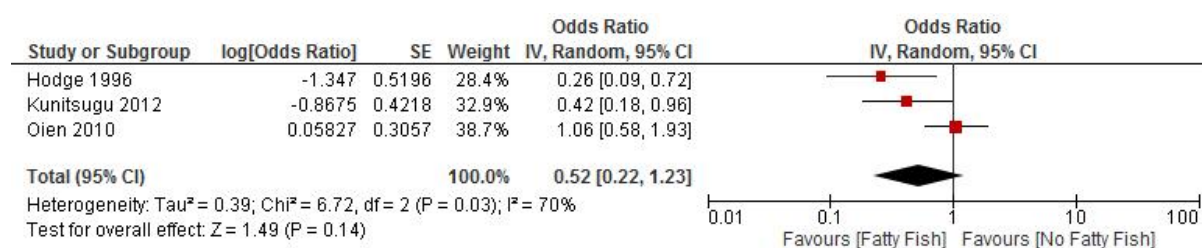


Fig S6. Forest plot comparing 'Fatty' Fish intake versus 'No Fatty' Fish and 'current asthma' in children 2-14 years old in the combined analysis.

1 Table S1. Characteristics of relevant studies in this systematic review

Author/Year Name of study/ Location/	Study design	Sample size	Age range/ Age Endpoints Assessed	Dietary Exposure	Asthma outcome Measured/ Respiratory Assessment	Dietary Assessment	Exposure estimate/ Confounders	Findings
Hodge et al, 1996(34); Australia	Case-control	584	8-11 y.o	All fish (Fresh fatty fish > 2% fat)	• Current asthma • Wheeze only • AHR Respiratory Assessment: Questionnaire	FFQ Categories: Daily, weekly, monthly, rarely or never. Fish categories: none, fresh fish, oily and non-oily.	Fatty fish intake $\geq 1x/wk$, Current asthma risk: • Fatty fish consumers: (ORadj: 0.26; 95%CI: 0.09-0.72; $p<0.01$) • Fresh fish consumers: (ORadj: 0.52; 95% CI: 0.24-1.15; $p>0.05$) • Non-fatty fish consumers (ORadj: 0.68; 95% CI: 0.3-1.54; $p>0.05$). Confounders: Sex, ethnicity, country of birth, atopy, respiratory infection in the first two years of life parental asthma, smoking	Lower prevalence of 'current asthma' 8.8% in fatty fish consumers, 15.6% non-fatty fish consumers and 23% never ate fish. Significant reduction in current asthma for children eating oily fish but not for wheeze only and AHR
Nafstad et al, 2003(40);	Cohort	2531		All fish	• Asthma risk	Qualitative : Fish intake:	• Asthma symptoms at 4 yrs: (ORadj:0.84; 95% CI=0.57-1.22,	Fish intake during first year

Oslo Birth Cohort Study Norway			0-4 y.o Follow-up: 1, 2, 4 y.o		Respiratory Assessment: Doctor diagnosed, Questionnaire	Yes/No	p=0.049) • Asthma risk in children with non-atopic parents: (ORadj 0.50; 95% CI: 0.30-0.83, p=0.031) • Asthma risk in children with atopic parents: (ORadj:1.00; 95%CI:0.61-1.63; p=0.093) Confounders: Parental atopy, atopic eczema at 0–6 months of age, gender, parity, birth weight, maternal age at delivery, birth order, uterus-related pregnancy complications, pets at home, lower respiratory tract infections during first year of life, maternal education, family income, maternal smoking, breast-feeding duration	of life ↓asthma symptoms at 4 yrs. Inverse relationship between fish intake and asthma risk in children with non-atopic parents.
Kull et al, 2006(11); BAMSE	Cohort	4,089	0-4 y.o	All fish	• Asthma risk • Multiple allergic disease • Persistent	FFQ : Categories: Never, 1x/mo;	• Early fish introduction at 3-8 mo, asthma risk at 4 y.o. (OR adj: 0.73, 95%CI: 0.55-	Early fish introduction at 3-8 mo ↓ asthma risk in

Study Sweden			Follow-up: 1, 2, 4 y.o		allergic disease Respiratory Assessment: Doctor-diagnosed	2-3x/mo; 1x/wk; ≥1x/wk	0.97) Fish intake at 1 yr life (1x/mth): • Asthma risk at 4 years: (ORadj:0.94; 95%CI: 0 .57- 1.56) • Allergy risk: (ORadj: 0.61; 95%CI: 0.45-0.84) Fish intake at 1 yr life: (2- 3x/mth) • Asthma risk at 4 yrs: (OR adj: 0.82; 95%CI: 0.51- 1.29) • Allergy risk at 4 yrs: (OR adj: 0.58; 95%CI: 0.45- 0.76) Fish intake 1x/wk: • Asthma risk at 4 yrs: (OR adj: 0.66, 95%CI: 0.43- 1.01) • Allergy risk OR adj: 0.50, 95%CI: 0.39- 0.64)	children at 4 y.o as compared to fish introduced later than 9 months. Regular fish consumption (≥ 2/month) during 1 st year life ↓risk of asthma and allergy (eczema, rhinitis and sensitization) at 4 y.o. A dose- dependent reduced risk was observed for asthma (p trend <0.003) and all allergy (p trend <0.001).
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							Fish intake $\geq 1x/wk$: • Asthma risk: (OR adj: 0.55; 95%CI: 0.34-0.87) p trend=0.003 • Allergy risk at 4 yrs: (OR adj: 0.46; 95%CI: 0.35-0.6) p trend<0.001 Confounders: Parental allergic disease, maternal age, maternal smoking and breastfeeding.	
Oien et al, 2010(42); Norway	Cohort	3,086	0-2 y.o Follow-up: 1, 2 y.o	All fish	• Parent-reported asthma • Doctor-diagnosed asthma Respiratory Assessment: Parent-report	FFQ Categories: Never, <1x/wk, 1x/wk, 2x/wk, 3x/wk, $\geq 4x/wk$.	Any kind fish $\geq 1x/wk$: • Doctor-diagnosed asthma (OR: 0.81: 95%CI:0.6-1.09) p=0.16 $\geq 1x/wk$ Oily fish • Doctor-diagnosed asthma (OR: 1.06: 95%CI:0.58-1.93) p=0.86 $\geq 1x/wk$ Lean fish • Doctor-diagnosed asthma: (OR: 0.76: 95%CI:0.52-1.13) p=0.17 Confounders: Gender, familial atopy, one parent & sibling, two parents & sibling, parental	No significant association between fish intake and doctor-diagnosed asthma (p=0.16)

							smoking 1 year after delivery, children's intake of cod liver oil, vegetables at 1 year of age, parental home-owner status, breast-feeding $\geq$ 4 months, pets.	
Willers et al, 2011(43); PIAMA Netherlands	Cohort	4,146	1-8 y.o Follow-up: 8 y.o	All fish	• Wheeze • Dyspnoea • Inhaled steroid use in previous 12 months • BHR • Asthma symptoms • Sensitization to inhaled allergens • Sensitization to food allergens Respiratory Assessment: ISAAC questionnaire, BHR by medical exam	FFQ Categories: Never; < 1x/wk; 1–2 days/wk; 3–5 days/wk; 6–7 days/wk	One consumption day/week increase in long-term intake of fish from 2-8 yrs and outcomes at 8 years: • Wheeze (OR: 1.32; 95%CI: 0.97–1.80) • Inhaled steroid use (OR: 1.36; 95%CI: 0.98–1.88) • Dyspnoea (OR: 1.01; 95%CI: 0.75–1.35) • Asthma symptoms (ORadj:1.23; 95%CI:0.97-1.57) • BHR (OR 0.79; 95% CI: 0.58–1.09) Early fish intake: • BHR (OR 0.76; 95% CI: 0.59–0.99) Confounders: Sex, maternal educational level, parental atopy, maternal smoking during	No statistically significant associations between early (2-3 years), late (7-8 years) or long-term fish intake on asthma or BHR at 8 y.o. However, early fish intake was inversely associated with BHR only.

							pregnancy, smoking in the house at 8 yrs, breast feeding, presence of older siblings, birth weight, overweight mother, overweight child at 8 yrs geographical region	
Goksor et al, 2011(39); BAMSE study Sweden	Cohort	4,171	0-4.5 y.o Follow-up: 4.5 y.o	All fish	• Recurrent wheeze • Multiple trigger wheeze • Episodic viral wheeze Respiratory Assessment: ISAAC Questionnaire	FFQ: ≥ 1x/mo	Introduction fish < 9 months: • Recurrent wheeze (ORadj: 0.6; 95% CI 0.4-0.8); p<0.05 • Multiple trigger wheeze (ORadj: 0.6; 95%CI:0.3-0.99); p<0.05 • Episodic viral wheeze (ORadj: 0.6; 95%CI:0.4-0.99); p<0.05 Confounders: Atopic hereditary, parental educational level, male, maternal smoking and medication during pregnancy, gestation age < 37 wks, caesarean section, antibiotics during 1 st year life, breast-feeding for ≥ 4 months,	Fish intake ≤ 9 mo ↓ wheezing risk at 4.5 y.o (P<0.05) for children treated with antibiotics during first week of life.

							doctor-diagnosed food allergy during 1 st year life, eczema during first year of life, introduction of fish before 9 months, fish $\geq$ 1x/month at age 1 year.	
Kiefte-de-Jong et al, 2012(37); Generation R Study Netherlands	Cohort	7,210	12 mo, 14 mo Follow-up 48 mo	All fish Fatty fish > 10g fat per 100g fish); Lean fish: <10g fat per 100g fish; Serving size= 120g raw fish	• Prevalence of wheezing Respiratory Assessment: Physician-diagnosed, ISAAC Questionnaire	FFQ Categories: No fish= <1/2 serving/ week; Eat fish: $\geq$ 1/2 serving/week	No fish introduction during 1st year of life • Wheezing risk at 48mo: (ORadj: 1.57, 95%CI: 1.07-2.31; p=0.03) Introduction of fish 0-6 mo: • Wheezing risk at 48 mo (ORadj: 1.53, 95%CI: 1.07-2.19; p=0.03) Introduction of fish at 6-12 mo of age: • Wheezing risk at 48 mo (ORadj:0.64; 95% CI: 0.43-0.94, p=0.03) Confounders: Maternal age,	Fish introduced between 6- 12 months lower prevalence of wheezing in children at 48 months compared to ‘no’ fish introduced during 1 st year of life and fish introduced between 0-6 months of age (p=0.03)

							maternal BMI, maternal alcohol, smoking during pregnancy, household income, maternal educational level, family history asthma, eczema, hay fever, allergy to house dust, maternal fish consumption during pregnancy, folic acid supplementation during pregnancy, parity, birth weight, gestational age, infant's gender, infant's ethnicity, breastfeeding duration, early day-care attendance, vitamin D supplementation in 1 st year life	
Magnusson et al, 2013(36); BAMSE Study Sweden	Cohort	3,285	1-12 y.o Follow-up: 1, 2, 4, 8, 12 y.o	All fish	• Prevalent asthma • Incidence asthma Respiratory Assessment: Questionnaire	FFQ : Categories: Never, 1 x/mo; 2-3 x/mo; 1x/wk; >1x/wk. Regular fish intake: ≥2-3 times/ mo ;	Fish intake at 1 year & prevalence asthma risk up to 12 y.o: Fish intake 1x/mth: • Prevalent asthma (ORadj:0.61; 95% CI:0.43-0.88, p≤0.001) Fish intake 2-3x/mth: • Prevalent asthma (ORadj:0.74; 95% CI:0.55-1.00, p≤0.001)	Regular fish intake at age 1 yr (≥2-3x/mo) ↓ prevalence and incidence of asthma up to 12 years. Reduced risk was dose-dependent for both outcomes (p<0.05).

						Irregular: ≤ 1 time/mo Fish intake 1x/wk: • Prevalent asthma (ORadj:0.49; 95% CI:0.37-0.65, p≤0.001) Fish intake >1x/wk: • Prevalent asthma (ORadj:0.54; 95% CI: 0.40-0.74, p≤0.001) Regular fish intake ≥2-3x/mo at 1 year and prevalence asthma up to 12 y.o: • Prevalent asthma (ORadj: 0.71; 95%CI: 0.57-0.87; p=0.001) • Overall Incidence asthma (ORadj: 0.80; 95%CI: 0.65-0.98; p=0.034) Confounders: Sex, parental allergy, maternal smoking, SES status, breast- feeding duration, maternal age, overweight, parental smoking at age 8 yrs,	
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							child's diet at age 8 yrs.	
Nwaru et al, 2013 (41); DIPP Study Finland	Cohort	3,781	5 y.o Follow-up: 3,6,12 mo; 5 y.o	All fish	• All Asthma • Atopic asthma • Non-atopic asthma Respiratory Assessment: ISAAC questionnaire	Questionnaire	Data not shown	Introduction of fish at 6-9 mo ↓ 'All asthma' (p<0.001) & 'atopic asthma' (p<0.05) at 5 yr .
Dotterund et al, 2013(38) PACT Study, Norway	Controlled Intervention Cohort	1,374	2 y.o Follow-up: 2 y.o	All fish Intervention 1.2g cod liver oil from 6-8 wks age and oily fish (x2/wk) from 6 mo.	• Parent-reported asthma • Used asthma medication last 12 months • Wheeze Respiratory Assessment:	FFQ: Frequency: ≥1x/wk	• Incidence of parent reported asthma: (ORc: 0.72 95%CI: 0.55-0.93; p=0.01) • Using asthma medication in last 12 months (ORc: 0.75; 95%CI: 0.58-0.96; p=0.02) • Wheeze (ORc: 0.92; 95%CI: 0.8-1.05; p=0.23)	Intake of oily fish twice a week significantly lowered incidence in parental-reported doctor diagnosed asthma (p=0.01) and use of asthma medication (p=0.02)

					Questionnaire adapted from ISAAC		After stratification by sex: • Parent-reported asthma Girls: (ORc: 0.41; 95%CI: 0.24-0.70) p<0.01 Boys: (ORc:0.93; 95%CI: 0.68-1.26) • Using asthma medication in last 12 months: Girls: (ORc: 0.46; 95%CI: 0.28-0.74) p<0.01 Boys: (ORc:0.95; 95%CI: 0.70-1.28) Confounders: Birth weight, maternal atopy, respiratory infections, use of antibiotics, maternal healthcare centre, proportion of participants from each cohort in each public health centre	for children in the intervention group compared to the control group at age 2 years. Impact on asthma and medication use was significant in girls (p<0.01) not boys. No differences observed between the groups for the risk of wheeze (p=0.23).
Lumia et al, 2015 (35); DIPP Study Finland	Nested case-control	182 asthma 728 control	0-6 y.o Follow-up: 3, 6, 12 mo;	All Fish & fish products	• All asthma • Atopic asthma • Non-atopic asthma	3-day food record	• All asthma: (ORadj:0.87; 95%CI: 0.77-0.98; p=0.02) • Introduction of fish at 6.1-8 mo:	Early consumption of fish and fish products (6.1-8 mo) was associated with a decrease risk of

			1-6 y.o		Respiratory Assessment: ISAAC Questionnaire		All asthma: (ORadj:0.45: 95%CI: 0.28-0.72; p<0.05) Confounders: Gestational age, maternal age, maternal smoking during pregnancy, duration of breastfeeding, number of siblings, parental asthma or allergic rhinitis, birth weight, mode of delivery, maternal vocational education, dogs at home during the first year of life, CMA, and age at introduction of solid foods (rye, wheat, barley, oats, fish, and egg)	all asthma in children at 6 years.
Peat et al, 1992(33) ; Australia	Cross-sectional	4,366	7-9 y.o, 11-14 y.o	All fish	• BHR Respiratory Assessment: Bronchial Challenge	FFQ Categories: Rarely, once/month, once/wk, >1/wk	Children born outside of Australia: • BHR: (OR:0.56: 95%CI: 0.4-0.9; p<0.03) Regular fish meal (>1x/wk) • BHR: (OR:0.35: 95%CI: 0.1-0.9; p<0.04)	Children born outside of Australia had lower BHR than children born in Australia (8% v 17.6%; p<0.03). And eating fish regularly (>x1/week) had a significant protective effect against BHR

							Confounders: Parental asthma, atopy parental smoking, early respiratory illness, gender, born outside Australia, race, dwelling region	compared to 'no' fish or eating fish ($\leq 1x/wk$) ($p<0.04$)
Takemura et al, 2002(32); Tokorozawa Childhood Asthma & Pollinosis Study Japan	Cross-sectional	23,782 (1,673 asthmatic 22,109 control)	6-15 y.o	All fish	• Current asthma Respiratory Assessment: Questionnaire (Japan Environment Agency)	FFQ: Categories: None, 1-2/mth; 1-2x/wk; $\geq 3-4/wk$	No fish: • Current asthma (ORadj:1.039; 95%CI:0.785-1.376) Fish intake 1-2x/wk: • Current asthma (ORadj:1.117;95%CI: 1.005-1.241) Fish intake: $\geq 3-4x/wk$: • Current asthma (ORadj:1.319; 95%CI:0.896-1.943) Fish intake: 1-2x/mo • Current asthma Reference: (OR: 1.00) (p trend =0.0394)	Frequency of fish intake was positively associated with prevalence of asthma. Children that consumed fish 1-2x/wk had a significantly higher prevalence of asthma as compared to those who ate fish 1-2x/mo or no fish (p trend= 0.0394)

							Confounders: Age, gender, parental history of asthma, fruit and vegetables	
Antova et al, 2003(29); CESAR Study 6 Central European countries	Cross-sectional	20,271	7-11 y.o	All fish	• Winter cough • Persistent cough • Wheeze ever • Current wheeze Respiratory Assessment: ISAAC Questionnaire	FFQ: Categories: ≥1x/mo <1x/mo	Low fish intake (<1x/mo): • Persistent cough (OR: 1.18, 95%CI:1.04-1.34; p=0.01) • Wheeze ever: (OR: 1.14, 95%CI:1.03-1.25; p=0.01) • Current wheeze: (OR:1.21, 95%CI: 1.06-1.39; p=0.01) • Winter cough: (OR: 1.10; 95%CI: 0.99-1.23; p=0.07) Confounders: Age, sex , area, presence of pets, presence of indoor moisture, use of gas oven for heating, additional unvented gas heating, number of smokers in household, mother's education, father's occupation, parent's allergy respondent ,	An increase in asthma symptoms was found for low fish intake (<1/month) and 'persistent cough' (p=0.01), 'wheeze ever' (p=0.01 and 'current wheeze' (p=0.01). But weakly associated with 'winter cough', (p=0.07).

							overcrowding (>1 person per room), all nutritional risk factors	
Farchi et al, 2003, (26); SIDRIA Study, Italy	Cross-sectional	5,257	6-7 y.o	Blue fish	• Occurrence of wheeze in past 12 months • Shortness of breath with wheezing in past 12 months Respiratory Assessment: ISAAC Questionnaire	FFQ Categories: Never, <`1x/wk, 1-2 x/wk, 3-4x/wk, 5-7x/wk	Fish intake: <1x/wk: • Occurrence of wheeze (OR:0.66; 95%CI:0.44-0.99) • Shortness of breath with wheeze (OR:0.84; 95%CI: 0.52-1.35) Fish intake: 1-2x/wk: • Occurrence of wheeze (OR:0.86; 95%CI:0.01-1.23) • Shortness of breath with wheeze (OR:0.77; 95%CI: 0.5-1.19) Fish intake: 3-4x/wk: • Occurrence of wheeze (OR: 0.77; 95%CI:0.32-1.86) • Shortness of breath with wheeze	No correlation found between frequency of fish consumption and occurrence of wheeze (p= 0.343) or shortness of breath with wheeze (p=0.743) in children aged 6-7 years.

							(OR:0.97; 95%CI:0.36-2.58)	
							Confounders: Sex, study area, parental education, dampness, mould in the child's room, household crowding.	
Kim et al, 2005(45); Sweden	Cross-sectional	1,482	5-14 y.o	All fish	• Current asthma • Night time breathlessness • Doctor diagnosed asthma Respiratory Assessment: ISAAC Questionnaire	FFQ Categories: Never, <1x/wk, 1x/wk, >1x/wk, daily	Regular consumption of fish: • Night time breathlessness (OR:0.36; 95%CI:0.17-0.78) p<0.05 • Doctor-diagnosed asthma (OR:0.54; 95%CI: 0.35-0.84) p<0.01 • Current asthma (OR:0.51; 95%CI: 0.31-0.84) p<0.01 Children with no food allergy/food intolerance: • Doctor-diagnosed asthma (OR: 0.44; 95%CI:0.25-0.76) p<0.01 • Current asthma (OR:0.37; 95%CI: 0.19-0.72) p<0.01	Children consuming fish regularly had less night time breathlessness (p<0.05) doctor-diagnosed asthma (p<0.01) and current asthma (p<0.01) even after excluding children with food allergy or intolerance (p<0.01).

							Confounders: Age, gender, type of fat and dietary factors	
Tabak et al, 2006(31); Netherlands	Cross-sectional	598	8-13 y.o	All fish	• Current wheeze • Current asthma • Atopic wheeze with BHR • Atopic asthma with BHR Respiratory Assessment: ISAAC Questionnaire	FFQ Categories: times per year/ month/week/day/never; Always, mostly /often/sometimes/seldom/never	• Current wheeze (OR:0.44: 95%CI: 0.21-0.93) p<0.01) • Current asthma (OR:0.34: 95%CI: 0.13-0.85; p<0.01) • Atopic asthma with BHR: (OR:0.12: 95%CI: 0.02-0.66) • Atopic wheeze with BHR: (OR:0.15: 95%CI: 0.03-0.63) Confounders: Maternal educational level, foreign descent, total energy intake.	High fish intake (15g/d) was inversely associated with current wheeze (p<0.01), current asthma (p<0.01), atopic wheeze and atopic asthma in children.
Chatzi et al, 2007 (10); Spain	Cross-sectional	460	6.5 y.o	All fish	• Current wheeze • Atopic wheeze • Atopy	FFQ Categories: Never, <1x/mo->6x/d	High intake of fish (60.5g/d) and prevalence of: • Current wheeze: (ORadj:0.48: 95%CI: 0.21-1.09; p=0.075)	High intake of fish (60.5g/d) was inversely associated with prevalence of atopy and not

					Respiratory Assessment: Questionnaire		• Atopic wheeze: (ORadj:0.56; 95%CI: 0.16-2.00; p=0.338) • Atopy: (ORadj:0.43; 95%CI: 0.21-0.90; p=0.033) Confounders: Gender, maternal and paternal asthma and atopy, maternal smoking, BMI at age 6.5 yrs, parental education, social class, breast-feeding, fish intake during pregnancy, number of siblings at age 6.5 yr, energy intake.	current or atopic wheeze.
Rodriguez et al, 2010,(25) Spain	Cross-sectional	638	8-13 y.o	All fish	• Current asthma Respiratory Assessment: Questionnaire	3-day dietary record	Fish consumption (59.8g/d) • Current asthma: (ORadj:1.22; 95%CI: 0.38-3.98 p=0.162) Confounders: Energy intake, fat intake, age, gender, BMI, parental asthma, atopic eczema, allergic rhinitis, parental cigarette smoking	No association between fish intake (59.8g/d) and asthma symptoms in children.
Nagel et al,	Cross-	50,004	8-12 y.o	All fish	• Asthma ever	FFQ	All children and fish intake	High intake of

2010(24); ISAAC International Study	sectional				• Wheeze in past year • SPT • BHR Respiratory Assessment: ISSAC Questionnaire	Categories: <1x/wk, >1x/wk, >1x/d	≥3x/wk: • Asthma ever (OR adj: 0.92; 95%CI: 0.78-1.08; p trend= 0.04) • Wheeze past year (OR adj: 0.87; 95%CI: 0.74-1.03; p trend= 0.29) All children and consumption of fish (>1-2x/wk) in affluent countries: • Wheeze in past year (ORadj:0.85; 95%CI:0.74-0.97) All children and consumption of fish (>1-2x/wk) in non- affluent countries: • Wheeze in past year (ORadj: 0.91; 95%CI:0.75-1.10) p=0.589 Children SPT positive in non-affluent countries and fish consumed (>1-2/week): • Wheeze in past year SPT positive (OR adj: 0.51; 95%CI: 0.32-0.81)	fish (≥3x/wk) as compared to never or occasionally was associated with lower prevalence of asthma (p=0.04). And regular consumption of fish (>1-2/week) resulted in lower prevalence of wheeze during the previous year for all children in affluent countries and in children with positive SPT in non-affluent countries
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							p=0.001 Children SPT positive in affluent countries and fish consumed(>1-2/week): • Wheeze in past year SPT positive (ORadj: 1.02; 95%CI:0.76-1.35) p=0.153 • BHR OR adj: 1.34; 95%CI: 0.83-2.15; p trend= 0.30) Confounders: Sex, age, exposure to tobacco smoke, no. of siblings, parental atopy, exercise, maternal education	
Kunitsugu et al, 2012(28); Shunan Child Health (SCH) Study Japan	Cross-sectional	410 (138 asthma, 137 control,	10-11y.o; 13-14 y.o	All fish & seafood	• Asthma Respiratory Assessment:	Self-reported Dietary History Questionnaire	All fish intake: • Asthma (OR: 0.34; 95%CI: 0.14-0.81; p trend= 0.083)	No statistically significant association was found between 'all fish' intake

		135 eczema)			ISAAC Questionnaire		Fatty fish/dried fish intake: • Asthma (OR: 0.42; 95%CI:0.18-0.96 p trend=0.374) Seafood intake : • Asthma (OR:0.34; 95%CI: 0.15-0.79; p p trend= 0.067) Confounders: Sex, school grade, parental smoking, single parent, siblings, school, residential area	(p trend= 0.083), ‘fatty/ dried fish’ (p trend =0.374), or seafood and asthma (p trend= 0.067)
Saadeh et al, 2015, (23); ISAAC Study, France	Cross- sectional	7,432	9-11 y.o	White fish	• Past year wheeze • Atopic wheeze • Lifetime asthma • SPT positive • BHR Respiratory Assessment: ISAAC Questionnaire	FFQ Frequencies: Never/occasional ly; 1-2x/wk, ≥3x/wk	Consumption of white fish (1- 2x/wk): • Past year wheeze: (ORadj:0.75; 95%CI: 0.53-0.93; p trend= 0.028) • Atopic wheeze (ORadj:2.78; 95%CI:0.66-11.61); p trend= 0.042 • SPT positive (ORadj:1.05; 95%CI: 0.69-1.61;	White fish intake (1- 2x/week) was associated with lower prevalence of wheezing in children (p=0.028), but not for atopic wheeze, life-time asthma or BHR. After stratification for SPT positive,

							p trend= 0.882) • Life-time asthma (ORadj:1.11; 95%CI: 0.61-2.03; p=0.261) • BHR (ORadj:1.44; 95%CI: 0.69-3.02 p trend= 0.524) Fish intake in SPT negative • Past year wheeze (ORadj:0.61; 95%CI: 0.43-0.87; p = 0.04) Confounders: Gender, place of residence, parental atopic disease number of siblings, maternal education, parental ethnic origins, breast-feeding, day care centre or nursery, overweight, obesity and current exposure to environmental tobacco smoke	fish intake was correlated significantly to less wheezing in non-atopic children (p= 0.04).
Xu et al,	Cross-	13,877	0-14 y.o	All fish &	•Prevalence asthma	Questionnaire	-	In 14% of children fish

2016(30); China	sectional			seafood	Respiratory Assessment: ISAAC Questionnaire, NEAAC Questionnaire			and shrimp consumption ↑ triggered asthma symptoms especially in children ≥ 6 years (p<0.05)
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Key: mo= Months; yr(s)=Year(s); wk(s)=Week(s); y.o=Years old; All fish = Lean & fatty fish; AHR: Airway Hyperresponsiveness ; BHR= Bronchial Hyperresponsiveness; SPT= Skin Prick Test for atopy; ≥ x1/wk = More than once a week; ORc= Odds Ratio crude; ORadj= Odds Ratio after adjusting for confounding factors, - = No data provided in study; ↓ = Reduction; ↑ = Increase; X= No effect or adverse effect on asthma symptoms; Ě= Improvement in asthma symptoms.

Supplement 1. PUBMED Literature search details

Box 1. Details of PubMed search strategies

Search	Query	Items found
S3 (S1 OR S2)	Search (fish or fatty fish or oily fish or omega 3 fatty acids or n-3 long chain polyunsaturated fatty acids) AND asthma AND children) OR ((Fish or fatty fish or oily fish or omega 3 fatty acids or n-3 long chain polyunsaturated fatty acids) AND childhood asthma)	333
S2	Search (Fish or fatty fish or oily fish or omega 3 fatty acids or n-3 long chain polyunsaturated fatty acids) AND childhood asthma	116
S1	Search (Fish or fatty fish or oily fish or omega 3 fatty acids or n-3 long chain polyunsaturated fatty acids AND asthma) AND children	326

Search retrieved from <http://www.ncbi.nlm.nih.gov>. Accessed on 5.7.17.

Supplement 2

Quality Assessment Tool for Fish intake & Paediatric Asthma according to Zaza et al (2000)

Reviewer name: _____ Date: _____

Paper title: _____

First author: _____

Year Published _____ Journal _____

#	Question	Responses	Notes/Answer/Score
1 (a)	Where was the study done?		
1 (b)	Population density	• Urban • Suburban • Rural • Mixed • Not reported	
2	How were outcome and other independent (or predictor) variables measured?	• Interview • Self-administered questionnaire • Hospital records • Record review • Observation • Not reported/did not assess	
3	Over what time period (include dates) and at what intervals were outcomes and other variables measured?		
4	Indicate the study design	(1) Expert opinion/case study (2) Observational study without control group (3) Controlled observational study (4) Case control study (5) Cohort study (6) Quasi experimental study (7) Experimental study Other, specify (0) Can't tell	
5	Was the population well described?	Yes (1) No (0) N/A	
6	Were the eligibility criteria required to enter the study population well described?	Yes (1) No (0) N/A	
7	Did the authors specify the sampling	Yes (1) No (0) N/A	

#	Question	Responses	Notes/Answer/Score
	frame or universe of selection for the study population?		
8	Was the population that served as the unit of analysis the entire eligible population or a probability sample at the point of observation?	Yes (1) No (0) N/A	
9	Was there attempt to measure exposure?	Yes (1) No (0) N/A	
10	Were the exposure measures valid measures?	Yes (1) No (0) N/A	
11	Were the exposure measures reliable?	Yes (1) No (0) N/A	
12	Were the outcome and other independent (or predictor) variables valid measures of the outcome of interest?	Yes (1) No (0) N/A	
13	Were the outcome and other independent (or predictor) variables reliable (consistent and reproducible) measures of the outcome of interest?	Yes (1) No (0) N/A	
14	Did the authors conduct appropriate analysis by conducting statistical testing?	Yes (1) No (0) N/A	
15	Did the authors report which statistical tests were used?	Yes (1) No (0) N/A	
16	Were the statistical tests appropriate for the study design?	Yes (1) No (0) N/A	
17	Was there controlling for design effects in the statistical model?	Yes (1) No (0) N/A	
18	Was there controlling for repeated measures in the analysis, for study designs in which the same population was followed with repeated measurements over time?	Yes (1) No (0) N/A	
19	Was there accounting for different levels of exposure in segments of the study population in the analysis?	Yes (1) No (0) N/A Can't tell (0)	
20	If the authors analysed group-level and individual-level covariates in the	Yes (1) No (0) N/A Can't tell (0)	

#	Question	Responses	Notes/Answer/Score
	same statistical model, was the model designed to handle multi-level data?		
21	Were there other problems with data analysis that limit interpretation of the results of the study? If yes, describe	No (1) Yes (0) N/A Can't tell (0)	
22	Considering study design, were appropriate methods for controlling confounding variables and limiting potential biases used?	Yes (1) No (0) N/A Can't tell (0)	
23	Did the authors identify and discuss potential biases or unmeasured/contextual confounders that may account for or influence the observed results and explicitly state how they assessed these potential confounders and biases? Describe these factors and, if possible, comment on the likely direction of bias.	Yes (1) No (0) N/A Can't tell (0)	
24	Are there are additional biases not covered in other categories that the authors did not address, if yes, list these as well.	Yes (0) No (1) N/A Can't tell (0)	

Ref: Zaza, S., Wright-De Agüero, L. K., Briss, P. A., Truman, B. I., Hopkins, D. P., Hennessy, M. H., . . . Teutsch, S. M. (2000). Data collection instrument and procedure for systematic reviews in the Guide to Community Preventive Services. *American journal of preventive medicine*, 18(1), 44-74.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-6, Supp 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, 22; Supp 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9; Supp 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	28-42
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18; Supp 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

Ref: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

LEGENDS (Unmarked)

MANUSCRIPT

Fig 1. Flow chart of search details

Fig 2. Forest plot of cohort studies children (0-4 years old) for 'All fish' intake versus 'No fish' and outcome 'current asthma'.

Fig. 3. Forest plot of cohorts comparing the effect of 'All fish' intake versus 'No fish' on 'current wheeze' in children aged 0-4.5 years.

Fig 4. Forest plot in the combined analysis comparing 'Fatty Fish' intake versus 'No Fatty Fish' in children (8-14 years) for 'current asthma'.

SUPPLEMENT LEGENDS:

Fig S1. Forest plot of 'all study designs' and 'All Fish' intake versus 'No Fish' for 'current asthma' in children aged 2-15 y.o.

Fig S2. Forest plot of case-control trials in children (6-11 years), cohorts (8-12 years) and cross-sectional studies (5-15 years) for 'All Fish' intake versus 'No Fish' and 'current asthma'

Fig S3. Forest plot of all study designs combined, children (0-13 years old) for 'All Fish' intake versus 'No Fish' and outcome 'current wheeze'

Fig S4. Forest plot of cross-sectional studies including children (6-13 years old) for 'All Fish' intake versus 'No Fish' and outcome 'current wheeze'.

Fig S5. Forest plot of cohort studies children (0-8 years old) for 'All Fish' intake versus 'No Fish' and outcome 'current wheeze'.

Fig S6. Forest plot comparing 'Fatty Fish' intake versus 'No Fatty Fish' and 'current asthma' in children 2-14 years old in the combined analysis.