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[Page 1] Title: The role of fish intake on asthma in children: A meta-analysis of observational studies.

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Running title: Fish and childhood asthma: Meta-analysis

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1

2 [Page 2] *Pediatr Allergy Immunol.*

3

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

6

7 Maria M Papamichael¹, Som Kumar Shrestha³, Catherine Itsiopoulos¹, Bircan Erbas²

8

9 **ABSTRACT**

10 **BACKGROUND**

11 The evidence is mixed on the use of long chain omega 3 fatty acids in the prevention and
12 management of childhood asthma.

13 **METHODS**

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

16 **RESULTS**

17 A total of 1,119 publications were identified. Twenty-three studies on fish intake in
18 association with childhood asthma were included in the final review. In 15/23 studies early
19 introduction of fish (6-9 months) and regular consumption (at least once a week) improved
20 asthma symptoms and reduced risk in children 0-14 years as compared to no fish
21 consumption; 6/23 showed no effect and 2/23 studies suggest adverse effects. Meta-analysis
22 revealed an overall 'beneficial effect' for 'all fish' intake on 'current asthma' [OR: 0.75;
23 95%CI: 0.60-0.95] and 'current wheeze' [OR: 0.62; 95%CI: 0.48-0.80] in children up to 4.5
24 years old. An overall protective effect of 'fatty fish' intake as compared to 'no fish' intake in
25 children 8-14 years old was also observed [OR: 0.35; 95%CI: 0.18-0.67].

26 CONCLUSION

27 This meta-analysis suggests that introduction of fish early in life (6-9 months) and regular
28 consumption of all fish (at least once a week) reduces asthma and wheeze in children up to
29 4.5 years old, while fatty fish intake may be beneficial in older children. Future well-
30 designed clinical trials are recommended to confirm the promising findings documented in
31 this literature analysis.

32
33 **Keywords:** asthma, children, fish, nutrition, oily fish, omega 3 fatty acids

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43 INTRODUCTION

44 Despite advances in pharmacotherapy, globally, the asthma epidemic in children is a
45 major public health problem as it continues to rise. Asthma is associated with morbidity,

46 substantial health care costs and decreased quality of life (1, 2). There is no cure for asthma,
47 symptoms can only be controlled by medication which on a long-term basis may cause side-
48 effects. Therefore, identifying potential non-pharmacological interventions which improve
49 management of asthma is of great public health significance.

50 The modern diet is low in fruits, vegetables, fish and high in refined grains, red meat
51 and fast food (3) which may have contributed to the high prevalence of asthma in
52 Westernized countries (1). As a result today's diet is deficient in anti-inflammatory nutrients
53 (from fruit/vegetables) and long chain omega 3 fatty acids (LC n-3 PUFA) (obtained from
54 fish) and high in omega 6 fatty acids mainly from processed fats and oils such as margarine
55 and vegetable oils (3, 4). It is believed that the change in anti-inflammatory status, fatty acid
56 composition, increase in omega 6 : omega 3 fatty acid ratio is associated with an increase in
57 oxidative stress and airway inflammation promoting the development and symptoms of
58 asthma (5, 6).

59
60 [Page 4] There has been considerable interest in the potential therapeutic and protective
61 properties of omega-3 fatty acids (EPA/DHA) in the pathogenesis of asthma due to anti-
62 inflammatory and immune-modulating properties (4, 7). To date, the evidence for the
63 beneficial effects of omega 3 fatty acid intake in asthma is controversial and intervention
64 trials investigating the impact of fish or fish oil supplementation in children are lacking (8).
65 Most of the epidemiological evidence which gave rise to the hypothesis that marine omega 3
66 fatty acids may have a protective effect is based on studies documenting that regular
67 consumption of fish has a prophylactic effect. (9-11). In addition, many systematic reviews
68 have investigated the impact of omega 3 fatty acid intake during pregnancy on allergy
69 outcome in offspring suggesting a beneficial effect (12-14). Little is known about fish intake
70 on asthma during childhood (post-infancy) and this warrants further investigation.

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

75 **METHODS**

76 This review was conducted according to PRISMA guidelines (15) (Supplement 4).

77

78 *Literature Search strategy*

79 We conducted a comprehensive literature search of publications up to July 2017 using the
80 following bibliographic databases: Cochrane Central Register of Controlled Trials,
81 MEDLINE, PUBMED, CINAHL (EBSCO), SCOPUS and EMBASE. No restrictions were
82 applied on language or publication dates. Supplementary studies were sought from
83 conference [Page 5] proceedings as well as clinical trials registries (International, European,
84 Australia and New Zealand) in order to identify published/unpublished trials Other potential
85 relevant citations were identified by hand search of the reference lists of relevant articles,
86 reviews, systematic reviews and meta-analysis. Databases were searched for relevant
87 publications, by a two-step search strategy using the following search terms:

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

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

92 The final search was a combination of both searches using the term "OR". The full search
93 strategy is provided in (Supplement 1).

94 *Study eligibility criteria*

95 *Inclusion criteria*

96 Inclusion criteria was based on Participants, Intervention, Comparator and Outcomes (PICO)
97 (16).

98 *Type of participants*

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

101 *Type of intervention*

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

103 *Outcome measures*

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

106

107 [Page 5] A publication was considered when exposures were measured and the presence of
108 asthma was based on the manifestation of symptoms, pulmonary tests or doctor-diagnosis

109 (17). In addition, studies examining the effect of omega 3 fatty acid intake on atopy in
110 children were considered relevant when results on fish intake and asthma outcome in children
111 could be separated.

112

113 *Type of studies:*

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

117

118 *Exclusion criteria*

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

126 *Selection of studies*

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

129 When there was insufficient information in the abstract to warrant exclusion of the article, the
130 full-text of the article was retrieved. Full-text papers were then independently appraised by
131 both reviewers for inclusion and details extracted. Discrepancies were resolved by discussion
132 [Page 6] and consensus that led to agreement. The search was supplemented by cross-
133 checking reference and bibliographies of relevant publications, systematic reviews and
134 reviews.

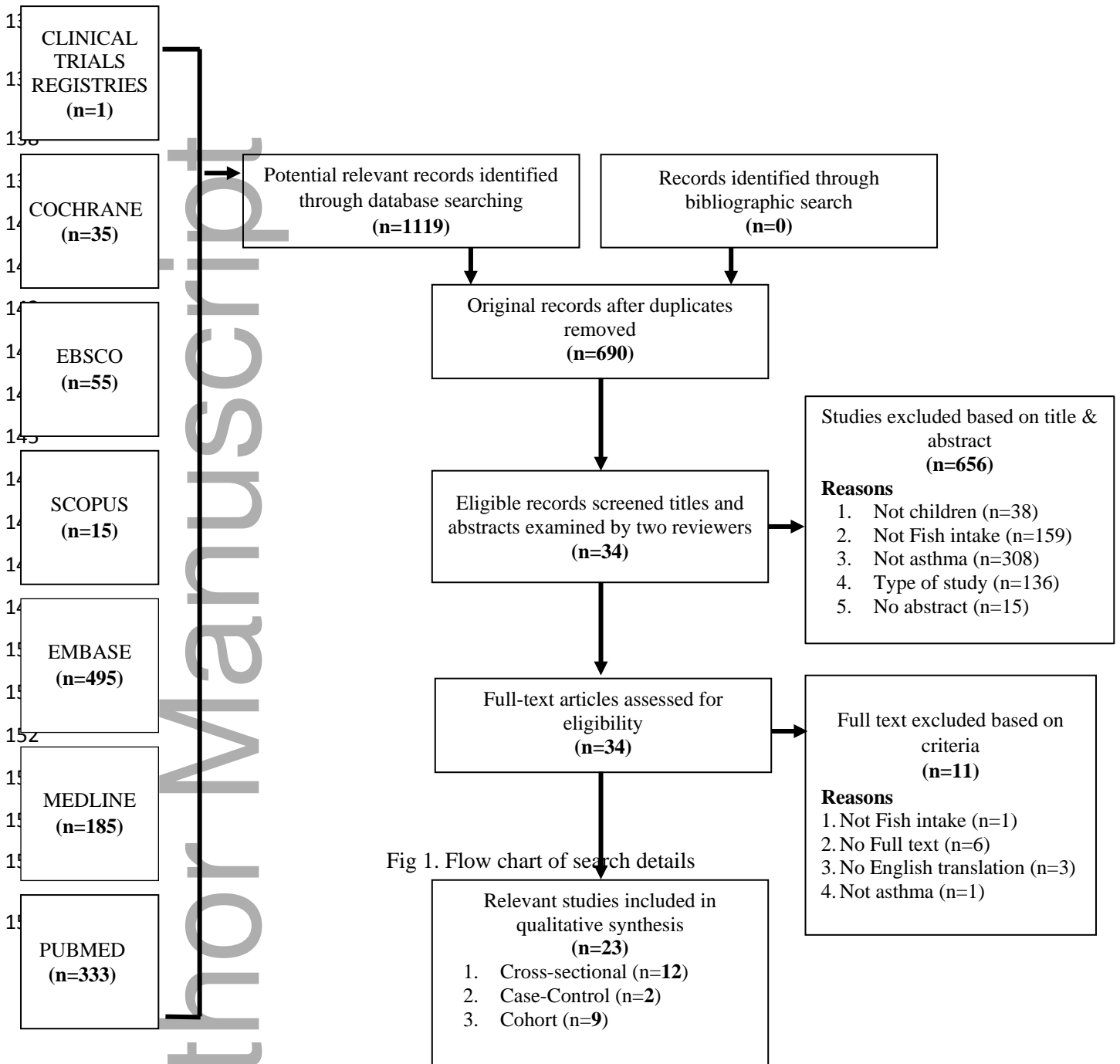


Fig 1. Flow chart of search details

160 SKS and MP independently rated all publications included in the meta-analysis using a
161 validated quality assessment tool according to Zaza et al (18) (Supplement 2). The scientific
162 soundness was rated using twenty four validity questions with possible responses of 'yes' or
163 'no'. A value of one was assigned to 'yes' and zero to 'no'. The final score was presented as
164 the percentage of total (maximum) probable scores for each study. Any discrepancies were
165 addressed with mutual agreement between the authors or with a third reviewer (BE). Finally,
166 the scores from both evaluators were averaged and presented as the final score. The observed
167 median study quality score was used as the dividing point between low and high quality (19).
168 We set the benchmark of 70% and above as a high quality study while below 70% as low
169 quality.

170 *Data Extraction*

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

175 *Data Synthesis and statistical analysis*

176 Study outcomes were synthesized and categorized into two groups based on the effect on
177 asthma symptoms (improvement or no improvement). Quantitative data were pooled in
178 statistical meta-analysis software using STATA software version 14.1 (Stata Corp, Texas).
179 For the purpose of the meta-analyses, publications assessing 'all' types of fish and 'fatty fish'
180 as the exposures and regular fish intake, at least once a week were deemed appropriate.
181 Studies were included in the meta- analysis when effect size was expressed as odds ratio
182 (OR) and their 95% confidence intervals (95%CI) were reported or could be calculated.
183 Eligible publications [Page 8] were categorized into two groups based on the common
184 outcome of interest "current asthma" or "current wheeze" as defined by ISAAC (20).

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

188 Two assessments were conducted for each outcome. One was a combination of all study
189 designs with 'all fish or 'fatty fish' exposure' and the other according to study design and

190 similar age group. Heterogeneity was assessed using the standard Chi-square test and I^2
191 statistic (21). Considerable heterogeneity was considered to be an I^2 value $> 75\%$ (21) and
192 statistical significance at the 5% level (22). We applied the random-effects model to estimate
193 the pooled ORs and 95% CIs for 'current asthma and 'current wheeze'.

194 **RESULTS**

195 *Electronic search:*

196 The literature search identified a total of 1,119 potential publications of which 690 remained,
197 after removal of duplicates (Fig. 1). No additional citations were found by cross-checking of
198 reference lists. Only one ongoing RCT was identified from international clinical trial
199 registries. Two reviewers (MP, CI) independently screened the 690 eligible papers by
200 scanning titles and abstracts. A total of 656 were excluded based on publication type (136),
201 no abstract (15) or on PICO criteria as they did not examine the effect of fish intake (160) in
202 association with asthma symptoms (308) in children (37), leaving 34 full-text articles to be
203 assessed for eligibility. Of the remaining 34 potential studies, 11 full-texts were deemed to be
204 inappropriate (1 not intervention, 1 not asthma, 6 no full-text available and 3 no English
205 translation), leaving a total of 23 relevant studies. Specifically, 12 cross-sectional (10, 23-33),
206 2 case-control (34, 35) and 9 cohort studies (11, 36-43) examining the effect of fish
207 consumption on asthma symptoms in children.

208 [Page 9] *Study Characteristics*

209 The database search identified 23 studies conducted from 1992 to July 2017 examining the
210 effect of fish consumption on asthma in children. Two were undertaken in Australia (33, 34),
211 Japan (28, 32), Spain (10, 25) and Finland (35, 41), three in Norway (38, 40, 44) and the
212 Netherlands (31, 37, 43), four in Sweden (11, 36, 39, 45), one in China (30), Italy (26),
213 France (23), Central Europe (29) and the ISAAC study which involved 20 countries globally
214 (24). Collectively, 163,744 children and adolescents up to 15 years old were investigated with
215 sample sizes ranging from 138 to 50,004. A variety of assessment methods were used to
216 assess dietary intake in children. Twenty studies evaluated fish intake using a number of
217 different
218 questionnaires (10, 11, 23, 24, 26, 27, 29-34, 36-43) ranging from one question to
219 questionnaires consisting of limited food groups/items and detailed Food Frequency
220 questionnaires (FFQ) comprising of a wide-variety of foods that capture the entire dietary
221 pattern. While two studies used a 3-day food record (25, 35) and one, a diet history
222 questionnaire (28).

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

229 *Cohort Studies: 0-12 years of age.*

230 The nine cohort studies identified, investigated the effect of early fish intake on asthma in 33,
231 673 children from birth until 12 years of age (11, 36-43). Seven studies revealed that early
232 introduction and regular consumption of 'all fish' were associated with a reduction in asthma
233 symptoms up to 12 years of age (11, 36-41) and two showed no effect (42, 43).

234 [Page 10] Two studies reported that early introduction of 'all fish' (at 6-9 months of age) and
235 regular consumption \geq 1/week) of 'all fish' (37) and 'fatty fish' (38) reduced asthma
236 incidence (OR_c: 0.72; 95%CI: 0.55-0.93) (38), prevalence of wheeze (OR: 0.64; 95% CI:
237 0.43-0.94) (37) and use of medication (OR: 0.75; 95%CI: 0.58-0.96) (38) in children up to 4
238 years of age (37) (38). Conversely, Kiefte-de-Jong et al, noted that no fish during the first 12
239 months of life and introduction of 'all fish' between 0-6 months was associated with an
240 increase in prevalence of wheezing [(OR: 1.57; 95%CI: 1.07-2.31), (OR:1.53; 95%CI: 1.07-
241 2.19)] respectively at 48 months as compared to a reduction in the prevalence of wheezing
242 with fish introduction at age 6-12 months (OR: 0.64; 95% CI: 0.43-0.94).

243 Beneficial effects of 'all fish' intake were also documented in children during the first 5
244 years of life. Fish consumption before 9 months had a protective effect for recurrent
245 wheezing (OR: 0.6; 95% CI 0.4-0.8) (39), multiple trigger wheeze (OR: 0.6; 95%CI:0.3-0.99)
246 (39), episodic viral wheeze (OR:0.6; 95%CI:0.4-0.99) (39) , asthma risk (OR: 0.73; 95%CI:
247 0.55-0.97) (11), (OR: 0.84; 95% CI=0.57-1.22) (40), all asthma (p<0.001) (41) and atopic
248 asthma (p<0.05) (41) up to 5 years as fish intake increased from two to three times per month
249 (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
250 least once a week (OR adj= 0.55; 95% CI 0.34-0.87; p trend=0.003) (11) a dose response was
251 observed.

252 A Swedish cohort which involved 3285 children with follow-up till 12 years of age,
253 regular 'all fish' intake (\geq 2-3 times/month) at age of 1 year was associated with reduced risk
254 of prevalence (OR_{adj}: 0.71; 95%CI: 0.57-0.87) and incidence (OR_{adj}: 0.80; 95%CI: 0.65-
255 0.98) of asthma up to age 12 years, after adjusting for confounders of parental history of
256 allergic disease, sex, maternal smoking during pregnancy (36). However, no significant
257 association was observed between fish intake at age 8 years and incidence of asthma at 12

258 years (p trend= 0.303) (36). This finding is in agreement with two other cohorts that
259 documented no relationship among early, late or long-term intake of any kind of fish on
260 asthma in children at ages 2 (42) (p=0.16) and 8 years (43). Although, Willers et al, did report
261 that early fish intake was inversely associated to BHR in children at age 8 years old (43).

262 [Page 11] *Case-control studies: 5-15 years of age*

263 A beneficial effect of fish intake on asthma in children was observed in 2 case-control
264 studies (34, 35). In a nested-cohort study which was a sub-group of the Finnish DIPP study,
265 182 children with asthma and 728 controls participated and were observed at 3, 6, 12 months
266 and thereby annually up to 6 years (35). Overall, early introduction of 'all fish' and fish-
267 products (6-8 months) was associated with a reduction in 'all asthma' risk (OR_{adj}: 0.87;
268 95%CI: 0.77-0.98) in children at 6 years adjusting for confounders. Another case-control
269 study investigating the impact of fish intake on asthma symptoms in 584 children aged 8-11
270 years also reported a protective effect (34). After adjusting for confounders, children who ate
271 fresh, 'fatty fish' at least once a week had a significantly reduced risk of current asthma
272 (OR_{adj}: 0.26; 95%CI: 0.09-0.72) as compared to 'any fresh' fish (OR_{adj}: 0.52; 95% CI: 0.24-
273 1.15) and 'non-fatty' fish (OR_{adj}: 0.68; 95% CI: 0.3-1.54) consumers. No reduction in asthma
274 risk was observed with canned fish consumption.

275

276 *Cross-sectional studies: 0-15 years*

277 The literature search retrieved 12 cross-sectional studies undertaken in 128,577 children aged
278 0-15 years (10, 23-26, 28-33, 45). Five studies observed that regular 'all fish' intake
279 (>1/week) was associated with a reduction in lifetime prevalence of asthma (OR_{adj}: 0.92;
280 95%CI: 0.78-1.08) (24), current wheeze [(OR_{adj}: 0.85; 95%CI:0.74-0.97)(24); (OR: 0.44;
281 95%CI: 0.21-0.93)] (31), current wheeze with atopy positive (OR_{adj}: 0.51; 95%CI: 0.32-0.81)
282 (24), doctor-diagnosed asthma (OR: 0.54; 95%CI: 0.35-0.84) (45), night-time breathlessness
283 (OR: 0.36; 95%CI:0.17-0.78) (45), current asthma (OR: 0.51; 95%CI: 0.31-0.84) (45), (OR:
284 0.34; 95%CI: 0.13-0.85) (31), past-year wheeze (OR_{adj}: 0.75; 95%CI: 0.53-0.93) (23), past-
285 year wheeze and atopy negative (OR: 0.61; 95%CI: 0.43-0.87) (23), atopic asthma with BHR
286 (OR:0.12; 95%CI: 0.02-0.66) (31), atopic wheeze with BHR (OR: 0.15; 95%CI: 0.03-0.63)
287 (31) and BHR (OR:0.35; 95%CI: 0.1-0.9) (33). While one study (29) reported that, irregular
288 fish intake [Page 11] (<1/month) was associated with an increase in 'persistent cough' (OR:
289 1.18; 95%CI:1.04-1.34), 'wheeze ever' (OR: 1.14; 95%CI:1.03-1.25) and 'current wheeze'
290 (OR: 1.21; 95%CI: 1.06-1.39) A recent study undertaken by Xu et al, including 13, 877
291 children, 0-14 years old, observed that fish and shrimp intake triggered asthma episodes by

292 14% ($p < 0.05$) (30), although estimated effect size was lacking. Adverse effects of 'all fish'
293 intake were also reported in a Japanese study of 1,673 asthmatic children and 22,109 controls
294 aged 6-15 years (32). After adjustment for confounders (age, gender, parental asthma), a
295 statistically significant higher prevalence of asthma was observed in children consuming fish
296 1-2 times/week (OR_{adj} : 1.117; 95%CI: 1.005-1.241) and more than or equal to 3-4
297 times/week (OR_{adj} : 1.319; 95%CI: 0.896-1.943) than among those who consumed no fish
298 (OR_{adj} : 1.039; 95%CI: 0.785-1.376).

299 *Quality assessment*

300 Twenty one out of 23 studies were rated as 'high quality'. The average quality score was
301 82.1% with the highest score 100% and the lowest score 64% (Table 1). Most of the cohort
302 studies included in the meta-analysis were of high quality, 8 out of 9 studies scored above
303 90%. The studies that were rated lower quality were due to their failure to control for
304 potential confounders and address possible biases. Using t-test, we checked if there were any
305 differences in the quality score for the selected studies between two reviewers and found no
306 major difference in average score (p-value=0.33).

[Page 13] Table 1. Summary table of Quality Assessment of relevant studies in this systematic review (Zaza, 2000).

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					
Peat et al, 1992	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	67.5%
Hodge et al, 1996	SKS/MP	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗	70.5%
Takemura et al, 2002	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	83.0%
Farchi et al, 2003	SKS/MP	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	73.0%
Nafstad et al, 2003	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	91.0%
Kim et al, 2005	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	79.5%
Kull et al, 2006	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	95.0%
Tabak et al, 2006	SKS/MP	✓	✗	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	75.0%
Chatzi et al, 2007	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	82.0%
Antova et al, 2003	SKS/MP	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	75.0%
Nagel et al, 2010	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	83.0%
Oien et al, 2010	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	95.0%
Rodriguez et al, 2010	SKS/MP	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗	73.0%
Goksor et al, 2011	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	91.0%
Willers et al, 2011	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	93.0%

Key: ✓: criteria satisfied ; ✗ : criteria not satisfied

[Page 14] Table 1. Summary table of Quality Assessment of relevant studies in this systematic review (Zaza, 2000).

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					
Kunitsugu et al, 2012	SKS/MP	✓	✗	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	73.0%
Kiefte de Jong et al, 2012	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	95.0%
Dotterund et al, 2013	SKS/MP	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	80.5%
Magnusson et al, 2013	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	91.0%
Nwaru et al, 2013	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	97.5%
Lumia et al, 2015	SKS/MP	✓	✗	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗	78.0%
Saadeh et al, 2015	SKS/MP	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	82.0%

Xu et al, 2016	SKS/MP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	64.0%
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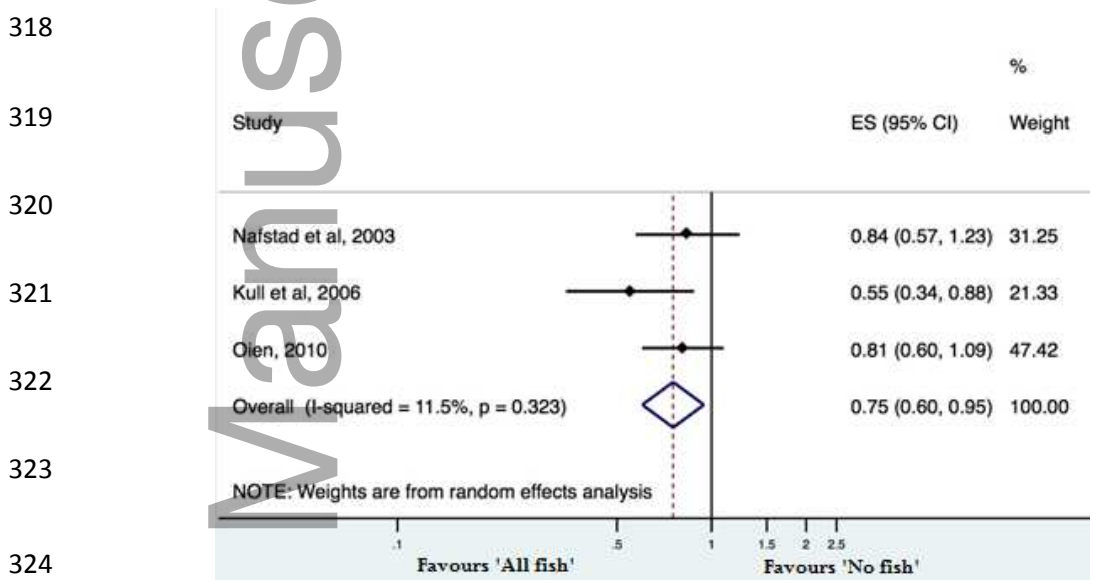
Key: ✓: criteria satisfied ; ✗: criteria not satisfied

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311 A total of nineteen studies were used in the meta-analysis (10, 11, 23-29, 31, 32, 34-
 312 37, 39, 40, 42, 43).

313 *Current Asthma*

314 Assessment of cohort studies alone (11, 40, 42) revealed a statistical significant
 315 effect (21) of ‘all fish’ intake on ‘current asthma’ in children 0-4 years ($I^2=11.5\%$;
 316 $p=0.32$; (OR: 0.75; 95% CI: 0.60-0.95). Overall, a 25% reduction in ‘current asthma’
 317 was observed with ‘all fish’ intake in children up to 4 years old (Fig 2).

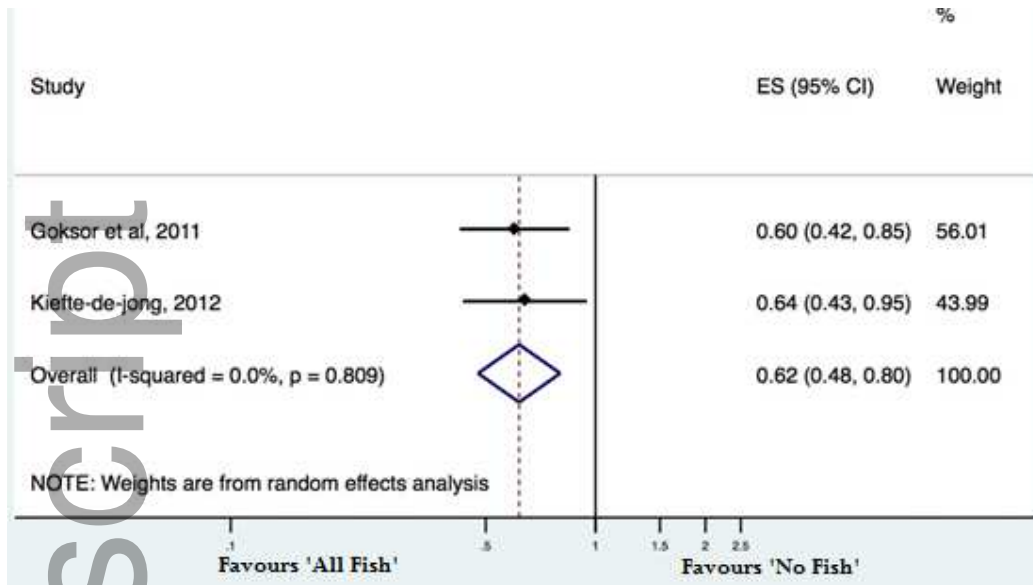


325 Fig 2. Forest plot of cohort studies children (0-4 years old) for ‘All fish’ intake versus ‘No fish’ and
 326 outcome ‘current asthma’.

328 *Current Wheeze*

329 A pooled effect for current wheeze and ‘All fish’ intake was found in cohort studies
 330 regarding children up to 4.5 years [$I^2 = 0\%$, $p=0.809$; (OR: 0.62; 95%CI: 0.48-0.80)]
 331 [Page 16] (Fig 3). A 38% reduction in ‘current wheeze’ was observed with ‘All fish’
 332 intake in children up to 4.5 years old.

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

343

344 *Fatty fish versus No fatty fish*

345 When analysing the effect of 'Fatty fish' intake in children aged 8-14 years (28, 34) for
346 'current asthma' in the combined sub-analysis, an overall effect was observed [$I^2 = 0\%$, p-
347 value=0.481; (OR: 0.35; 95%CI: 0.18-0.67)](Fig 4). Fatty fish intake reduced 'current
348 asthma' in children aged 8-14 years by 65% as compared to 'no fish' intake.

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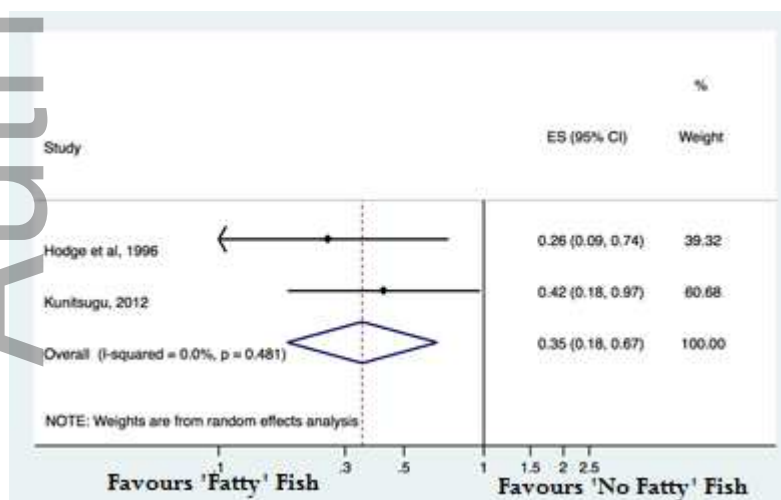
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358 [Page 18] Fig 4. Forest plot in the combined analysis comparing 'Fatty Fish' intake versus 'No Fatty
359 Fish' in children (8-14 years) for 'current asthma'.

360

361 In contrast, no association was observed for 'all fish' intake on 'current asthma in
362 children aged (2-15 years) when combining all study designs (11, 24, 25, 28, 31, 32, 34-36,
363 40, 42, 43, 45) (Supplement, Fig S1) or in sub-analysis based on study designs separately
364 (Supplement, Fig S2). No pooled age specific effects were also found for 'current wheeze'
365 and 'All fish' intake in children (0-13 years) irrespective of study design (Supplement, Fig(s)
366 S3-S5). The same trend was established for 'Fatty fish' intake vs 'current asthma' in children
367 (0-14 years) in the combined sub-analysis (Supplement, Fig S6).

368

369 **DISCUSSION**

370 The aim of this qualitative synthesis and meta- analysis was to clarify the role of fish intake
371 on different asthma outcomes in children. Although the meta-analysis produced mixed
372 results, three important findings were highlighted. Firstly, early introduction of ' all fish'
373 intake during [Page 18] infancy (6-9 months of age) and regular consumption (at least
374 once/week) of 'all fish' reduced 'current asthma' by 25% and 'current wheeze' by 38% in
375 children up to 4.5 years old (11, 37, 39, 40, 42). While 'fatty fish' intake seems to confer an
376 overall ' prophylactic effect' in older children 8-14 years and reduced 'current asthma' by
377 65% (28, 34).

378 Summarizing the results of the database search, in 15/23 studies a protective effect
379 was observed between fish consumption on asthma symptoms in children (11, 23, 24, 27,
380 29, 31, 33-41), 6/23 no effect (10, 25, 26, 28, 42, 43) and 2/23 an adverse effect (30, 32).
381 Two important results were highlighted in these observational studies. Early introduction
382 during the first year of life (between 6-9 months) and regular consumption of fish (at least
383 once a week) decreased risk, prevalence and asthma symptoms in children up to 14 years of
384 age. This finding is in accordance with other observational studies that have found early
385 introduction and frequent consumption of fish were associated with decreased asthma
386 symptoms and improvement in pulmonary function in children and adolescents (9, 46-48).

387 Our meta-analysis of nineteen (19) publications showed an overall beneficial' effect of
388 'all fish' intake on 'current asthma' and 'current wheeze' in children up to 4.5 years old in
389 five cohort studies alone (11, 37, 39, 40, 42) and of 'fatty fish' intake on 'current asthma' in
390 8-14 year olds(28, 34). The prophylactic effects documented in the cohort studies for young
391 children up to 4.5 years old may be explained from research on biological mechanisms that
392 have shown that, the development and maturation of the immune system starts early in foetal
393 life, continues through infancy and early childhood (49); (50). Infancy is a period in which
394 the immune cells have an increased vulnerability and susceptibility to environmental
395 exposures such as diet. A diet rich in omega 3 fatty acids and lower omega 6: omega 3 fatty
396 acid ratio may result in an increased incorporation of EPA and DHA into cell membranes at
397 the expense of arachidonic acid. More EPA and DHA in the cell membrane results in
398 decreased production of arachidonic acid-derived pro-inflammatory eicosanoids. EPA and
399 DHA act as substrates for COX and LOX [Page 19] enzymes producing anti-inflammatory
400 eicosanoids, protectins, resolvins and maresins that appears to exert anti-inflammatory and
401 inflammatory resolving actions (51). Apart from anti-inflammatory properties, omega 3 fatty
402 acids are able to modulate immune responses by promoting Th 1 cell generation thereby
403 reducing airway inflammation, improving pulmonary function and decreasing asthma
404 symptoms (13).

405 Additional protective effects on asthma symptoms were observed in two studies
406 examining the effect of 'fatty fish' as opposed to 'all fish' in children aged 8-11 years old
407 (34, 38). Hodge et al reported a 25% reduction in 'current asthma' when fatty fish was
408 consumed as compared to lean or no fish in children (34). Furthermore, no reduction in
409 asthma risk was observed with the consumption of canned and processed fish. Perhaps,
410 processing and food additives may alter the biological activity of omega 3 fatty acids in fish
411 oils. Dotterud et al, reported a 32% reduction in incidence of asthma with fatty fish
412 consumption in infants at 2 years old, after adjusting for confounders (38). A beneficial effect
413 of fatty fish intake was also noted in the studies undertaken by Kunitsugu and Oien, although
414 results were not statistically significant, most probably explained by heterogeneity between
415 study designs and small sample size (28, 44). Our meta-analysis confirmed an overall
416 'prophylactic' effect of fatty fish intake in older children (28, 34). A 65% reduction in
417 'current asthma' was observed in children aged 8-14 years (28, 34).

418 The findings of this meta-analysis highlight that the type of fish consumed whether
419 fatty or lean may matter. Fatty fish as compared to lean fish is a rich source of omega 3 fatty

420 acids which are able to counteract the action of omega 6 fatty acids metabolites by down-
421 regulating pro-inflammatory and immunological pathways thereby preventing asthma
422 development (52); (53). Another possible explanation why fish consumption reduced asthma
423 risk in children as compared to null effects reported from fish oil supplementation during
424 childhood (54) is that regular fish consumption may be a proxy for other healthy lifestyle
425 habits that might promote [Page 20] the beneficial effect. In addition, fresh fish might have
426 better bioavailability and absorption rate as opposed to fish oil. And apart from EPA/DHA,
427 fresh fish contains other bioactive molecules such as selenium, iodine, vitamin D, potassium
428 and B-vitamins that might interact synergistically providing these prophylactic properties
429 (55).

430 On the other hand, our meta-analysis showed no statistical significant results for 14
431 studies (10 cross-sectional, 2 cohorts and 2 case-controls) on 'current asthma' or 'current
432 wheeze' in children 6-15 years old (10, 23-26, 28, 29, 31, 32, 34, 35, 42, 43, 45). A possible
433 reason for the null effects observed might be due to heterogeneity among study
434 methodologies which included: population differences, sample size, children's age, gender,
435 asthma definition, exposure and outcome measures, possible confounders, design of dietary
436 questionnaires and food frequency categories, amount or type of fish consumed (fatty versus
437 lean), quantity EPA/DHA, fish consumption patterns since nutritional guidelines may vary in
438 each country and food preparation methods. Use of invalidated and self-administered food
439 frequency questionnaires, 3-day diet history for the recording of dietary intake require
440 education and expertise, are prone to information bias and response errors (43);(28). Even
441 though data on habitual diet were collected retrospectively from parents, in young children, it
442 is well-established that parents provide reliable information on children's diet (56).
443 Misclassification of asthma may have occurred in young children, since the diagnosis of
444 asthma is uncertain in children younger than 5 years and wheezing is often the result of
445 respiratory infection (57);(58). Furthermore, spirometry which is considered to be the 'gold-
446 standard' of pulmonary function testing in the diagnosis of asthma, cannot be performed
447 efficiently in children younger than 5 years and diagnosis of asthma in young children is
448 based on parents' report of symptoms (57). In addition, parental allergic disease and early
449 onset of allergic disease in children may cause parents to delay introduction or to avoid fish
450 in the child's diet, thus influencing asthma outcome.

451 [Page 21] Two cross-sectional studies documented increased risk of asthma prevalence
452 in children consuming fish in Japan and China (30, 32). Today, the eating patterns of
453 Japanese and Chinese children have changed to a more Westernized diet (59, 60). Processed
454 (23, 61) and pickled foods (62) as well as a high salt intake (63, 64) have been associated
455 with an increase in bronchial hyperresponsiveness and asthma symptoms in children. In both
456 studies confounding factors such as overweight, socio-economic level, maternal education,
457 type of fish consumed (lean vs fatty), poor adherence to asthma therapy were not included
458 in regression models and may have contributed to the adverse effects.

459 One of the strengths of this systematic-review is the extensive literature search and
460 large number of recent high quality publications included which increases the power of the
461 analysis. There are very few meta-analysis in the literature that examine fish intake and
462 asthma in children (Yang, 2013; Zhang, 2017) (14, 65) and recent reviews (Best, 2016;
463 Miles, 2017) address omega 3 fatty acid intake during pregnancy (12, 13). Our meta-analysis
464 focuses exclusively on children and adolescents, and adds to the existing evidence. Another
465 strong point is the inclusion of cohort studies in the meta-analysis which are considered
466 robust and provide strong scientific evidence because they measure events in temporal
467 sequence thereby distinguishing causes from effects (66). Another drawback might be
468 publication bias where studies reporting no association between fish intake and asthma may
469 not be published by periodicals.

470

471 CONCLUSION

472 We conducted an up-to-date systematic search to determine the impact of fish intake in
473 childhood asthma. This meta-analysis suggests that introduction of fish early in life (6-9
474 months) and regular consumption of all fish (at least once a week) reduces asthma and
475 wheeze in children up to 4.5 years old, while fatty fish intake may be beneficial in older
476 children. [Page 21] Future well-designed clinical trials are recommended to confirm the
477 promising findings documented in this literature analysis.

478

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481 **Author disclosure:** MP and CI jointly conducted searches, assessed inclusion, extracted
482 data and assessed validity. MP drafted the manuscript and conducted the meta-analysis. BE

483 and SSK made substantial contributions to analysis and interpretation of data quality. All
484 authors critically reviewed the manuscript and approved the final version as submitted.

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485 [Page 23] REFERENCES

- 486 1 Asher M, Montefort S, Björkstén B, *et al.* Worldwide time trends in the prevalence of
487 symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases
488 One and Three repeat multicountry cross-sectional surveys. *The Lancet*. 2006; **368**: 733-43.
- 489 2 Lai C, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. The ISAAC Phase Three
490 Study Group: global variation in the prevalence and severity of asthma symptoms: Phase
491 Three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*.
492 2009; **64**: 476-83.
- 493 3 Devereux G. Session 1: Allergic disease Nutrition as a potential determinant of
494 asthma. *Proceedings of the Nutrition Society*. 2010; **69**: 1-10.
- 495 4 Simopoulos AP. Omega-6/omega-3 essential fatty acid ratio and chronic diseases.
496 *Food Reviews International*. 2004; **20**: 77-90.
- 497 5 Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty
498 acids. *Biomedicine & pharmacotherapy*. 2002; **56**: 365-79.
- 499 6 Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes:
500 nutrition or pharmacology? *British journal of clinical pharmacology*. 2013; **75**: 645-62.
- 501 7 Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects,
502 mechanisms and clinical relevance. *Biochimica et Biophysica Acta (BBA)-Molecular and*
503 *Cell Biology of Lipids*. 2015; **1851**: 469-84.
- 504 8 Thien FC, De Luca S, Woods R, Abramson MJ. Dietary marine fatty acids (fish oil)
505 for asthma in adults and children. *The Cochrane database of systematic reviews*. 2010; **2**.
- 506 [Page 23] 9 Alm B, Goksör E, Thengilsdottir H, *et al.* Early introduction of fish decreases
507 the risk of preschool wheezing disorder. *Allergy: European Journal of Allergy and Clinical*
508 *Immunology*. 2009; **64**: 64-65.
- 509 10 Chatzi L, Torrent M, Romieu I, *et al.* Diet, wheeze, and atopy in school children in
510 Menorca, Spain. *Pediatric allergy and immunology : official publication of the European*
511 *Society of Pediatric Allergy and Immunology*. 2007; **18**: 480-5.

- 512 11 Kull I, Bergström A, Lilja G, Pershagen G, Wickman M. Fish consumption during the
513 first year of life and development of allergic diseases during childhood. *Allergy*. 2006; **61**:
514 1009-15.
- 515 12 Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA
516 intake during pregnancy and allergic disease outcomes in the offspring: a systematic review
517 and meta-analysis of observational studies and randomized controlled trials. 2016; **103**: 128-
518 43.
- 519 13 Miles EA, Calder PC. Can Early Omega-3 Fatty Acid Exposure Reduce Risk of
520 Childhood Allergic Disease? *Nutrients*. 2017; **9**.
- 521 14 Yang H, Xun P, He K. Fish and fish oil intake in relation to risk of asthma: a
522 systematic review and meta-analysis. *PloS one*. 2013; **8**: e80048.
- 523 15 Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for
524 Systematic Reviews and Meta-Analyses: The PRISMA Statement. . *PLoS Med*. 2009; **6**:
525 e1000097.
- 526 16 Liberati A, Altman D, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J. The PRISMA
527 Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate
528 Health Care Interventions: Explanation and Elaboration. . *PLoS Med* 2009; **6**.
- 529 [Page 24] 17 GINA. 2017 Pocket Guide for Asthma Management and Prevention: for adults
530 and children older than 5 years. 2017.
- 531 18 Zaza S, Wright-De Agüero LK, Briss PA, *et al*. Data collection instrument and
532 procedure for systematic reviews in the Guide to Community Preventive Services. *American*
533 *journal of preventive medicine*. 2000; **18**: 44-74.
- 534 19 Brouwers MC, Johnston ME, Charette ML, Hanna SE, Jadad AR, Browman GP.
535 Evaluating the role of quality assessment of primary studies in systematic reviews of cancer
536 practice guidelines. *BMC Medical Research Methodology*. 2005; **5**: 8-8.
- 537 20 Asher M, Keil U, Anderson H, *et al*. International Study of Asthma and Allergies in
538 Childhood (ISAAC): rationale and methods. *European respiratory journal*. 1995; **8**: 483-91.
- 539 21 Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*:
540 John Wiley & Sons 2011.

- 541 22 Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ: British Medical Journal*. 1997; **315**: 1533.
- 543 23 Saadeh D, Salameh P, Caillaud D, *et al.* Prevalence and association of asthma and
544 allergic sensitization with dietary factors in schoolchildren: data from the french six cities
545 study. *BMC public health*. 2015; **15**: 993.
- 546 24 Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan D, Group tIPTS. Effect
547 of diet on asthma and allergic sensitisation in the International Study on Allergies and
548 Asthma in Childhood (ISAAC) Phase Two *Thorax* 2010; **65**: 516-22.
- 549 25 Rodríguez-Rodríguez E, Perea J, Jiménez A, Rodríguez-Rodríguez P, López-Sobaler
550 A, Ortega R. Fat intake and asthma in Spanish schoolchildren. *European journal of clinical*
551 *nutrition*. 2010; **64**: 1065-71.
- 552 [Page 25] 26 Farchi S, Forastiere F, Agabiti N, *et al.* Dietary factors associated with
553 wheezing and allergic rhinitis in children. *European Respiratory Journal*. 2003; **22**: 772-80.
- 554 27 Kim JL, Elfman L, Mi Y, Johansson M, Smedje G, Norback D. Current asthma and
555 respiratory symptoms among pupils in relation to dietary factors and allergens in the school
556 environment. *Indoor Air*. 2005; **15**: 170-82.
- 557 28 Kunitsugu I, Okuda M, Murakami N, *et al.* Self-reported seafood intake and atopy in
558 Japanese school-aged children. *Pediatrics International*. 2012; **54**: 233-37.
- 559 29 Antova T, Pattenden S, Nikiforov B, *et al.* Nutrition and respiratory health in children
560 in six Central and Eastern European countries. *Thorax*. 2003; **58**: 231-36.
- 561 30 Xu D, Wang Y, Chen Z, *et al.* Prevalence and risk factors for asthma among children
562 aged 0–14 years in Hangzhou: a cross-sectional survey. *Respiratory Research*. 2016; **17**: 1-8.
- 563 31 Tabak C, Wijga AH, de Meer G, Janssen NA, Brunekreef B, Smit HA. Diet and
564 asthma in Dutch school children (ISAAC-2). *Thorax*. 2006; **61**: 1048-53.
- 565 32 Takemura Y, Sakurai Y, Honjo S, *et al.* The relationship between fish intake and the
566 prevalence of asthma: the Tokorozawa childhood asthma and pollinosis study. *Preventive*
567 *medicine*. 2002; **34**: 221-25.

- 568 33 Peat J, Salome C, Woolcock A. Factors associated with bronchial
569 hyperresponsiveness in Australian adults and children. *European Respiratory Journal*. 1992;
570 **5**: 921-29.
- 571 34 Hodge L, Salome C, Peat J, Haby M, Xuan W, Woolcock A. Consumption of oily fish
572 and childhood asthma risk. *The Medical journal of Australia*. 1996; **164**: 137-40.
- 573 35 Lumia M, Takkinen HM, Luukkainen P, *et al*. Food consumption and risk of
574 childhood asthma. *Pediatr Allergy Immunol*. 2015; **26**: 789-96.
- 575 [Page 26] 36 Magnusson J, Kull I, Rosenlund H, *et al*. Fish consumption in infancy and
576 development of allergic disease up to age 12 y. *The American journal of clinical nutrition*.
577 2013; **97**: 1324-30.
- 578 37 Kieft-de Jong JC, de Vries JH, Franco OH, *et al*. Fish consumption in infancy and
579 asthma-like symptoms at preschool age. *Pediatrics*. 2012; **130**: 1060-68.
- 580 38 Dotterud CK, Storrø O, Simpson MR, Johnsen R, Øien T. The impact of pre-and
581 postnatal exposures on allergy related diseases in childhood: a controlled multicentre
582 intervention study in primary health care. *BMC Public Health*. 2013; **13**: 1.
- 583 39 Goksör E, Alm B, Thengilsdottir H, Pettersson R, Åberg N, Wennergren G. Preschool
584 wheeze—impact of early fish introduction and neonatal antibiotics. *Acta Paediatrica*. 2011;
585 **100**: 1561-66.
- 586 40 Nafstad P, Nystad W, Magnus P, Jaakkola JJ. Asthma and allergic rhinitis at 4 years
587 of age in relation to fish consumption in infancy. *Journal of Asthma*. 2003; **40**: 343-48.
- 588 41 Nwaru BI, Takkinen H-M, Niemelä O, *et al*. Timing of infant feeding in relation to
589 childhood asthma and allergic diseases. *Journal of Allergy and Clinical Immunology*. 2013;
590 **131**: 78-86.
- 591 42 Oien T, Storro O, Johnsen R. Do early intake of fish and fish oil protect against
592 eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *J Epidemiol
593 Community Health*. 2010; **64**: 124-9.
- 594 43 Willers SM, Wijga AH, Brunekreef B, *et al*. Childhood diet and asthma and atopy at 8
595 years of age: the PIAMA birth cohort study. *European Respiratory Journal*. 2011; **37**: 1060-
596 67.

597 [Page 27] 44 Oien T, Storrø O, Johnsen R. Do early intake of fish and fish oil protect
598 against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *Journal of*
599 *epidemiology and community health*. 2010; **64**: 124-29.

600 45 Kim J-L, Elfman L, Mi Y, Johansson M, Smedje G, Norbäck D. Current asthma and
601 respiratory symptoms among pupils in relation to dietary factors and allergens in the school
602 environment. *Indoor air*. 2005; **15**: 170-82.

603 46 D'Innocenzo S, Matos S, Prado MS, *et al*. Dietary pattern, asthma, and atopic and
604 non-atopic wheezing in children and adolescents: SCAALA study, Salvador, Bahia State,
605 Brazil. *Cadernos de Saúde Pública*. 2014; **30**: 1849-60.

606 47 Ellwood P, Asher M, Björkstén B, Burr M, Pearce N, Robertson C. Diet and asthma,
607 allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of
608 the International Study of Asthma and Allergies in Childhood (ISAAC) data. *European*
609 *Respiratory Journal*. 2001; **17**: 436-43.

610 48 Arvaniti F, Priftis KN, Papadimitriou A, *et al*. Adherence to the Mediterranean type
611 of diet is associated with lower prevalence of asthma symptoms, among 10–12 years old
612 children: the PANACEA study. *Pediatric Allergy and Immunology*. 2011; **22**: 283-89.

613 49 Noutsios GT, Floros J. Childhood asthma: causes, risks, and protective factors; a role
614 of innate immunity. *Swiss medical weekly*. 2014; **144**: w14036.

615 50 Prescott SL. Early-life environmental determinants of allergic diseases and the wider
616 pandemic of inflammatory noncommunicable diseases. *Journal of allergy and clinical*
617 *immunology*. 2013; **131**: 23-30.

618 51 Galli C, Calder PC. Effects of fat and fatty acid intake on inflammatory and immune
619 responses: a critical review. *Annals of Nutrition and Metabolism*. 2009; **55**: 123-39.

620 [Page 27] 52 Kremmyda L-S, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC.
621 Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain
622 omega-3 fatty acids: a systematic review. *Clinical reviews in allergy & immunology*. 2011;
623 **41**: 36-66.

624 53 Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on
625 patients with asthma and allergies. *Journal of Allergy and Clinical Immunology*. 2014; **133**:
626 1237-44.

- 627 54 Muley P, Shah M, Muley A. Omega-3 Fatty Acids Supplementation in Children to
628 Prevent Asthma: Is It Worthy?-A Systematic Review and Meta-Analysis. *Journal of allergy*.
629 2015; **2015**: 312052.
- 630 55 Weichselbaum E, Coe S, Buttriss J, Stanner S. Fish in the diet: A review. *Nutrition*
631 *Bulletin*. 2013; **38**: 128-77.
- 632 56 Livingstone M, Robson P. Measurement of dietary intake in children. *Proceedings of*
633 *the Nutrition Society*. 2000; **59**: 279-93.
- 634 57 Katsardis C, Koumbourlis A, Anthracopoulos M, Paraskakis E. *Paediatric Pulmonary*
635 *Function Testing*. New York, USA: Nova 2015.
- 636 58 Lasso-Pirot A, Delgado-Villalta S, Spanier AJ. Early childhood wheezers: identifying
637 asthma in later life. *Journal of asthma and allergy*. 2015; **8**: 63-73.
- 638 59 Murata M. Secular trends in growth and changes in eating patterns of Japanese
639 children. *The American journal of clinical nutrition*. 2000; **72**: 1379s-83s.
- 640 60 Zhang J, Wang H, Wang Y, *et al*. Dietary patterns and their associations with
641 childhood obesity in China. *British Journal of Nutrition*. 2015; **113**: 1978-84.
- 642 61 Patel S, Custovic A, Smith JA, Simpson A, Kerry G, Murray CS. Cross-sectional
643 association of dietary patterns with asthma and atopic sensitization in childhood - in a cohort
644 [Page 28] study. *Pediatric allergy and immunology : official publication of the European*
645 *Society of Pediatric Allergy and Immunology*. 2014; **25**: 565-71.
- 646 62 Akcay A, Tamay Z, Hocaoglu AB, Ergin A, Guler N. Risk factors affecting asthma
647 prevalence in adolescents living in Istanbul, Turkey. *Allergologia et immunopathologia*.
648 2014; **42**: 449-58.
- 649 63 Arvaniti F, Priftis K, Papadimitriou A, *et al*. Salty-snack eating, television or video-
650 game viewing, and asthma symptoms among 10- to 12-year-old children: the PANACEA
651 study. *Journal of the American Dietetic Association*. 2011; **111**: 251-7.
- 652 64 Corbo G, Forastiere F, De Sario M, *et al*. Wheeze and asthma in children: associations
653 with body mass index, sports, television viewing, and diet. *Epidemiology (Cambridge, Mass)*.
654 2008; **19**: 747-55.

655 65 Zhang GQ, Liu B, Li J, *et al.* Fish intake during pregnancy or infancy and allergic
656 outcomes in children: A systematic review and meta-analysis. *Pediatric allergy and*
657 *immunology : official publication of the European Society of Pediatric Allergy and*
658 *Immunology*. 2017; **28**: 152-61.

659 66 Song JW, Chung KC. Observational studies: cohort and case-control studies. *Plastic*
660 *and reconstructive surgery*. 2010; **126**: 2234-42.

661

662 **Websites:**

663 Australian and New Zealand Clinical trial registry: <http://www.anzctr.org.au/trialSearch.aspx>

664 International Clinical trials registry: <http://www.clinicaltrials.gov>

665 European Union clinical trials registry: <http://www.clinicaltrialsregister.eu>

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