

Received Date : 10-May-2016

Revised Date : 24-Aug-2016

Accepted Date : 01-Sep-2016

Article type : Review

Fish intake during pregnancy or infancy and allergic outcomes in children: a systematic review and meta-analysis

Guo-Qiang Zhang¹, Bo Liu¹, Jun Li¹, Chun-Qi Luo¹, Qiao Zhang¹, Jin-Liang Chen², Anju Sinha³, Zhong-Yue Li¹

¹Department of Gastroenterology, Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Chongqing, China, ²Department of Geriatrics, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China, ³Division of Reproductive and Child Health, Indian Council of Medical Research, New Delhi, Delhi, India

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12648

This article is protected by copyright. All rights reserved.

Running title: Fish intake on childhood allergy

Corresponding author: Zhong-Yue Li, Department of Gastroenterology, Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, No.136, Zhongshan 2nd Road, Yuzhong District, 400014, Chongqing, China; E-mail: lizhongyue1001@hotmail.com.

Zhang GQ, Liu B, Li J, Luo CQ, Zhang Q, Chen JL, Sinha A, Li ZY

Fish intake during pregnancy or infancy and allergic outcomes in children: a systematic review and meta-analysis

Title of journal: Pediatr Allergy Immunol

ABSTRACT

Background: It has been suggested that n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) have anti-inflammatory properties and may reduce the risk of allergic disease. Fish is a great source of n-3 LC-PUFAs. However, the effect of fish on allergic disease remains controversial.

This article is protected by copyright. All rights reserved.

Methods: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched for randomized controlled trials (RCTs) and prospective cohort studies regarding the effect of fish intake during pregnancy or infancy on allergic outcomes in children. The outcomes of interest were atopy, eczema, allergic rhinitis, wheeze, asthma, and food allergy.

Results: One RCT and seventeen publications from thirteen prospective cohort studies were included for maternal fish intake during pregnancy, and eight publications from five prospective cohort studies for fish intake in infancy. Pooled analysis suggested that maternal fish intake during pregnancy was not associated with lower risk of any allergic outcome, both in RCT and observational studies. Consumption of fish during the first year of life reduced the risk of eczema (RR 0.61; 95% CI 0.47, 0.80; $P = 0.0003$; $I^2 = 68\%$) and allergic rhinitis (RR 0.54; 95% CI 0.36, 0.81; $P = 0.003$; $I^2 = 74\%$).

Conclusions: Current evidence indicates that fish intake in infancy could reduce the risk of eczema and allergic rhinitis in children, whereas maternal fish intake during pregnancy does not affect any atopic outcome. The intake of fish per se in infancy, not specially n-3 LC-PUFAs, may have an allergy protective effect. High-quality and adequately powered RCTs are warranted to confirm this.

Key words: allergy, allergic outcome, allergenic foods, children, fish, nutrition

Name and address for offprints: Zhong-Yue Li, No.136, Zhongshan 2nd Road, Yuzhong District, 400014, Chongqing, China

INTRODUCTION

Over the last few decades, the worldwide prevalence of allergic disease has noticeably increased (1). Changes in the diet have been proposed to partly contribute to this (2, 3). Special attention was given to fish intake in the primary prevention of allergic disease. Fish, especially oily fish, is rich in n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are suggested to lower the risk of allergic disease through their anti-inflammatory effects (4). Two systematic reviews (5, 6) were conducted on fish intake in the prevention of allergic disease, and concluded that most epidemiological studies found a protective effect of fish intake during pregnancy, infancy, or childhood on atopic outcomes in children. However, a recent meta-analysis by Beckhaus et al (7) found no significant associations between maternal fish intake during pregnancy and any atopic outcome in children.

It may be noted that compounds other than n-3 LC-PUFAs in fish, such as certain proteins (rich in essential amino acids), vitamins (A, D, and B₁₂), minerals (selenium) and trace elements, might individually or in combination interfere with the development of allergic disease (8). Fish can also bioaccumulate environmental contaminants, such as polychlorinated biphenyls (PCBs), perfluorinated chemicals (PFCs), dioxins, methylmercury and lead, which could probably increase the risk of allergy (9-13). Moreover, fish is highly

This article is protected by copyright. All rights reserved.

allergenic (14), and an early encounter with food allergens prenatally or postnatally could significantly influence infant immune development and subsequently alter the risk of allergic disease (15, 16). Recent randomized controlled trials (RCTs) have suggested that early introduction of allergenic foods (such as peanut, egg, cow's milk, and wheat) into the infant's diet reduces the incidence of food allergies through induction of oral tolerance (17-19). Hence, fish oil supplements (or n-3 LC-PUFAs) may not have the same effect as fish intake from the normal diet.

So far, the effect of fish intake during pregnancy or infancy on childhood allergic disease remains a highly live issue. To our knowledge, no systematic review or meta-analysis primarily focusing on dietary fish intake during pregnancy or infancy and allergic outcomes in children has been performed. Thus, we systematically reviewed the current available literature to investigate whether dietary fish intake during pregnancy or infancy reduced the risk of atopic disease in children.

METHODS

This systematic review and meta-analysis was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (20, 21).

Literature search and selection criteria

PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for records reporting the effect of dietary fish intake during pregnancy or infancy on clinical outcomes of allergic disease or sensitization in children. The search strategy is shown in Table 1. The last search was run on February 07, 2016. Two independent reviewers (G-QZ and BL) conducted the initial search, deleted duplicate records, screened the titles and abstracts for relevance, and identified as excluded or requiring further assessment. Then we reviewed the full-text articles for inclusion. The bibliographies of retrieved articles and previous reviews were manually scrutinized to identify additional eligible studies.

Studies meeting the following inclusion criteria were included: (i) population: children in whom outcomes were measured between birth and age 18 years; (ii) intervention: high intake of fish during pregnancy or infancy; (iii) comparison: low fish intake or none; (iv) outcome: eczema/allergic rhinitis/wheeze/asthma/food allergy defined as parental report of symptoms of allergic disease, parental report of physician diagnosis, or direct diagnosis by a physician, and sensitization defined as a positive skin prick test (SPT) or elevated specific immunoglobulin (Ig) E ($\geq 0.35\text{kU/L}$) to any food or inhalant allergen; (v) design: RCTs and prospective cohort studies. Excluded from our review were studies that evaluated fish oil or n-3 LC-PUFAs intake during pregnancy or infancy, maternal fish intake before pregnancy or during lactation, or fish intake beyond 1 year of age in association with allergic outcomes. Agreement between reviewers regarding study inclusion was assessed by using the Cohen κ statistic (22).

Data extraction and quality assessment

Data extraction was performed by JL and confirmed independently by G-QZ. The following information was extracted from each study: first author, year of publication, country, study design, study population, exposure to/supplementation of fish during pregnancy or infancy, outcome data (sensitization, eczema, allergic rhinitis, wheeze, asthma and food allergy), type of exposure measure, timing of fish intake, and statistical methods for potential confounder factor adjustments. Extracted data was entered into a standardized Word file. Disagreements were further checked on the original articles, and were resolved. The Cochrane Risk-of-Bias Tool was adopted to evaluate the risk of bias for each RCT (23). The methodologic quality of prospective cohort studies was assessed by using the Newcastle-Ottawa Scale (24).

Statistical analysis

Only one RCT investigating maternal oily fish intake during pregnancy and allergic outcomes in the offsprings was included in this review (25). We reported results for this RCT descriptively. For cohort studies, the study-specific most-adjusted odds ratios (ORs) or hazard ratios with 95% confidence intervals (CIs) (highest compared with lowest amounts of fish intake) were used to compute a summary risk ratio (RR) with its 95% CI. When the lowest category was not analyzed as reference category (26), the method of Hamling et al was used to convert the results (27). One study (28) could not be converted because of limited data available, and so we used the estimates for the highest compared with the middle

This article is protected by copyright. All rights reserved.

category of fish intake. For those studies providing only frequency or percentage distributions (29, 30), we collected data on the number of subjects with and without the disease in the exposed and nonexposed groups to calculate unadjusted ORs and their 95% CIs. Some studies using the same study population reported multiple estimates at different time of follow-up. When this happened, we included in the meta-analysis the estimates that fulfilled the following ordered criteria: (i) outcome assessment occurring at longest follow-up; (ii) outcome assessment over a time period, rather than at a given end point. If only continuous ORs were provided (31), authors of the respective publications were addressed to obtain the ORs for the highest quantile compared with the lowest quantile, but no replies were received. For studies of fish intake in infancy and risk of allergy in children, fish is likely to be postponed or even avoided in infants with family history of allergic disease or early symptoms of allergic disease. To avoid heredity- and disease-related modification of exposure (32), we used, when available, the estimates adjusted for family history of allergy and/or early occurrence of allergic disease or from analyses restricted to children without family history of allergy and/or early allergic manifestations.

Cohort studies included in this review varied markedly in terms of population, type of fish consumed, amounts of fish intake compared, exposure timing, type of exposure measure and reported outcome measure, and adjusted confounder factors. Therefore, the inverse variance method with random-effects model was used to calculate pooled RRs and 95% CIs. Random-effects models not only weight each study by its inverse variance, but also consider both within- and between- study variations by using the DerSimonian and Laird method (33, 34). We presented RRs from random-effects models that assume that the exposure effects

observed in the studies are a random sample from a distribution of exposure effects, thus yielding a more global and conservative estimate (35, 36). Heterogeneity across studies was tested by using the I^2 statistic, which is a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of greater than 50% were considered to have significant heterogeneity (37). A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result, by excluding each study one by one and recalculating the combined RR on the remaining studies. A P value less than 0.05 was considered as statistically significant, except where otherwise specified. All statistical analyses were performed with Review Manager Software 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Fig 1 shows a flow diagram for selection process. A total of 5,028 records were initially identified from databases search. 866 records were excluded for duplicates, and 4,133 records were excluded after screening the titles and abstracts. The remaining twenty-nine full-text articles were assessed for eligibility, four of which were further excluded because of fish intake before pregnancy (38), retrospective cohort studies (39, 40), and nested case-control studies (41). Finally, one RCT (25) and seventeen publications from thirteen unique prospective cohort studies (26, 28, 30, 31, 42-54) were included for maternal fish intake during pregnancy, and eight publications from five unique prospective cohort studies (29, 49, 55-60) for fish intake in infancy. The Cohen κ statistic for agreement on study inclusion was

0.92. Characteristics of the included studies are summarized in Table S1 and outcome data of each included study is presented in Table 2. No study reported the association between fish intake during pregnancy or infancy and risk of food allergy in children.

Quality assessment

Risk-of-bias assessment of the included studies is presented in Table 3 and Table 4. The included trial (25) reported adequate randomization and blinding of outcome assessment. The allocation concealment and blinding of personnel were not achieved because of its single-blinded design. This trial also had a high attrition rate, with only 62% of the control group attending the 6-month follow-up. When using the Newcastle-Ottawa Scale to assess the risk of bias of the prospective cohort studies, fifteen studies (26, 31, 42-45, 47, 48, 50-54, 58, 59) were rated as a total score of more than 6, and nine studies (28-30, 46, 49, 55-57, 60) as a score of 6 or less indicating a high risk of bias.

Maternal fish intake during pregnancy

One RCT and seventeen publications from thirteen unique prospective cohort studies were included. These studies were published between 2007 and 2014. The RCT (25) enrolled infants at risk of atopy (at least one first-degree relative affected by atopy, asthma or allergy by self-report). Twelve of the cohort studies (with 14 publications) enrolled healthy pregnant women, regardless of their atopic status (26, 30, 42-45, 47-54). The remaining one (with 3

publications) was nested within the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study and recruited infants with human leukocyte antigen-conferred risk of type 1 diabetes (28, 31, 46). Various potential confounders were adjusted for in data analyses, except two studies in which only crude ORs with 95% CIs were available (30, 49), shown in Table 2.

Randomized controlled trials

A total of 123 mother-child pairs were enrolled in this RCT (25). From 20 weeks gestation until delivery, women in the intervention group were supplied with 2 portions of farmed salmon per week (300 g/week) and women in the control group continued their habitual diet (low in oily fish). 86 infants attended the clinic visit at 6 months of age. The study concluded that maternal consumption of oily fish during pregnancy modified neonatal immune cell responses, such as interleukin (IL)-2, IL-4, IL-5, IL-10, et cetera. However, no significant differences in IgE concentrations, incidence and severity of atopic dermatitis, wheeze, or sensitization rates (positive SPT) were found between the salmon and control groups.

Prospective cohort studies

Sensitization

One study (31) including 931 mother-child pairs evaluated the relation between maternal fish intake during pregnancy and sensitization to any food or inhalant allergen at 5 years of age. In this study, continuous ORs were reported and no significant associations were

observed. Two studies (50, 52) with 3,099 children contributed sensitization data for meta-analysis. We did not find significant association between maternal fish intake and sensitization (RR 0.88; 95% CI 0.65, 1.21; $P = 0.44$; $I^2 = 33\%$).

Eczema

Ten studies examined maternal dietary intake of fish during pregnancy and childhood eczema (30, 43-45, 47-50, 52, 53). Our pooled analysis included 15,945 children and found no significant association between fish intake and eczema (RR 0.88; 95% CI 0.75, 1.04; $P = 0.13$; $I^2 = 53\%$), shown in Fig 2. Further exclusion of any single study did not materially alter the overall combined RR, with a range from 0.85 (95% CI 0.71, 1.02) to 0.92 (95% CI 0.78, 1.07). When only adjusted ORs were pooled from eight cohort studies (43-45, 47, 48, 50, 52, 53), the result remained nonsignificant and RR was 0.84 (95% CI 0.69, 1.01; $P = 0.07$; $I^2 = 56\%$).

Allergic rhinitis

Three studies (26, 28, 53) reported on maternal fish intake during pregnancy and childhood allergic rhinitis. The pooled analysis including 32,589 children showed no significant association between fish intake and allergic rhinitis (RR 0.95; 95% CI 0.62, 1.45; $P = 0.81$; $I^2 = 44\%$).

Wheeze

Eight studies evaluated the relation between maternal fish intake during pregnancy and childhood wheeze (26, 28, 43, 45, 47, 48, 50, 54). Our pooled analysis included 42,096 children and found no significant association between fish intake and wheeze (RR 0.94; 95% CI 0.83, 1.07; $P = 0.36$; $I^2 = 26\%$), shown in Fig 3. Further exclusion of any single study did not materially alter the overall combined RR, with a range from 0.91 (95% CI 0.78, 1.07) to 0.98 (95% CI 0.88, 1.08).

Asthma

Four studies examined maternal dietary intake of fish during pregnancy and childhood asthma (26, 28, 49, 54). The pooled analysis including 37,295 children showed no significant association between fish intake and asthma (RR 0.94; 95% CI 0.75, 1.18; $P = 0.58$; $I^2 = 52\%$). When only adjusted ORs were pooled from three cohort studies (26, 28, 54), the result remained nonsignificant (RR 0.93; 95% CI 0.68, 1.28; $P = 0.66$; $I^2 = 66\%$).

Fish intake in infancy

Eight publications from five unique prospective cohort studies were included (29, 49, 55-60). These studies were published between 2003 and 2013. All of them were based on unselected population. To avoid reverse causation, two of these studies (58, 59) adjusted for parental allergic disease and restricted analysis to children without onset of eczema and/or

wheeze during the first year of life. One study (49) adjusted for familial atopy and restricted analysis to children without early symptoms of eczema and/or asthma during the first year of life for outcome of eczema, but not for asthma. Another (57) adjusted for family history of allergic disease and excluded children with any asthmalike symptoms at the age of 12 and 24 months in their analyses. Nafstad et al (60) considered the reverse causation by adjusting for parental atopy and atopic eczema during the first 6 months, and Goksor et al (56) by adjusting for atopic heredity and food allergy/eczema during the first year of life. In the remaining two studies (29, 55), the attempts to avoid reverse causation resulted in fish consumption frequency was not significant, but rather the early introduction of fish, and only crude ORs were reported for fish consumption frequency. The adjusted variables in each included study were summarized in Table 2.

Prospective cohort studies

Sensitization

Two studies reported the association between fish intake in infancy and IgE antibodies against any inhalant or food allergen. Kull et al (58) found a borderline statistically significant effect for children with fish consumption ≥ 2 -3 times per month compared with ≤ 1 time per month at 4 years of age (RR 0.76; 95% CI 0.57, 1.00). Further follow-up was performed (59) and no significant association at 8 years was found (RR 0.98; 95% CI 0.73, 1.30).

Eczema

Four studies (29, 49, 59, 60) including 13,823 children contributed eczema data for meta-analysis, shown in Fig 4. The overall analysis showed 39% reduction in risk of eczema with high intake of fish (RR 0.61; 95% CI 0.47, 0.80; $P = 0.0003$), however with significant heterogeneity ($I^2 = 68\%$). After excluding the study with a crude OR (29), the effect remained and no heterogeneity was observed (RR 0.71; 95% CI 0.61, 0.82; $P < 0.00001$; $I^2 = 0\%$).

Allergic rhinitis

Three studies (55, 59, 60) including 9,987 children contributed allergic rhinitis data for meta-analysis, shown in Fig 5. The overall analysis showed 46% reduction in risk of allergic rhinitis with high intake of fish (RR 0.54; 95% CI 0.36, 0.81; $P = 0.003$; $I^2 = 74\%$). Further exclusion of the study with a crude OR (55) did not materially alter the overall combined result (RR 0.61; 95% CI 0.37, 0.98; $P = 0.04$; $I^2 = 72\%$).

Wheeze

Two studies (56, 57) including 8,597 children contributed wheeze data for meta-analysis. No effect of fish intake in infancy on wheeze was found (RR 0.94; 95% CI 0.77, 1.14; $P = 0.51$; $I^2 = 0\%$).

Three studies (49, 59, 60) including 8,902 children contributed asthma data for meta-analysis. No effect of fish intake in infancy on asthma was found (RR 0.84; 95% CI 0.69, 1.02; $P = 0.09$; $I^2 = 0\%$). Further exclusion of the study with a crude OR (49) did not materially alter the overall combined result (RR 0.87; 95% CI 0.67, 1.12; $P = 0.28$; $I^2 = 0\%$).

DISCUSSION

Our systematic review and meta-analysis identified one RCT and twenty-four publications from seventeen prospective cohort studies investigating the effect of fish intake during pregnancy or infancy on childhood allergic disease. Our analysis showed that fish intake in infancy decreased the risk of eczema and allergic rhinitis, whereas maternal fish intake during pregnancy did not affect any allergic outcome, both in RCT and prospective cohort studies.

The epidemic rise in allergic disease has been preceded and paralleled by a decline in dietary intake of n-3 LC-PUFAs and oily fish (2, 61). This, together with the known role of n-3 LC-PUFAs in inhibiting inflammation (62), led to speculation that n-3 LC-PUFAs or fish may protect against allergy development. In support of this hypothesis, a large number of trials have demonstrated that n-3 LC-PUFAs supplementation during pregnancy or infancy was able to increase levels of circulating n-3 LC-PUFAs and alter immune response in the fetus or early life (63-66). Despite this, it is still unclear whether these findings are of clinical

relevance and whether they persist into older age. A meta-analysis by Gunaratne et al (67) evaluated the effect of n-3 LC-PUFAs supplementation of pregnant and/or breastfeeding women on allergic outcomes in their children. The authors included eight RCTs, involving 3,366 women and their 3,175 children, and concluded that supplementation of n-3 LC-PUFAs was associated with a reduction of food allergies in the first 12 months and IgE-mediated eczema between 12 and 36 months. However, this benefit did not persist beyond 12 months or 36 months of age, respectively. In another meta-analysis focusing on maternal intake of n-3 LC-PUFAs during pregnancy (6), Best et al found that increased maternal n-3 LC-PUFAs intake was associated with a reduction of atopic eczema only in the first 12 months. Both meta-analyses found no significant associations at any time point for other allergic outcomes such as allergic rhinitis, wheeze, or asthma. Also, several RCTs were conducted on n-3 LC-PUFAs supplementation in infancy and atopic diseases. D’Vaz et al (68) included 420 infants at high atopic risk and they were allocated to receive either a daily supplement of fish oil or olive oil as the control from birth to age 6 months. Atopic outcomes (sensitization, eczema, asthma, and food allergy) were assessed at 12 months of age and no effects of fish oil were found. In the Childhood Asthma Prevention Study (CAPS), the largest trial to date, a total of 616 infants at high risk of asthma were randomized to consume either a diet rich in n-3 LC-PUFAs and low in n-6 LC-PUFAs or a diet low in n-3 LC-PUFAs and relatively high in n-6 LC-PUFAs as the control from 6 months to 5 years of age. The CAPS assessed clinical outcomes of atopic disease at five different time points (18 months, 3 years, 5 years, 8 years and 11.5 years of age) (69-73). There was a decreased prevalence of wheeze at 18 months of age (69) and atopic cough (cough with positive SPT) but not wheeze at 3

years of age (70) in the active diet group, and no effects were seen for any of allergic outcomes at the other time points. Overall, only limited benefit of pre- or post-natal supplementation of n-3 LC-PUFAs on allergic disease was found in very early life. This might, in part, explain the negative associations between fish intake and childhood allergic disease observed in our review. In addition, this limited effect of n-3 LC-PUFAs may not persist as other components in fish come into play. Contaminants in fish, such as PCBs, PFCs, methylmercury and lead, could probably counterbalance in part the effect of n-3 LC-PUFAs or even increase the risk of allergy (38, 45).

In 2000, the American Academy of Pediatrics (AAP) recommended a delayed introduction of highly allergenic foods in infants at high risk of allergy for the prevention of atopic diseases and that fish should be introduced until 3 years of age (74). This recommendation was revised in 2008 and no specific guidelines on how and when to introduce the highly allergenic foods were made (75). Until recently, Fleischer et al (76) provided general guidelines and suggestions recommending that allergenic foods may be introduced as complementary foods at home once a few other complementary foods were tolerated first, at a rate of one new food every 3 to 5 days if no reactions occurred. However, because of limited data available most of these recommendations reflected opinion and were not evidence based. In our study, we found that high consumption of fish during the first year of life was associated with a lower risk of childhood eczema and allergic rhinitis. Underlying mechanisms why fish intake in infancy protects against allergic disease are speculative. Fish contains various allergens (14), and regular exposure to these allergens in early life appears to promote immune tolerance in infants. Lots of observational studies have suggested that early

This article is protected by copyright. All rights reserved.

regular ingestion rather than delayed introduction of allergenic foods reduces the risk of allergic disease in children (77, 78). These results were further confirmed in several recent trials. A RCT by Palmer et al (17) showed that regular consumption of egg in infants with eczema from 4 to 8 months of age was associated with higher egg-specific IgG4 levels suggestive of oral tolerance to egg, and a lower prevalence of egg allergy (33%) at 12 months compared with control group (51%). Another RCT by Du Toit et al (18, 79) demonstrated that regular consumption of peanut in infants with egg allergy and/or eczema from 4-11 months to 5 years of age had a higher level of peanut-specific IgG4 and a higher ratio of peanut-specific IgG4:IgE indicative of oral tolerance to peanut, and a lower prevalence of peanut allergy at 5 and 6 years of age compared with peanut avoidance. Perkin et al (19) studied exclusively breast-fed infants in whom six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) started to be introduced into the infant's diet at 3 months of age. It also showed the efficacy of early introduction of allergenic foods in preventing food allergies in children between 1 year and 3 years of age in per-protocol analysis, although this result was not replicated in intention-to-treat analysis. Overall, evidence is building that early, regular consumption of allergenic foods is likely to be effective as a strategy for the primary prevention of allergic disease, probably through induction of oral tolerance. Our findings of a protective effect of high fish intake in infancy on allergic outcomes are in line with this reasoning. Future high-quality RCTs are warranted to confirm this.

Accepted Article

It has been suggested that not only the amount of fish intake (19, 58, 59) but the timing of introduction of fish during the first year of life (29, 55-57) are of importance for the prevention of allergic diseases. So far, studies investigating optimal timing of introduction of fish in infancy and childhood allergic disease have reported conflicting results. A birth cohort study from Sweden (29, 55, 56) reported that introduction of fish before 9 months of age could reduce the risk of eczema, allergic rhinitis and wheeze, relative to introduction after 9 months. These results were replicated in DIPP nutrition study (80-83), which demonstrated that introduction of fish at 9 months or less was inversely associated with atopic sensitization and allergic rhinitis. However, the Generation R study in Netherlands (57) reported that introduction of fish between 6 and 12 months rather than before 6 months of age was associated with a lower prevalence of wheezing, while others found no significant effect whenever fish was introduced, 0-6 months, >6 months, 6-12 months, <7 months, or ≥ 7 months (32, 84-87). Interestingly, a 'dose-response' relation was found in the ALLERGYFLORA birth cohort study indicating that the earlier fish was introduced into the child's diet the lower was the frequency of eczema in the first 18 months (88). Of note, all studies were observational studies and misclassification on the timing of fish would probably occur. In all, a window of opportunity might exist in the first year of life in which fish may protect against allergic disease, although the optimal timing for this intervention remains unknown. Future trials are warranted to define the optimal timing of introduction of fish in infancy.

Several potential limitations should be taken into consideration when interpreting our results. First, heterogeneity was significant in meta-analyses of several outcomes (eczema, allergic rhinitis, and asthma). It was not surprising because of variations in study population, amounts of fish intake compared, type of exposure measure, diagnostic procedures, and adjustments across studies. Although we adopted random-effects model to try to account for this variability, it may have had an effect on the estimation of pooled effects. Reassuringly, most component studies of each outcome reported consistent results, except for studies of maternal fish intake during pregnancy and eczema. Four (44, 50, 52, 53) of the ten included studies did find a protective effect of fish against eczema. However, the infant's diet during the first year of life was not accounted for in their data analyses. Maternal dietary habits to some degree reflected the offspring's dietary habits. In addition, our analysis found a strong correlation between fish intake in infancy and childhood eczema. Therefore, the infant's diet should be considered in future cohort studies on this topic. Second, for studies of fish intake in infancy and risk of allergy in children, parental allergic disease and early allergic manifestations in child itself might lead to delay or avoidance of fish intake and thus to reverse causation. We tried to overcome this problem by using, when available, estimates adjusted for family history of allergy and/or early occurrence of allergic disease, or from analyses restricted to children without family history of allergy and/or early allergic manifestations. Third, our findings were likely to be influenced by the misclassification of fish consumption because of the use of food-frequency questionnaires or diet history questionnaires. This misclassification could be nondifferential and would bias results toward the null. Fourth, all individual study ORs were adjusted for potential but varying confounding

factors, and therefore, residual confounding cannot be excluded. Fifth, one study (with 2 publications) (58, 59) observed a dose-response relation between fish intake in infancy and allergic diseases, which we were not able to investigate due to limited data available. Finally, publication bias cannot be ruled out in view of limited number of studies included in meta-analysis.

In conclusion, the present systematic review and meta-analysis suggested that fish intake in infancy could reduce the risk of eczema and allergic rhinitis in children, whereas maternal fish intake during pregnancy does not affect any atopic outcome. Our results are in line with previous reviews (6, 67), which lend meagre support to the hypothesis that n-3 LC-PUFAs reduce the risk of allergic disease. The intake of fish per se in infancy, not specially n-3 LC-PUFAs, may have an allergy protective effect. High-quality and adequately powered RCTs are warranted to confirm this. The optimal timing of introduction of fish in infancy remains to be defined.

ACKNOWLEDGMENTS

This study was supported by the Clinical Innovation Program of Children's Hospital of Chongqing Medical University (2014-04).

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368: 733-43.
2. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005; 115: 1109-17.
3. Netting MJ, Middleton PF, Makrides M. Does maternal diet during pregnancy and lactation affect outcomes in offspring? A systematic review of food-based approaches. *Nutrition* 2014; 30: 1225-41.
4. Miles EA, Calder PC. Omega-6 and omega-3 polyunsaturated fatty acids and allergic diseases in infancy and childhood. *Curr Pharm Des* 2014; 20: 946-53.
5. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allergy Immunol* 2011; 41: 36-66.
6. Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Am J Clin Nutr* 2016; 103: 128-43.

- Accepted Article
7. Beckhaus AA, Garcia-Marcos L, Forno E, Pacheco-Gonzalez RM, Celedon JC, Castro-Rodriguez JA. Maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood: a systematic review and meta-analysis. *Allergy* 2015; 70: 1588-604.
 8. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011; 127: 724-33.
 9. Stolevik SB, Nygaard UC, Namork E, et al. Prenatal exposure to polychlorinated biphenyls and dioxins is associated with increased risk of wheeze and infections in infants. *Food Chem Toxicol* 2011; 49: 1843-8.
 10. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants. *Environ Health Perspect* 2010; 118: 1429-33.
 11. Kim KN, Bae S, Park HY, Kwon HJ, Hong YC. Low-level Mercury Exposure and Risk of Asthma in School-age Children. *Epidemiology* 2015; 26: 733-9.
 12. Jedrychowski W, Perera F, Maugeri U, et al. Intrauterine exposure to lead may enhance sensitization to common inhalant allergens in early childhood: a prospective prebirth cohort study. *Environ Res* 2011; 111: 119-24.
 13. Wang IJ, Hsieh WS, Chen CY, et al. The effect of prenatal perfluorinated chemicals exposures on pediatric atopy. *Environ Res* 2011; 111: 785-91.

- Accepted Article
14. Kuehn A, Hilger C, Lehnert-Weber C, et al. Identification of enolases and aldolases as important fish allergens in cod, salmon and tuna: component resolved diagnosis using parvalbumin and the new allergens. *Clin Exp Allergy* 2013; 43: 811-22.
 15. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. *J Allergy Clin Immunol* 2014; 133: 1373-82.
 16. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: implications for future treatment. *J Allergy Clin Immunol* 2008; 121: 1344-50.
 17. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: A randomized controlled trial. *J Allergy Clin Immunol* 2013; 132: 387-92.
 18. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; 372: 803-13.
 19. Perkin MR, Logan K, Tseng A, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med* 2016 Mar 4 (Epub ahead of print; DOI: [doi:10.1056/NEJMoa1514210](https://doi.org/10.1056/NEJMoa1514210)).
 20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264-9.

- Accepted Article
21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12.
 22. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33: 159-74.
 23. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
 24. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available from www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 2 March 2016).
 25. Noakes PS, Vlachava M, Kremmyda LS, et al. Increased intake of oily fish in pregnancy: effects on neonatal immune responses and on clinical outcomes in infants at 6 mo. Am J Clin Nutr 2012; 95: 395-404.
 26. Maslova E, Strom M, Oken E, et al. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. Br J Nutr 2013; 110: 1313-25.
 27. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27: 954-70.

- Accepted Article
28. Erkkola M, Nwaru BI, Kaila M, et al. Risk of asthma and allergic outcomes in the offspring in relation to maternal food consumption during pregnancy: a Finnish birth cohort study. *Pediatr Allergy Immunol* 2012; 23: 186-94.
 29. Alm B, Aberg N, Erdes L, et al. Early introduction of fish decreases the risk of eczema in infants. *Arch Dis Child* 2009; 94: 11-5.
 30. Ozawa N, Shimojo N, Suzuki Y, et al. Maternal intake of Natto, a Japan's traditional fermented soybean food, during pregnancy and the risk of eczema in Japanese babies. *Allergol Int* 2014; 63: 261-6.
 31. Nwaru BI, Ahonen S, Kaila M, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr Allergy Immunol* 2010; 21: 29-37.
 32. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006; 117: 401-11.
 33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-88.
 34. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987; 9: 1-30.
 35. Bradburn MJ, Deeks JJ, Altman DG. Metan-an alternative meta-analysis command. *Stata Tech Bull* 1999; 8.

- Accepted Article
36. Pelucchi C, Galeone C, Bach JF, La Vecchia C, Chatenoud L. Pet exposure and risk of atopic dermatitis at the pediatric age: a meta-analysis of birth cohort studies. *J Allergy Clin Immunol* 2013; 132: 616-22.
 37. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-60.
 38. Pele F, Bajeux E, Gendron H, et al. Maternal fish and shellfish consumption and wheeze, eczema and food allergy at age two: a prospective cohort study in Brittany, France. *Environ Health* 2013; 12: 102.
 39. Ushiyama Y, Matsumoto K, Shinohara M, et al. Nutrition during pregnancy may be associated with allergic diseases in infants. *J Nutr Sci Vitaminol* 2002; 48: 345-51.
 40. Calvani M, Alessandri C, Sopo SM, et al. Consumption of fish, butter and margarine during pregnancy and development of allergic sensitizations in the offspring: role of maternal atopy. *Pediatr Allergy Immunol* 2006; 17: 94-102.
 41. Salam MT, Li YF, Langholz B, Gilliland FD. Maternal fish consumption during pregnancy and risk of early childhood asthma. *J Asthma* 2005; 42: 513-8.
 42. Chatzi L, Torrent M, Romieu I, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax* 2008; 63: 507-13.
 43. Chatzi L, Garcia R, Roumeliotaki T, et al. Mediterranean diet adherence during pregnancy and risk of wheeze and eczema in the first year of life: INMA (Spain) and RHEA (Greece) mother-child cohort studies. *Br J Nutr* 2013; 110: 2058-68.

- Accepted Article
44. Jedrychowski W, Perera F, Maugeri U, et al. Effects of prenatal and perinatal exposure to fine air pollutants and maternal fish consumption on the occurrence of infantile eczema. *Int Arch Allergy Immunol* 2011; 155: 275-81.
 45. Leermakers ET, Sonnenschein-van der Voort AM, Heppe DH, et al. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: the Generation R Study. *Eur J Clin Nutr* 2013; 67: 353-9.
 46. Lumia M, Luukkainen P, Tapanainen H, et al. Dietary fatty acid composition during pregnancy and the risk of asthma in the offspring. *Pediatr Allergy Immunol* 2011; 22: 827-35.
 47. Miyake Y, Sasaki S, Tanaka K, Ohfuji S, Hirota Y. Maternal fat consumption during pregnancy and risk of wheeze and eczema in Japanese infants aged 16-24 months: the Osaka Maternal and Child Health Study. *Thorax* 2009; 64: 815-21.
 48. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal fat intake during pregnancy and wheeze and eczema in Japanese infants: the Kyushu Okinawa Maternal and Child Health Study. *Ann Epidemiol* 2013; 23: 674-80.
 49. Oien T, Storro O, Johnsen R. Do early intake of fish and fish oil protect against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *J Epidemiol Community Health* 2010; 64: 124-9.
 50. Romieu I, Torrent M, Garcia-Esteban R, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clin Exp Allergy* 2007; 37: 518-25.

- Accepted Article
51. Saito K, Yokoyama T, Miyake Y, et al. Maternal meat and fat consumption during pregnancy and suspected atopic eczema in Japanese infants aged 3-4 months: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2010; 21: 38-46.
 52. Sausenthaler S, Koletzko S, Schaaf B, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr* 2007; 85: 530-7.
 53. Willers SM, Devereux G, Craig LC, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax* 2007; 62: 773-9.
 54. Willers SM, Wijga AH, Brunekreef B, et al. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med* 2008; 178: 124-31.
 55. Alm B, Goksor E, Thengilsdottir H, et al. Early protective and risk factors for allergic rhinitis at age 4(1/2) yr. *Pediatr Allergy Immunol* 2011; 22: 398-404.
 56. Goksor E, Alm B, Thengilsdottir H, Pettersson R, Aberg N, Wennergren G. Preschool wheeze - impact of early fish introduction and neonatal antibiotics. *Acta Paediatr* 2011; 100: 1561-6.
 57. Kieft-de Jong JC, de Vries JH, Franco OH, et al. Fish consumption in infancy and asthma-like symptoms at preschool age. *Pediatrics* 2012; 130: 1060-8.

- Accepted Article
58. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006; 61: 1009-15.
 59. Magnusson J, Kull I, Rosenlund H, et al. Fish consumption in infancy and development of allergic disease up to age 12 y. *Am J Clin Nutr* 2013; 97: 1324-30.
 60. Nafstad P, Nystad W, Magnus P, Jaakkola JJ. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. *J Asthma* 2003; 40: 343-8.
 61. Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997; 10: 6-12.
 62. Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. *J Allergy Clin Immunol* 2014; 133: 1255-64.
 63. Lee HS, Barraza-Villarreal A, Hernandez-Vargas H, et al. Modulation of DNA methylation states and infant immune system by dietary supplementation with omega-3 PUFA during pregnancy in an intervention study. *Am J Clin Nutr* 2013; 98: 480-7.
 64. Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG* 2011; 118: 916-25.
 65. Damsgaard CT, Lauritzen L, Kjaer TM, et al. Fish oil supplementation modulates immune function in healthy infants. *J Nutr* 2007; 137: 1031-6.

- Accepted Article
66. D'Vaz N, Meldrum SJ, Dunstan JA, et al. Fish oil supplementation in early infancy modulates developing infant immune responses. *Clin Exp Allergy* 2012; 42: 1206-16.
 67. Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database Syst Rev* 2015; 7: CD010085.
 68. D'Vaz N, Meldrum SJ, Dunstan JA, et al. Postnatal fish oil supplementation in high-risk infants to prevent allergy: randomized controlled trial. *Pediatrics* 2012; 130: 674-82.
 69. Mahrshahi S, Peat JK, Marks GB, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2003; 111: 162-8.
 70. Peat JK, Mahrshahi S, Kemp AS, et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2004; 114: 807-13.
 71. Marks GB, Mahrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006; 118: 53-61.
 72. Toelle BG, Ng KK, Crisafulli D, et al. Eight-year outcomes of the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2010; 126: 388-9.
 73. Toelle BG, Garden FL, Ng KK, et al. Outcomes of the childhood asthma prevention study at 11.5 years. *J Allergy Clin Immunol* 2013; 132: 1220-2.

- Accepted Article
74. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000; 106: 346-9.
 75. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121: 183-91.
 76. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. *J Allergy Clin Immunol Pract* 2013; 1: 29-36.
 77. Elizur A, Katz Y. Timing of allergen exposure and the development of food allergy: treating before the horse is out of the barn. *Curr Opin Allergy Clin Immunol* 2016; 16: 157-64.
 78. Palmer DJ, Prescott SL. Does early feeding promote development of oral tolerance? *Curr Allergy Asthma Rep* 2012; 12: 321-31.
 79. Du Toit G, Sayre PH, Roberts G, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. *N Engl J Med* 2016 Mar 4 (Epub ahead of print; DOI: [doi:10.1056/NEJMoa1514209](https://doi.org/10.1056/NEJMoa1514209)).
 80. Nwaru BI, Takkinen HM, Niemela O, et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. *J Allergy Clin Immunol* 2013; 131: 78-86.

81. Virtanen SM, Kaila M, Pekkanen J, et al. Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis. *Br J Nutr* 2010; 103: 266-73.
82. Nwaru BI, Erkkola M, Ahonen S, et al. Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* 2010; 125: 50-9.
83. Nwaru BI, Takkinen HM, Niemela O, et al. Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. *Allergy* 2013; 68: 507-16.
84. Nwaru BI, Craig LC, Allan K, et al. Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. *Clin Exp Allergy* 2013; 43: 1263-73.
85. Zutavern A, von Mutius E, Harris J, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child* 2004; 89: 303-8.
86. Niinivirta K, Isolauri E, Nermes M, Laitinen K. Timing of complementary feeding and the risk of atopic eczema. *Acta Paediatr* 2014; 103: 168-73.
87. Filipiak B, Zutavern A, Koletzko S, et al. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. *J Pediatr* 2007; 151: 352-8.

88. Hesselmar B, Saalman R, Rudin A, Adlerberth I, Wold A. Early fish introduction is associated with less eczema, but not sensitization, in infants. *Acta Paediatr* 2010; 99: 1861-7.

Table 1 Search strategy

Search terms
1. diet OR Mediterranean diet OR dietary OR dietary pattern OR food OR seafood OR fat OR fatty acid OR fish OR fatty fish OR oily fish OR lean fish
2. allergy OR atopy OR sensitization OR eczema OR dermatitis OR rhinitis OR wheeze OR asthma OR food allergy
3. pregnancy OR maternal OR infancy
4. offspring OR infant OR child*
5. Humans
6. 1 AND 2 AND 3 AND 4 AND 5

Table 2 Outcome data of studies of fish intake and allergic outcomes included into meta-analysis

Study	Sensitization	Eczema	Allergic rhinitis	Wheeze	Asthma
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<i>Maternal fish intake during pregnancy</i>					
Chatzi et al., 2013 ¹ (43)	NR	1.07 (0.86, 1.33)	NR	1.08 (0.84, 1.38)	NR
Erkkola et al., 2012 ² (28)	NR	NR	0.92 (0.67, 1.28)	0.99 (0.78, 1.25)	1.09 (0.66, 1.78)
Jedrychowski et al., 2011 ³ (44)	NR	0.57 (0.35, 0.93)	NR	NR	NR
Leermakers et al., 2013 ⁴ (45)	NR	0.96 (0.73, 1.28)	NR	0.83 (0.62, 1.12)	NR
Maslova et al., 2013 ⁵ (26)	NR	NR	1.23 (0.76, 2.08)	1.02 (0.84, 1.25)	0.73 (0.58, 0.92)
Miyake et al., 2009 ⁶ (47)	NR	0.73 (0.30, 1.75)	NR	0.67 (0.30, 1.48)	NR
Miyake et al., 2013 ⁷ (48)	NR	1.29 (0.86, 1.93)	NR	0.74 (0.51, 1.06)	NR
Øien et al., 2010 ⁸ (49)	NR	1.02 (0.82, 1.26)	NR	NR	0.99 (0.72, 1.37)
Ozawa et al., 2014 ⁸ (30)	NR	1.54 (0.68, 3.50)	NR	NR	NR
Romieu et al., 2007 ⁹ (50)	0.74 (0.50, 1.09)	0.73 (0.55, 0.98)	NR	0.55 (0.31, 0.96)	NR
Sausenthaler et al., 2007 ¹⁰ (52)	1.02 (0.73, 1.43)	0.75 (0.57, 0.98)	NR	NR	NR

Willers et al., 2007 ¹¹ (53)	NR	0.57 (0.35, 0.92)	0.28 (0.06, 1.19)	NR	NR
Willers et al., 2008 ¹² (54)	NR	NR	NR	1.10 (0.83, 1.47)	1.11 (0.84, 1.48)
<i>Fish intake during infancy</i>					
Alm et al., 2009 ⁸ (29)	NR	0.37 (0.24, 0.56)	NR	NR	NR
Alm et al., 2011 ⁸ (55)	NR	NR	0.43 (0.29, 0.62)	NR	NR
Goksor et al., 2011 ¹³ (56)	NR	NR	NR	0.90 (0.50, 1.80)	NR
Kieft-de Jong et al., 2012 ¹⁴ (57)	NR	NR	NR	0.94 (0.76, 1.18)	NR
Magnusson et al., 2013 ¹⁵ (59)	0.98 (0.73, 1.30)	0.78 (0.63, 0.97)	0.74 (0.60, 0.90)	NR	0.89 (0.63, 1.27)
Nafstad et al., 2003 ¹⁶ (60)	NR	0.66 (0.52, 0.84)	0.45 (0.28, 0.74)	NR	0.84 (0.57, 1.22)
Øien et al., 2010 ¹⁷ (49)	NR	0.62 (0.42, 0.91)	NR	NR	0.81 (0.60, 1.09)

CI, confidence interval; NR, not reported; OR, odds ratio.

¹ Adjusted for maternal age, education, history of asthma or eczema, smoking during pregnancy, parity, duration of breastfeeding, child's age at assessment and child's sex.

² Adjusted for sex, place of birth, duration of gestation, maternal age at delivery, maternal basic education, smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, atopic eczema by 6 months of age, pets at home by 1 year of age, duration of breastfeeding, and day care at 1 year of age.

³ Adjusted for gender of the child, maternal age and education, maternal atopy, older siblings, exclusive breastfeeding >3 months and damp house.

⁴ Adjusted for maternal age, parity, highest completed education level, household income, history of asthma or atopy, use of periconceptional folic acid supplements, prepregnancy body mass index, pet keeping, smoking and alcohol use during

This article is protected by copyright. All rights reserved.

pregnancy, total daily energy intake, vegetable intake, distress during pregnancy, gestational age at enrollment and child's birth weight, gestational age at birth, sex, breastfeeding, timing of introduction of complementary feeding, daycare attendance in the first year, lower respiratory tract infections in the first year.

⁵ Adjusted for maternal age, smoking, parity, prepregnancy BMI, physical activity, breastfeeding, socioeconomic status, maternal history of asthma and allergies, paternal history of asthma and allergies, and child sex.

⁶ Adjusted for maternal age, gestation at baseline, residential municipality at baseline, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in same room as infant, breastfeeding duration and time of delivery before third survey.

⁷ Adjusted for maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, family income, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, baby's birth weight, baby's sex, maternal smoking during pregnancy, household smoking during the first year of life, and breastfeeding duration.

⁸ No variables were adjusted.

⁹ Adjusted for maternal asthma, gender, maternal atopy and maternal social class for 'atopy'; maternal asthma, type of fish and smoking during pregnancy for 'eczema'; maternal asthma, gender and maternal social class for 'wheeze'.

¹⁰ Adjusted for study area, sex, maternal age at delivery, smoking during second or third trimester of pregnancy, parental education, exclusive breastfeeding for ≥ 4 month, family history of atopy, season of birth, and all dietary variables.

¹¹ Adjusted for maternal age of leaving full time education, paternal social class, maternal age, maternal smoking during pregnancy, smoking in the home during childhood, energy intake, maternal atopy, birth weight, presence of older siblings, sex of child and breastfeeding for 'eczema'; additionally adjusted for maternal asthma for 'allergic rhinitis'.

¹² Adjusted for sex, maternal educational level, parental atopy, maternal smoking during pregnancy, smoking in the house at age 8 years, breastfeeding, presence of older siblings, birth weight, overweight mother, maternal supplement use during pregnancy without folic acid and iron, region, and study arm (intervention study or natural history study).

¹³ Adjusted for atopic heredity, male gender, maternal medication during pregnancy, gestational age < 37 wk, caesarean section, treatment with antibiotics during the first week, doctor-diagnosed food allergy during the first year, eczema during the first year, introduction of fish before 9 mo of age, maternal smoking during pregnancy, any breastfeeding for 4 mo or more, and parental level of education.

¹⁴ Adjusted for maternal age, maternal BMI, maternal alcohol and smoking during pregnancy, household income, maternal educational background, family history of asthma, eczema, hay fever or 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, and any vitamin D supplementation in first year of life.

This article is protected by copyright. All rights reserved.

¹⁵ Adjusted for parental history of allergic disease, sex, maternal smoking during pregnancy or when the child was an infant.

¹⁶ Adjusted for parental atopy, atopic eczema 0-6 mo of age, gender, parity, birth weight, maternal age at delivery, birth order, uterus-related pregnancy complications, keeping pets at home when the child was born, an episode of lower respiratory tract infections during first year of life, maternal education, family income per year, maternal smoking at the end of pregnancy, and length of breastfeeding.

¹⁷ Adjusted for gender, familial atopy, parental smoking status 1 year after delivery, children's consumption of cod liver oil and vegetables at 1 y of age, parental homeowner status and exclusively breastfeeding for more than 4 mo for 'eczema'; no variables were adjusted for 'asthma'.

Table 3 Risk-of-bias assessment of the randomized controlled trials¹

Study	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Noakes et al. (25)	Yes	No	No	Yes	Yes	No	Unclear	High

¹ Risk-of-bias was assessed with use of the Cochrane Risk-of-Bias Tool.

Table 4 Risk-of-bias assessment of the prospective cohort studies¹

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Chatzi et al. (42)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Chatzi et al. (43)	☆	☆	☆	☆	☆☆	-	☆	-	7
Erkkola et al. (28)	-	☆	☆	☆	☆☆	-	☆	-	6
Jedrychowski et al. (44)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Leermakers et al. (45)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Lumia et al. (46)	-	☆	☆	☆	☆☆	-	☆	-	6
Maslova et al. (26)	☆	☆	☆	☆	☆☆	-	☆	-	7
Miyake et al. (47)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Miyake et al. (48)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Nwaru et al. (31)	-	☆	☆	☆	☆☆	☆	☆	☆	8

Øien et al. (49)	☆	☆	☆	-	☆☆	-	☆	-	6
Ozawa et al. (30)	☆	☆	-	☆	☆	-	☆	-	5
Romieu et al. (50)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Saito et al. (51)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Sausenthaler et al. (52)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Willers et al. (53)	☆	☆	☆	☆	☆☆	-	☆	-	7
Willers et al. (54)	☆	☆	☆	☆	☆☆	-	☆	☆	8
Alm et al. (29)	☆	☆	☆	-	☆☆	-	☆	-	6
Alm et al. (55)	☆	☆	☆	-	☆☆	-	☆	-	6
Goksor et al. (56)	☆	☆	☆	-	☆☆	-	☆	-	6
Kieft-de Jong et al. (57)	☆	☆	☆	-	☆☆	-	☆	-	6

Table 4 (*Continued*)

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Kull et al. (58)	☆	☆	☆	-	☆☆	-	☆	☆	7
Magnusson et al. (59)	☆	☆	☆	-	☆☆	-	☆	☆	7
Nafstad et al. (60)	☆	☆	☆	-	☆☆	-	☆	-	6

¹ Risk-of-bias was assessed with use of the Newcastle-Ottawa Scale. A higher overall score corresponds to a lower risk of bias; a score of 6 or less (out of 9) indicates a high risk of bias.

Figure Legends

Fig 1 Selection process for the studies included in the meta-analysis.

Fig 2 Association between maternal fish intake during pregnancy and eczema in the offspring. Squares represent study-specific estimates and horizontal lines indicate 95% CIs. Pooled estimates with 95% CIs from random-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols.

Fig 3 Association between maternal fish intake during pregnancy and wheeze in the offspring. Squares represent study-specific estimates and horizontal lines indicate 95% CIs. Pooled estimates with 95% CIs from random-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols.

Fig 4 Association between fish intake in infancy and childhood eczema. Squares represent study-specific estimates and horizontal lines indicate 95% CIs. Pooled estimates with 95% CIs from random-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols.

Fig 5 Association between fish intake in infancy and childhood allergic rhinitis. Squares represent study-specific estimates and horizontal lines indicate 95% CIs. Pooled estimates with 95% CIs from random-effects models are represented by filled black diamonds. Relative sample sizes are represented by the sizes of symbols.









