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Title	Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology
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Dietary factors during pregnancy and atopic outcomes in childhood: a systematic review from the European Academy of Allergy and Clinical Immunology

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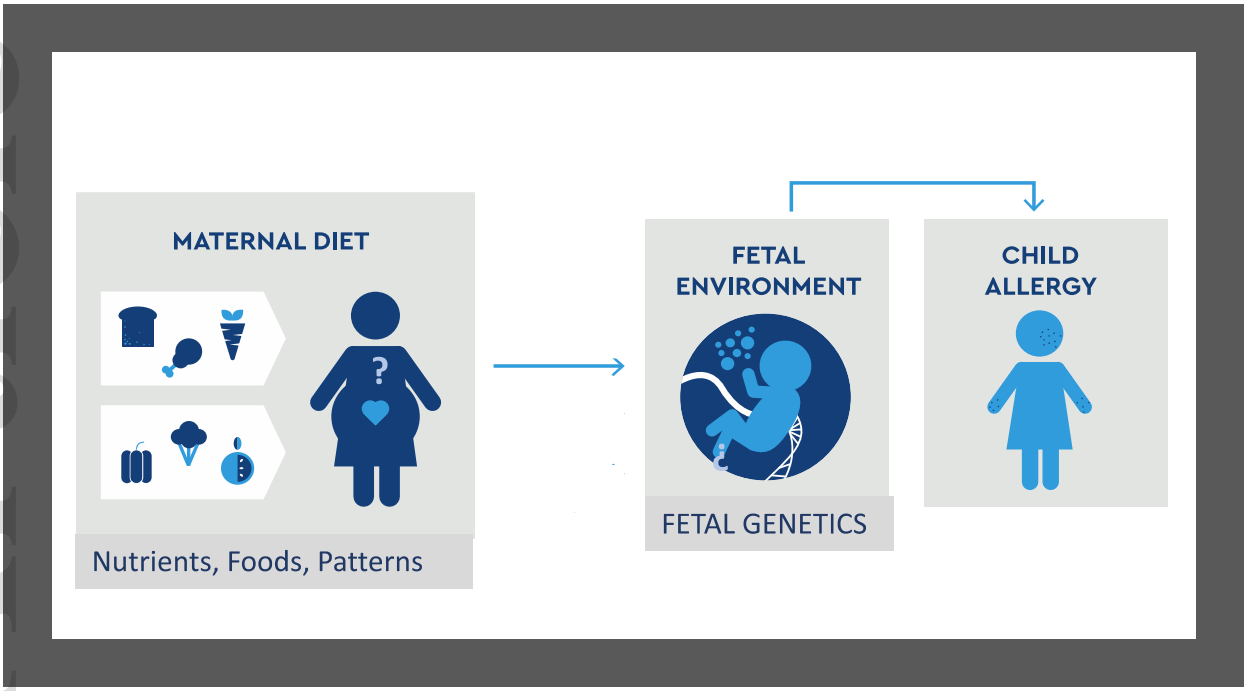
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Key words: Allergy, Prevention, Pregnancy, Diet, Nutrition

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Abstract and keywords

RATIONALE: Allergic diseases are an increasing public health concern and early life environment is critical to immune development. Maternal diet during pregnancy has been linked to offspring allergy risk. In turn, maternal diet is a potentially modifiable factor, which could be targeted as an allergy prevention strategy. In this systematic review, we focused on non-allergen specific modifying factors of the maternal diet in pregnancy on allergy outcomes in their offspring.

METHODS: We undertook a systematic review of studies investigating the association between maternal diet during pregnancy and allergic outcomes (asthma/wheeze, hay fever/allergic rhinitis/seasonal allergies, eczema/atopic dermatitis (AD), food allergies and allergic sensitization) in offspring. Studies evaluating the effect of food allergen intake were excluded. We searched three bibliographic databases (MEDLINE, EMBASE, and Web of Science) through February 26, 2019. Evidence was critically appraised using modified versions of the Cochrane Collaboration Risk of Bias tool for intervention trials and the National Institute for Clinical Excellence methodological checklist for cohort and case–control studies and meta-analysis performed from RCTs.

RESULTS: We identified 95 papers: 17 RCTs and 78 observational (case-control, cross-sectional and cohort) studies. Observational studies varied in design and dietary intakes and often had contradictory findings. Based on our meta-analysis, RCTs showed that vitamin D supplementation (OR: 0.72; 95% CI: 0.56 – 0.92) is associated with a reduced risk of wheeze/asthma. A positive trend for omega-3 fatty acids was observed for asthma/wheeze but this did not reach statistical significance (OR: 0.70; 95% CI: 0.45 – 1.08). Omega-3 supplementation was also associated with a non-significant decreased risk of allergic rhinitis (OR: 0.76; 95% CI: 0.56 – 1.04). Neither vitamin D nor omega-3 fatty acids were associated an altered risk of AD or food allergy.

CONCLUSIONS:

Prenatal supplementation with vitamin D may have beneficial effects for prevention of asthma. Additional nutritional factors seem to be required for modulating the risk of skin and gastrointestinal outcomes. We found no consistent evidence regarding other dietary factors, perhaps due to differences in study design and host features that were not considered. Whilst confirmatory studies are required, there is also a need for performing RCTs beyond single nutrients/foods.

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Keywords: Maternal diet, Pregnancy, Allergic diseases, Asthma, Wheeze, Eczema, AD, Allergic rhinoconjunctivitis, Allergic rhinitis, Hay fever, Seasonal allergies, Food allergy, Prevention, Children, Infants

Abbreviations:

AI: Adequate intake

PC: Prospective cohort study

RDI: Recommended dietary intake

AD: AD.

FA: Food allergy

Impact statement:

The systematic review focused on diet during pregnancy only, as not all mothers breast feed or introduce solids to their infants in a similar fashion. Thus we hence provide here pregnancy-specific dietary recommendations. Based on RCTs, we found that prenatal supplementation with vitamin D in doses higher than recommended by most countries, may have beneficial effects for prevention of asthma in the offspring. Doses used in RCTs were 800 IU, 2400 IU, 4000 IU. The European Food Safety Authority (EFSA) (https://www.efsa.europa.eu/en/press/news/161028) and the Institute of Medicine (https://www.aafp.org/news/health-of-the-public/20101201iomrpt-vitdcal.html) recommend 600 IU per day for pregnant women. Summarizing the data from observational studies, we found that the following nutrients, foods and diet patterns appears to be associated with reduced allergic outcomes: Vitamin A (allergic rhinitis), vitamin D (asthma, allergic rhinitis, sensitization) copper (food allergy, eczema, allergic sensitization), vitamin C (food allergy, allergic sensitization), Vitamin E (eczema, asthma), calcium (eczema), zinc (eczema, asthma), beta-carotene (eczema), magnesium (eczema), dairy/probiotic containing foods (eczema, allergic rhinitis), Mediterranean and Western diet (asthma/wheeze), Mediterranean and soy/fish/nuts diet (allergic sensitization), fruit and vegetables (asthma, eczema), fish (sensitization), nuts (asthma, allergic rhinitis), fish/fatty fish (asthma) and meat (asthma). However, the doses of foods or nutrients studied were heterogeneous and we were unable to relate these to current nutrition guidelines. We found no consistent evidence regarding other dietary factors, perhaps due to differences in study design and host features such as nutrient intake/levels at the start of the study that were not considered. There is a need for confirmatory studies and RCTs beyond single nutrients.

Introduction

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Allergic diseases are an increasing public health concern.[1] The most common allergic conditions are asthma, allergic rhinitis/hay fever/seasonal allergies, eczema/atopic dermatitis (AD) (from now on referred to as eczema) and food allergies. World-wide, an estimated 300 million people suffer from asthma, and an additional 400 million have allergic rhinitis.[2] In addition, 570 million children and 116 million adults suffer from eczema, and 200 to 250 million people suffer from food allergies.[3] These allergic diseases may often co-exist in one individual.[4] Allergies can affect quality of life, reduce academic performance and income,[5] and in rare cases can be fatal.[6,7]

Maternal diet in pregnancy is an important, potentially modifiable factor in allergy prevention. Several studies have investigated the role of prenatal diet on offspring allergy, but the findings are conflicting, and there is a paucity of randomized controlled trials (RCTs). An evidence synthesis is paramount in order to adequately appreciate the underlying evidence.

A number of review papers have been published focusing on maternal diet during pregnancy, lactation, or early life[8-11] and allergy prevention.[8-12] Our review follows and extends a recent systematic review and meta-analysis by Garcia-Larsen et al.[13], who summarized the evidence up to December 2017. Garcia-Larsen et al. [13] considered not only dietary intake during pregnancy, but also in lactation and infancy; their main conclusions [13] were that maternal omega-3 fatty acid supplementation during pregnancy and lactation may reduce the risk of allergic sensitization to egg and peanut. However, only three of the interventional studies regarding omega-3 fatty acids included in that review were conducted in pregnancy only. In addition, the review[13] showed that maternal probiotic supplementation in the post-natal period reduced the risk of offspring eczema and allergic sensitization to cow's milk, and none of the probiotic studies were limited to pregnancy. Since the publication of that systematic review, new studies[14-40] evaluating maternal diet during pregnancy and childhood allergic outcomes have been published. We reviewed diet during pregnancy only as not all mothers breast feed or introduce solids to their infants in a similar fashion. We therefore reviewed literature regarding the pregnancy period only, to investigate specific pregnancy related dietary associations.

Globally, recommendations on dietary intake during pregnancy for prevention of allergic disease are sparse. The Australasian guideline recommends eating fatty fish or taking omega-3 fatty acid supplements during pregnancy to reduce eczema in the offspring.[41] Other guidelines from the UK[42],

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Europe[43] and the US[44] only give recommendations pertaining to food allergen avoidance in pregnancy. They state that food allergens should not be avoided during pregnancy, but give no further dietary recommendations for allergy prevention. The German allergy prevention guidelines[45] recommend that pregnant women should follow a healthy diet, need not avoid food allergens, and should eat fish regularly. In support of this, the UK prevention guidelines state that omega-3 fatty acids (found in oily fish such as salmon, trout, mackerel and fresh [not canned] tuna) during pregnancy may help reduce the risk of eczema and allergic sensitization (development of antibodies to allergens) in early life.

The goal of this review was to summarize studies which examined the impact of maternal diet during pregnancy on offspring's allergic outcomes. We also compared the amount of nutrients or foods consumed and food patterns identified, which have been shown to have an allergy preventative effect to current US dietary guidelines.

Methods

Studies included in this review

Types of Studies

We included RCTs, observational (cross-section and cohort) and case-control studies, which 1) considered the time period of pregnancy alone, 2) reported allergic outcomes or allergic sensitization status in the offspring, and 3) were written in English. Studies examining food allergen intake were excluded. Studies that included intake of major allergens such as milk or nuts were included, as long as the outcome did not relate to the particular food allergen. As an example, studies on tree nut intake were included only when an association with an allergy outcome other than a tree nut were studied, such as asthma.[46] The latest data indicate that early introduction of a food allergen specifically prevent food allergy to that allergen only.[47] We were therefore confident that any outcome noted was less likely to be related the nutritional composition, rather than the allergen content of the food. We also excluded case studies, case series, systematic reviews and meta-analyses, expert reviews and opinions, and editorials.

Types of publications

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A consensus was reached on including full text publications only, as there were discrepancies in some of the data published in abstract form (as presented at conferences) when compared to the full paper publications.

Types of Participants

Pregnant women were the target group for this systematic review, provided there was allergic outcome data published for their offspring. Both general population and populations at high risk of atopy were included.

Types of Interventions in RCT

Studies that used supplementation or specific foods (e.g. fatty fish) during pregnancy alone, irrespective of dose, formulation, or mode of delivery and composition (e.g., oil, tablet) were included. Trials were not included if the intervention(s) had been continued beyond pregnancy through breastfeeding or given only to the infant.

Types of Outcome Measures

Studies were included if they reported on allergic outcomes or allergic sensitization status in the offspring, either as a primary or secondary endpoint. Allergic outcomes were defined as wheeze/asthma, allergic rhinitis/rhinoconjunctivitis/hay fever, food allergy, eczema, allergic sensitization measured by skin prick tests/specific IgE tests to food/aero/any allergen, or total IgE levels. Please see Supplementary file 1 for a list of the search terms used in respective databases. An expert panel from the US, Europe and Australia commented on the search strategy and the list of identified and included studies. Additional studies were located through searching the references cited in identified studies and systematic reviews, and through discussion with the expert panel.

Dietary guidelines for food/nutrient intake in pregnancy

To compare our study findings with current dietary guidelines, we used the following approach to calculate food or nutrient intake: for micronutrients comparisons, the US dietary reference intakes (DRI) and the United States Department of Agriculture (USDA) www.choosemyplate.gov guidelines[48]for pregnant women were used. Macronutrient requirements and number of portions for the second trimester of pregnancy were calculated, assuming a daily caloric intake of 2400 kcal,

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comprising 71 g of protein, 53.33-93.33g of total fat, <27 g of saturated fat, 13 g of linoleic acid (LA), 1.4 g of alpha-linolenic acid (AI), 175 g of carbohydrates, 28 g fiber, <12 g of added sugar, 2 cups (2x approx. 125 g) of fruit, 3 cups (3 x 125 g) of vegetables, 8 oz of grains (8 x 30 g), 6.5 oz of high-protein foods (6.5 x 30g) and 3 cups (3 x 200 – 250 mls) of dairy. Recommended fish intake was assumed to be 2-3 servings (in total approx. 8 – 12 oz/240 – 360 g) per week as per the United States Food and Drug Administration (FDA) (Best Choices: https://www.fda.gov/food/consumers/eating-fish-what-pregnant-women-and-parents-should-know).

Data Collection

Ethics application/Institutional review Board

This study is considered exempt from Institutional Review Board review by the University of Colorado School of Medicine Combined Institutional Review Board.

Study selection

The titles and abstracts of articles considered for inclusion were independently assessed by MBA, MP, and AM and categorized as included, not included, or potentially relevant. CV then checked each assessment. For studies considered potentially relevant, full-text copies were obtained, and inclusion of the studies was discussed by CV, MBA, MP and AM. Any discrepancies were resolved either by consensus among the authors, or, if there was lack of consensus, by discussion with the expert panel. All the studies in this publication were reviewed and approved by both the authors and the expert panel.

Risk of bias assessment

Risk of bias assessment was undertaken independently by MBA and CV using a similar approach as in Garcia-Larsen et al.[13] As in the paper by Garcia-Larsen-et al.[13], we used modified versions of the Cochrane Collaboration Risk of Bias tool for intervention trials and the National Institute for Clinical Excellence methodological checklist for cohort and case–control studies.[49] For intervention trials, risk of bias assessment included assessment of: 1) Selection bias, including sequence generation and allocation concealment; 2) Assessment bias, included blinding of outcome assessors and ensuring outcomes were determined by validated assessment tools; and 3) Attrition bias, which was considered high when outcome data was reported in <70% of randomized participants. Risk of bias for cohort and case-control studies included assessment of: 1) Selection bias, which was considered

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low if cases and controls were recruited from similar populations and had a similar attrition rate <20%; 2) Assessment bias, including were blinding of outcome assessors and use of validated assessment tools; and 3) Confounding bias (did study design and analysis account for relevant confounders?). Conflicts of interest were noted if industry was involved in any aspect of the study or if authors received funding for other activities from relevant industry partners. Using these components, each study was graded as high, medium or low. Supplementary File 2 includes the grading for risk of bias assessment. In order to minimize publication bias we performed a comprehensive search of the literature, and included experts in the field to ensure that no relevant study was missed. We did not include grey literature (unpublished information or information that is not produced by commercial publishers) in order to avoid discrepancies with published data. None of the meta-analyses included more than 10 papers, and we therefore did not use funnel plot and Egger tests to formally test for publication bias.

Data Extraction and reporting

Data were extracted by three authors (AM, MBA and MP). New articles were added into the excel sheets downloaded from Garcia-Larsen et al.[13] Inclusion and exclusion criteria differed between the current review and that of Garcia-Larsen et al.,[13] some entries were edited, modified or deleted. The edited files were reviewed for quality and completeness by CV. Detailed information on study characteristics were recorded by CV, MP and MBA, and appear in Supplementary File 3. Any discrepancies regarding the classification of dietary measures and offspring allergic outcomes were discussed and resolved within the group of authors. Classification of maternal dietary measures and offspring allergic outcomes were double-checked by the expert panel. The authors' names, institutions, journals, or data were not blinded during data extraction.

Data analysis

Observational studies

For wheeze, studies were split into two categories: infants and young children (0-<3 years) and older children (3 years and older). All studies reporting on allergic rhinitis included offspring with ages over 5 years. All ages were included for food allergy, eczema and allergic sensitization.

The reported data were plotted. If multiple odds ratios (ORs) were reported for a single study, only the highest exposure compared to the lowest exposure OR was used. Meta-analysis of observational

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studies was not appropriate because the studies were heterogeneous in focus, design, and in target populations. We used forest plots to visually summarize all significant outcomes found by the studies, i.e., the adjusted OR, adjusted hazard ratio (HR) or adjusted risk ratio (RR) and their corresponding 95% confidence intervals. If more than one significant outcome was found in a manuscript, then only the largest observed difference was included in this review. For example, if authors compared quartiles, by comparing Q1 vs. Q2 and Q1 vs. Q4 for one nutrient in the same age group, only the largest difference would have been included. We understand that it is better to report the estimates regardless of their statistical significance in order to give readers an appreciation of the magnitude of the effect sizes, and that statistical significance is purely a function of the sample size of a study and hence provides information only of the random error. It does not give any indication of the magnitude of the estimates or potential systematic errors. However, our goal here was to provide a visual presentation of the data, and the supplementary files contain the full set of information. Therefore, findings from observational studies were synthesized narratively by grouping studies according to allergy outcome and nutrient, food or diet pattern studied: nutrients, including vitamins and minerals, omega-3 fatty acids and fatty fish, fruit and vegetables, other foods, and food patterns.

Randomized Clinical Trial Meta Analyses

For each exposure-disease outcome pair included in the RCTs, separate meta-analyses were performed. Because the number of studies was limited, several meta-analyses included fewer than four data points. All meta-analyses included at least two studies. [50] DerSimonian-Laird random effects models were used to perform the meta analyses and estimate the pooled ORs using the rmeta (v 3.0)[51] package in R. The heterogeneity of the studies was calculated using the Cochran χ^2 and I^2 statistics. Forest plots were created for each of the diseases using the forestplot (v1.9)[52] package in R (v3.5.1). Where studies reported outcomes in the same children at more than one time-point, we included each outcome in the meta-analysis as well as the combined outcomes. As the different analyses showed no changes in the outcomes, the overall decision was to use food allergy outcomes at 3 years; eczema at 3 years; allergic sensitization at 3 years; and asthma, rhinitis, and allergic sensitization at 6 years.

RESULTS

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Results of literature search and characteristics of included studies

We included all the relevant published studies on the topic of maternal dietary intake during pregnancy alone identified by Garcia-Larsen et al.[13] (n=68 papers). [14-40,46,53-119] An additional search was performed using the same search terms to include studies published after, or potentially missed by their search, including observational studies from August 2013 – February 2019 and intervention studies from January 2017 – February 2019 (Figure 1). Based on this additional search, we identified an additional 27 publications. Of them, 25 were cohort or case-control studies [14-38] and 2 were RCTs [39,40]. In total, our systematic review is based on 95 papers (17 RCTs and 78 cohort and case control studies). The numbers of pregnant women and their offspring studied at different time points and presented in different publications are shown in the supplementary Excel files. Supplementary file 4 has information on nutrients, including vitamins and minerals; Supplementary file 5 contains information on fats and fatty fish; Supplementary file 6 is on fruit and vegetables; Supplementary file 7 contains information on other foods; and Supplementary file 8 is on food patterns.

Sufficient numbers (at least two) of RCTs were found for vitamin D, vitamins C and/or E, and omega 3 fatty acids. We performed a total of 9 meta-analyses.

Quality and Risk of bias assessment

The 95 papers were generated from 50 studies. The 50 studies included 11 RCTs[39,40,53-67] (7/11 normal risk), 2 cross-section[21,74] (both normal) and 30 cohort studies[15,18-20,22-30,32-37,46,68-70,72,73,75-78,80-108,110,112,115-119] (all normal risk) 3 case-control designs nested within cohorts[16,17,31,38,79,113,114] (all normal risk) and 4 case-control studies[14,71,109,111] (3 normal and 1 high risk). Due to low numbers of RCTs that could be included in the meta-analysis and low numbers of studies including high risk populations in the observational studies, these were not separated. Of the studies, 8 (7 observational and 1 RCT) (16%;) were considered to be of high quality, 10 (8 observational and 2 RCTs) (20%) were of uncertain quality, and 32 (24 observational and 8 RCTs) (64%) of low quality. The results for the quality assessment of the studies are shown in Supplementary file 2.

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Prevention strategies in pregnant women

Supplementary excel files 4-8 summarize the results of all the 95 publications. The excel files contain, if available for each paper, the last name of the first author, publication year, study design, dietary exposure, dietary intake time, outcome type, offspring's age at assessment, and every relevant point estimate reported with its associated 95% confidence intervals and p-values, as well as the relevant comparison of interest that each point estimate describes. Due to the heterogeneity between papers on the measurement of dietary intake, the analysis of the data, and the reporting of the results, data from observational studies were not pooled in meta-analyses.

Dietary intake

Dietary associations measured in observational studies depend on the validity of the measures used to study dietary intake.[120] This important methodological factor has so far been omitted from past systematic reviews. Methods for measuring dietary intake differ greatly between studies. We have summarized the approaches for assessing dietary intake and adherence to study interventions used in the RCTs in Supplementary file 3. Of the 17 publications reporting on RCT outcomes, 8 papers [39,40,59-62,65,66] mentioned that they monitored adherence and 6 papers[54,55,57,58,63,64] did not monitor intake. For the observational studies, instruments used to measure food or nutrient intake were validated food frequency questionnaires (FFQs),[15,18,21,23,25-27,30,33,34,36,46,70,75-78,80-84,87-107,110,115,118] unvalidated FFQs,[16,17,19,28,29,31,32,73,111-114,119] questionnaires,[14,20,22,35,38,68,69,71,72,74,79,85,86,108,116] interviews,[24] information obtained from medical records[109], 3/5-day food records and/or 24 hour recalls and questionnaires[37,117] These points are important to take into account when reading the data.

Asthma/wheeze outcomes

Early childhood wheeze may not lead to allergic asthma outcomes in later childhood.[121,122]To distinguish between transient wheeze/asthma in infancy and early childhood, and later wheeze/asthma, which may be a stronger predictor of subsequent allergic asthma outcomes, we have separately reported observational studies manuscripts on maternal diet and wheeze/asthma into those which considered offspring wheeze/asthma between 0- <3 years and that for offspring 3 years and older. For the meta-analysis we have included all ages. Allergic outcomes and how these were measured are shown in supplementary file 3.

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Randomized controlled trials

We had a limited number of studies to perform meta-analysis of anti-oxidant (vitamin C and E; 2 studies – children 1-2 years),[58,61] vitamin D (3 studies – children 3 years old),[55,57,60] and omega-3 fatty acid (4 studies; 5 papers; children age 6m, 5 - 16 years) [62,63,66,67,72] intake or supplementation against wheeze/asthma outcomes in the offspring (Figures 2a, b, c,). Our meta-analyses indicate that Vitamin D during pregnancy had a statistically significant protective effect on wheeze/asthma in the offspring (OR: 0.72; 95% CI: 0.56 – 0.92). Although there was a trend towards a protective effect, maternal supplementation/intake during pregnancy with omega-3 fatty acid (OR: 0.70; 95% CI: 0.45 – 1.08) did not reach statistical significance on wheeze/asthma outcomes in the offspring. If we remove the study by Noakes et al. who reported on wheeze in the first six months of life, significance is still not reached (OR:0.63; 95% CI: 0.4 – 1.00 – meta-analysis not shown). Using data from children at 1-2 years, anti-oxidant did not show a protective effect against asthma/wheeze (OR: 0.67; 95% CI: 0.29 – 1.56).

Observational studies

Many different outcomes have been reported as summarized in supplementary file 9. Sixty-two papers from observational studies[14-16,19-26,28,30-33,35-38,46,68-70,74-80,82-93,95,96,98-101,103-111,113,117-119] reported on the association between maternal diet during pregnancy and asthma/wheeze as an outcome (Table 1; figures 3a and b and 4a and b). We summarized all the significant outcomes reported in Figure 3 to give a visual presentation of the outcomes rather than making a statistical conclusion. Figure 4 indicates that a large number of foods/nutrients/food patterns were associated with an increased or reduced risk of asthma/wheeze in children 3 years and over. The most significant protective factors were foods associated with a Mediterranean diet, meat, vitamin D and fatty fish. The most significant factors associated with an increased risk were pasta, fish sticks and arachidonic acid. From the summarized data, no firm conclusion can be drawn in regard to the protective effect of nutrients/foods/food patterns studied on allergic disease. However, when considering asthma, reduced offspring allergic outcomes were associated with intake of copper, vitamin D, Mediterranean diet and Western diet, fish/fatty fish, tree nuts, fruit and meat (type of meat not specified) in the observational studies included.

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Allergic rhinitis outcomes

Figures 5 and 6 summarize allergic rhinitis outcomes in the offspring for both observational and randomized controlled studies, respectively. All observational studies with significant outcomes are shown in Figures 6a and 6b. The studies shown in both these figures included results for offspring aged 3 years and above.

Randomized controlled trials

We were able to perform meta-analysis of omega-3 fatty acid supplementation (2 studies, 3 papers – all children over 5 years) [39,54,66,67] against allergic rhinitis outcomes in the offspring (Figure 5). Although we found a potential protective effective based on the meta-analysis combining two studies of omega-3 supplementation during pregnancy on allergic rhinitis in the offspring, the effect was showed a trend towards statistical significance (OR: 0.76; 95% CI: 0.56 – 1.04).

Observational Studies

Nineteen papers from observational studies[15,16,18,21,24,25,31,32,46,70,90-93,103,104,106,107,113] reported an association between maternal diet during pregnancy and offspring allergic rhinitis/rhino-conjunctivitis as an outcome. Different studies reported different terms to describe outcomes and definitions (i.e some studies referred to ever suffering from hay fever and others reported on current allergic rhinitis) were not always similar, though the same disease group was being studied. The results are described and summarized in both Table 1 and Figure 6.

Figures 6a and 6b indicates that vitamin D, vitamin A, fatty fish, poly-unsaturated fatty acids (PUFA), alpha-linolenic acid, peanut, pistachio and probiotic milk products were associated with reduced risk of allergic rhinitis. Fish (unspecified type), the ratio of omega-6 to omega-3 fatty acids, butter and fruit were all associated with increased risk of allergic rhinitis. As above, due to heterogeneity between studies, these data were summarized narratively and not pooled for meta-analysis. Vitamin A, vitamin D, dairy, nuts and probiotic containing foods showed associations with reduced allergic rhinitis outcomes.

Eczema outcomes

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Eczema usually develops in infancy [123] prior to food allergy and other allergic manifestations, making it a target for allergy prevention studies. Data presented in this systematic review includes offspring data from 6 months onwards.

Randomized controlled trials

We were able to perform meta-analysis on the effects of vitamin D[55,57,60] (3 studies) and omega-3 fatty acid intake[62] or supplementation[39,53,54,56,65-67] (4 studies, 8 papers; 4 used in meta-analysis) on offspring eczema outcomes (Figure 7a, b). None of the dietary exposures during pregnancy had a significant effect on offspring eczema (vitamin D [OR: 0.90; 95% CI: 0.71 – 1.15] and omega-3 [OR: 1.07; 95% CI: 0.82 – 1.40]).

Observational studies

Thirty-eight papers from observational studies[15,16,19,20,24,26,29,31,37,68,70,72,76,77,81,82,84-88,90,94-101,103,104,107,108,112,113,116,118] reported the association between maternal diet during pregnancy and eczema in their offspring (Table 1; Figure 8). Due to heterogeneity between studies, these data were not pooled for meta-analysis.

Figures 8a and 8b summarize the significant associations published between various components of maternal diet during pregnancy and offspring eczema that were reported from observational studies. In terms of vitamins and minerals, studies presented significant associations for a decreased risk of offspring eczema with maternal intake during pregnancy of beta-carotene, vitamin E, zinc, calcium, magnesium and copper. Paradoxically, studies showed both positive and protective associations between maternal intake of vitamins C and D and offspring eczema. Intake of fatty fish, margarine, vegetable oil, total fat, omega-6 fatty acid, Omega 3/Omega 6 ratio, linoleic acid, alpha linoleic acid, natto and MUFAs all were positively associated with offspring risk of eczema. Cholesterol, and arachidonic acid showed a decreased association with eczema. Looking at other foods, fast foods, shellfish, alcohol, and meat (not defined) were associated with an increased risk of offspring dermatitis. Maternal intake of milk, fish, vegetables and apples was associated with a reduced risk of developing AD. Intake of copper, vitamin E, calcium, zinc, beta-carotene, magnesium, dairy/probiotic foods, vegetables and fruit were associated with reduced eczema outcomes

Food allergy outcomes

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Randomized controlled trials

There were two (three papers)[56,65,66] RCTs that studied the effect of maternal intake of omega-3 fatty acid during pregnancy and food allergy outcomes in the offspring. The meta-analysis is shown in Figure 9, revealing that maternal intake/supplementation of omega-3 fatty acids during pregnancy had no significant effect on food allergy in offspring (OR: 1.18; 95% CI: 0.56 – 2.46).

Observational studies

Five publications from observational studies[34,71,77,115,118] discussed associations between maternal diet during pregnancy and food allergy in their offspring (Table 1). Figure 10 summarizes significant results from observational studies regarding the association between various components of maternal diet during pregnancy and food allergy in offspring. The studies reported protective associations between maternal intake of copper and vitamin C and risk of food allergy outcomes in the offspring. Maternal intake of vegetables and vitamin D were associated with increased risk of food allergy in the offspring.

Allergic sensitization outcomes

Allergic sensitization in the included studies measured both allergic sensitization to food and/or aero-allergens, using skin prick test (SPT) and/or specific IgE levels. Different outcome measures were used, including increased total IgE, a range of specific IgE or SPT to foods and aero-allergens, and amalgamation using the term atopy to indicate any level of allergic sensitization.

Randomized controlled studies

Three[55,57,60] RCTs reported results on the effects of Vitamin D on allergic sensitization in the offspring, and five reported on the effects of omega-3 fatty acid intake[62] or supplementation[39,54,56,65-67] on the same outcome. The meta-analysis is shown in Figures 11 a, b. The meta-analyses showed no effects for either maternal intake of vitamin D (OR: 0.91; 95% CI: 0.68 – 1.21) or of omega-3 fatty acid (OR: 01.02; 95% CI: 0.77 – 1.36) intake/supplementation during pregnancy with offspring allergic sensitization outcomes.

Observational studies

Nineteen papers from observational studies [16-18,24,27,31,68,73,75-77,82,86,102,110,112-114,118] studied the association between maternal diet during pregnancy and allergic sensitization as an outcome.

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Data shown in Figure 12a and b and summarized in Table 1 indicate that vitamin C, vitamin D, copper, omega-6 PUFAs, PUFA, butter, fish, the Mediterranean diet, the Seafood and Noodle diet pattern, were associated with reduced allergic sensitization. Fruit, celery, sweet pepper, free sugar, fatty fish, vegetable fat, vegetarian and health conscious diet, were associated with increased prevalence of allergic sensitization. Intake of vitamin D, copper, Vitamin C, diet containing soy, fish and nuts, intake were associated with reduced prevalence of sensitization.

Dietary intake and its association with allergy outcomes

Where data allowed, we summarized the dose of nutrients/foods intake associated with allergy outcomes in observational studies (Table 2 and 3). We find no clear association between dose of nutrient/food required to reduce or increase any specific allergy outcomes. Of note is that the dose/amount showing an association frequently does not comply with national dietary recommendations from the US. [124] Vitamin A (allergic rhinitis), vitamin D (asthma, allergic rhinitis, sensitization) copper (food allergy, eczema, allergic sensitization), vitamin C (food allergy, allergic sensitization), Vitamin E (eczema, asthma), calcium (eczema), zinc (eczema, asthma), beta-carotene (eczema), magnesium (eczema), dairy/probiotic containing foods (eczema, allergic rhinitis), Mediterranean diet and Western diet (asthma/wheeze), Mediterranean and soy/fish/nuts diet (allergic sensitization), fruit and vegetables (asthma, eczema), fish (sensitization), nuts (asthma, allergic rhinitis) and meat (asthma). We suggest that researchers use nutrition guidelines to set predetermined cut-offs for food intake to 1) compare outcomes in observational studies and 2) determine dose given during RCTs. This will help ensure safe dietary interventions and will also allow comparison of future studies.

Discussion

Summary of findings

We find insufficient evidence to provide guidance on diet diversity (no published reports), diet patterns, diet indices or specific foods, food groups, macro or micro-nutrients that should be consumed or avoided during pregnancy for the prevention of allergic diseases in the offspring. However, based on 3 RCTs, we did find that intake of vitamin D, higher than EFSA and IOM recommendations, was significantly associated with a reduced risk of wheeze/asthma. This need to be further studied before guidelines are changed, particularly as intake of vitamin D in both lactation[125] and early life is associated with increased food allergy in the offspring.

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Strengths and limitations

We included the most up-to-date studies on dietary intake during pregnancy and prevention of allergic disease in their infants. Studies from Europe, North America, Asia, and Australia were included. We used the stringent standard employed by Garcia-Larsen et al.[13] to conduct the search, perform the risk of bias assessment and data extraction. We brought together a panel of international experts to review the data and conclusions of this review.

The review was limited by the quality of studies included. Some 64% of the studies included were deemed to be of low-quality. The pool of data is also relatively small with 50 studies contributing to 95 papers. The observational studies were highly heterogeneous and were therefore not considered to be suitable for meta-analysis. There is a paucity of RCTs in this field; only four meta-analysis were performed using data from RCTs. Finally, none of the studies looked at diet diversity during pregnancy, this may be partly due to the uncertainties in defining diet diversity, which has now been addressed in an EAACI position paper.[9]

Comparison of findings to previous studies

The systematic review by Vadhaninia et al.[126] based on RCTs assessed the impact of omega-3 fatty acid supplementation solely in pregnancy and found that based on pooled estimates, omega-3 fatty acid intake significantly reduces allergic sensitization to egg and peanut in the offspring. We did not find a significant effect on any allergic sensitization outcome. The discrepancy may be attributed to the fact that one of the studies included by Vadhaninia et al.[126] was excluded from our review, as maternal supplementation continued up to 2.5 months post-delivery.[127] Our findings are also different from the conclusions drawn by Garcia-Larsen et al.[13]. The difference probably lies in the choice of studies included in each systematic review. Garcia-Larsen et al.[13] included studies in pregnancy, lactation and early life. We considered studies in pregnancy alone. It is therefore possible that supplementation with omega-3 fatty acid, which continues during breast feeding and early life may be more effective than just during pregnancy alone

In terms of probiotic supplementation, published literature suggests that probiotic supplementation during late pregnancy, breastfeeding and early life[13,43,128-135] may be associated with reduced risk of the development of eczema. Substantial uncertainties remain regarding the specific strain required and the optimal timing of supplementation. We were unable to find any RCTs using probiotic

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supplementation in pregnancy only. We did find only one observational study that examined the association between maternal intake of probiotics and offspring allergy, but the authors found no association with allergic outcomes.[106]

We were able to demonstrate that vitamin D supplementation in pregnancy may reduce the risk of wheeze/asthma.[55,57,60] Vadhadania et al.[136] also concluded that prenatal supplementation of vitamin D might be associated with reduced odds of recurrent wheezing in children. We were unable to find any RCT on folic acid supplementation in pregnancy only and observational studies provided conflicting evidence.[14,22,28,30,33,35,38,68,71,77,79,83,100,103,114,115,119] There is lack of evidence on the effect of other vitamins for the prevention of respiratory and/or allergic outcomes.

Many systematic reviews have made recommendations, which relate to maternal diet in pregnancy and allergy prevention in the offspring. The review by Lodge et al.[137] did not identify any nutritional factors during pregnancy that reduced the risk of food allergy in the offspring. Four reviews recommended omega-3 fatty acid intake in pregnancy, vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet for the prevention of asthma. [43,137-140] Reviews focusing on allergy prevention in general concluded that pregnant women should consume their normal diet and that maternal intake of Mediterranean dietary patterns, diets rich in fruits and vegetables, fish, and vitamin D containing foods may be associated with reduction of offspring allergic disease.[10,43,131,132,137,140-146] We were unable to make generalized recommendations from the current review. Another factor that needs to be considered is whether family, paternal and/or specifically maternal history of allergy, play a role in the outcomes measured.

Since the review was performed, one study has shown an association between Diet inflammatory index (DII) scores in pregnancy and childhood asthma outcomes over 10 years.[147] Another study found an association with wheeze trajectories in the child, but not asthma up to 7.5 years of age[148] indicating that perhaps, the inflammatory potential of the diet needs to be assessed when focusing on asthma and/or wheeze outcomes.

Interpretation of the evidence

The heterogeneity of the results from observational studies yields little guidance regarding changes in the maternal diet that may be associated with reduction in offspring allergic diseases. Several nutrients and foods such as Vitamin A, vitamin D, copper, vitamin C, Vitamin E, calcium, zinc, beta-

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carotene, magnesium, dairy/probiotic containing foods, Mediterranean diet and Western diet, Mediterranean and soy/fish/nuts diet, fruit and vegetables, fish, nuts, fish/fatty fish and meat. but amounts consumed do not relate to current nutrition guidelines. Yet our meta-analysis of RCTs conducted in pregnancy does show some significant and replicable results. Randomized intervention trials in pregnancy show a preventative effect of vitamin D supplementation of 800[57], 2400[55] or 4000[60] IU per day on wheeze/asthma; though EFSA and the IOM recommend only 600 IU of vitamin D per day during pregnancy.

Clinical, policy, research implications of the findings

The current systematic review does not lead to any changes in clinical practice or policies but clearly highlights the research need for more RCTs in this field, particularly focusing on diet patterns or total dietary intake. There may be a particular need to review vitamin D recommendations during pregnancy.

Conclusions

The lack of consistent results across the different studies presented in this review may largely be influenced by the lack of a standardized approach to supplementation in terms of dose and duration, disease definition/outcomes used and individual host features that are difficult to compare across studies. Polymorphisms in genes associated with catabolism and utilization will influence nutrient requirements and function. GWAS-led prevention and intervention studies, including functional microbiome, immunological, metabolomic and lipidomic assessments are required and will increase our understanding of the importance of specific nutrients in the natural course of allergies and asthma. It is likely that a custom-individual-tailored approach to nutrition, focusing on overall dietary intake which may include supplementation, is required to observe the optimal benefits that can potentially be derived from dietary factors in the prevention and treatment of allergies and asthma. Future research and clinical efforts should be focused on large, adequately powered human studies of rigorous methodological design. These studies should focus on identifying the key host characteristics (i.e. genetics, environmental factors, microbiome, biochemical and inflammatory parameters and functional clinical characterization) that influence responses, whilst also taking, levels of nutrient intake, history of allergic diseases and the composition of the total underlying diet and nutrient interactions into account. Improving our understanding of potential strategies to prevent the development of allergic diseases would

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significantly reduce morbidity, mortality and costs from allergic diseases. The current evidence mainly focused on single dietary factors, and the data from observational studies were very heterogeneous. Meta-analysis based on 3 RCTs showed some benefits of vitamin D supplementation on asthma/wheeze, but doses used were higher than recommended by EFSA and the IOM. Before routine supplementation during pregnancy for the prevention of allergic disease can be advised more studies are required.

Author contributions

CV drafted the paper. MBA, MP, DG, AMai, LV people performed the data extraction and analysis. CA, DF, MG, EU, GR, CR, DP, AMu, KM, NL, MG, GdT, SHA, PKS, MN, RM reviewed and contributed to multiple versions of the paper. LOM and BN assisted with data interpretation and reviewed and edited the final version of the paper ,

Declarations of interest

Venter C provided educational material or reviewed educational materials for Abbott Laboratories, Danone, and Reckitt Benckiser. Agostoni C is an advisor for Ferrero and Dicofarm. Fleischer D is a consultant to Aquestive, Aravax, Genentech, Nasus , AllerGenis, Intrommune and DOTS Technology Corp. He has provided educational maternal for Nutricia. He has the following organizational declarations: DBV Technologies - Clinical Medical Advisory Board; Food Allergy & Anaphylaxis Connection Team - Medical Advisory Board; Food Allergy Research & Education - Clinical Advisory Board; National Peanut Board - Allergy Education Advisory Council. Greenhawt M is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, AllerGenis, Aravax, Glaxo Smith Kline, Prota, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the Eurpoean Academy of Allergy and Clinical Immunology; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice

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Parameters. Meyer R has grants from Danone, personal fees from Nutricia and Mead Johnson and is an advisor to CoMISS group from Nestle. Netting MJ has received honorarium to her institution for speaker fees from Nestle. Smith PK has provided lecture material and/or consultancy to Abbot, NNI, Danone. He is a PI for DBV and has received investigator-initiated funding from Nestle. O'Mahony L has provided consultancy with Alimentary Health, research grant from GSK. The following authors have no conflict of interest: Vanderlinden L, Untersmayr E, Roberts G, Roduit C, Palumbo MP, Palmer DJ, Nwaru BI, Muraro A, Maiorella A, Maslin K, Lunjani N, Groetch M, Glueck DH, Du Toit G, Ben-Abdallah M, Arshad S.H.

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Table 1 Nutritional factors assessed in observational studies

Food and dietary patterns	Asthma/Wheeze	Hayfever/Rhinitis	Eczema	Food Allergy	Sensitization
Total	62 papers [9-11,14-21,23,25-28,30-33,61-63,67-73,75-87,89,90,92-95,97-105,107,111-113]	19 papers [10,11,13,16,19,20,26,27,63,83-87,97,98,100,101,107]	38 papers [10,11,14,15,19,21,24,26,32,61,63,65,69,70,74,75,77-81,83,88-95,97,98,101,102,106,107,110,112]	5 papers [29,64,70,109,112]	19 papers [11-13,19,22,26,61,66,68-70,75,79,96,104,106-108,112]
Fruit and /or vegetables (Supplementary excel file 6 Fruits and Vegetables)	11 papers [15,23,31,62,68,71,83,93,100,102] Fruit, vegetables, leafy vegetables, roots and potatoes, citrus fruits, Malaceous fruits, berries, fruit and berry juices, Green and yellow vegetables, Cruciferous vegetables, Folate vegetables, apples	1 paper [100] classified as fruits, vegetables, leafy and root vegetables, berries, malicious, citrus fruit and juices;	4 papers [15,93,102,106] fruits, vegetables, citrus fruits, apples, green leafy vegetables, green and yellow vegetables, carrots, spinach, cabbage, celery, tomato, sweet pepper, salad, and juice	1 papers [109] fruit and berries, vegetables and roots	3 papers [12,96,106] fruits, vegetables, malicious fruits, citrus fruits, berries, apples, bananas, strawberry, exotic fruit, root vegetables, carrots, spinach, cabbage, celery, tomatoes, sweet pepper, salad, and fruit and vegetable juices
Fats and fatty fish (Supplementary excel file 5 Fish and Fats) Fat and fatty acid intake (4 papers), classified as total fat intake, omega 3 or omega 6 poly-unsaturated fatty acids or other types of fatty acids, and specific fatty acids (we also included fish intake and fish oil supplementation in this group);	12 papers [15,27,31,67,71,78,89,90,98-100,105]	4 [27,83,98,100]	9 [15,24,78,89-91,98,106,110]	1	4 papers [22,66,96,106]
Vitamin and mineral intake	33 papers	6 papers [10,13,20,97,101]	14 papers	4 papers	9 papers [12,13,61,70,79,96,104,108,112]

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(Supplementary excel file 4 vitamins and minerals)	9,10,17,18,20,21,23,25,28,30,31,33,61,70,72,76,77,79-82,85,92-94,101,104,111-113 multivitamin, pre-natal vitamins, folic acid, vitamin A, vitamin C, vitamin D, vitamin E, vitamin K,B-vitamins and their precursors, zinc, calcium, selenium, copper, magnesium, and manganese.	folate, riboflavin, retinol, vitamin A, vitamin D, vitamin E, vitamin K, and their precursors, zinc, copper, selenium, magnesium, calcium, manganese	10,21,61,70,77,80,81,92-94,97,101,110,112 vitamins A, C, E, and their precursors, vitamin D, vitamin B and folic acid, mineral intake zinc, calcium, copper, magnesium, manganese and selenium	64,70,109,112 antioxidant vitamins C, E, and B-carotene, vitamin D and folic acid, mineral intake, copper and zinc	Vitamin A, Vitamin C, Vitamin D, Vitamin E, Folic acids, Prenatal vitamins, Multivitamins, Anti-oxidants and their precursors, Zinc, Selenium
Other dietary exposures (Supplementary excel file 7 other foods)	25 papers 11,14,15,21,26,27,32,62,63,68,69,73,78,84,86,87,89,90,92,99,100,102,103,105,111 sugar, milk/dairy products, grains (pasta), nuts, meat, fish, chocolate candy, soft drinks/artificial sweeteners, egg, alcohol, glucose and dietary water	8 papers 11,26,27,63,84,86,87,100 sugar, milk/dairy products, cereals/grains, fish, seafood, meat, chocolate candy, nuts, soft drinks/artificial sweetener, alcohol.	22 papers 11,14,15,21,24,26,32,63,65,69,74,78,83,88-92,102,106,110 alcohol, probiotic drinks, fast foods, meat, dairy, cereals, fish and shellfish, chocolate, cheese, natto, eggs, cream, seeds and nuts.	1 papers 109 Cereal and dairy	7 papers 11,22,26,66,69,96,106sugar, fish, nuts, legumes, seeds, mild/dairy products, cereals/grains, egg, chocolate candy, juices and alcohol.
Food patterns (Supplementary excel file 8 dietary patterns)	8 papers 15,16,19,67,68,75,95,107 Mediterranean, Health conscious, Vegetarian, Prudent, Western, Confectionery, Traditional, Japanese, Vegetable, Fruit and white Rice, Seafood and	3 papers 16,19,107 Mediterranean, Health conscious, Traditional, Processed, Vegetarian, Confectionery, Japanese, Vegetable, Fruit and white Rice, Seafood and Noodles Pasta, Cheese	5 15,19,75,95,107 Mediterranean, Health conscious, Vegetarian, Prudent, Western, Confectionery, Traditional, Japanese, Vegetable, Fruit and white Rice, Seafood and	0	5 papers 12,19,22,68,75,96,106,107 Mediterranean diet, Alternate Healthy Eating Index modified for Pregnancy score , Prudent diet, Western diet, Vegetable, Fruit and white Rice, Seafood and Noodles, Pasta, Cheese and Processed meat, Vegetable, Fruit and white

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	Noodles Pasta, Cheese and Processed meat , Alternative Healthy Eating index	and Processed meat Vegetable, Fruit and white Rice as well as the Alternative Healthy Eating index.	Noodles Pasta, Cheese and Processed meat Vegetable, Fruit and white Rice (VFR) as well as the Alternative Healthy Eating index during pregnancy		Rice, Seafood and Noodles, Pasta, Cheese and Processed meat, Healthy Conscious, Traditional, Confectionery, Traditional and Vegetarian

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Table 2 : Food intake vs. RDA or AI

Wheeze/asthma				
Food/nutrient intake	**Reference***	**Intake**	**RDI or AI**	**% RDI or AI**
Alpha-tocopherol[23]	increase	6.5 mg	15 mg	*43%*
Calcium[92]	increase	571.1 mg	1000 mg	*57.1%*
folate[25]	increase	>578	600 ug	*>96.3%*
vitamin D[10]	reduce	4.69-35 µg	15 ug	31.2-233%
vitamin D[10]	reduce	3.51-4.68 µg	15 ug	*23.4-31.2%*
vitamin D[77]	reduce	724 IU (18.1 ug)	15 ug	**120%**
vitamin D[18]	reduce	4.86-17	15 ug	32.4-113%
vitamin D[18]	reduce	3.44-4.85	15 ug	*22.9-32.3*
vitamin D[85]	increase	8.2, 13, 16.5	15 ug	54.7, 86.7, 110%
Vitamin D[92]	reduce	5.1, 6.4	15 ug	*34, 42.7%*
vitamin E[10]	reduce	6.22-7.08 mg	15 mg	*41.5, 47.2%*
vitamin E[81]	reduce	7.07-30.30	15 mg	47.1-202%
vitamin E[18]	reduce	10.3-29.4	15 mg	*68.7-98%*
Vitamin E[93]	reduce	7.3 mg	15 mg	*48.6%*
Zinc[81]	reduce	14.25-30.30 mg	11 mg	**126-268%**
Zinc[93]	reduce	7, 8.5 mg	11 mg	*61.9-75.2%*
Omega 6[99]	reduce	<8.03g	13 g	*61.8%*
Alpha-Linolenic acid[99]	increase	<7.78g	13 g	*58.9%*
N-3 poly-unsaturated fatty acid[99]	increase	<2.24g	1.4 g	**160%**
n-3 poly-unsaturated fatty acid[90]	reduce	2.2g	1.4 g	**157%**
Alpha-Linolenic[90]	reduce	2.3g	1.4 g	**164%**
Vegetables[100]	increase	<149.1	375g	*39.7%*
Fruit[100]	increase	326.2	250g	130.5%
Vegetables[23]	reduced	206-286g/d	375g	*54.9-76.3%*
Free sugar[11]	increase	82.4-345.1g/day	<12 g	687%-2875.8%
Meat[90]	reduce	63.6g/d	71g	*89.6%*
Dairy products[92]	reduce	280.7 g/d	250g	**115.%**
Allergic rhinitis				
Vitamin D - food[101]	reduce	4.4-5.72 mg	15 ug	*29-38.1%*
Alpha-linolenic acid[98]	reduce	6.4-8.9 g	1.4g	457-635.7%
Fruit[100]	increase	145.7-1700 g/d	250g	58.3-680%
Atopic dermatitis				
Beta-carotene[93]	reduce	1923.9 mg and 4218.0 mg	770 ug	*41.5%% and 91.3%*
Vitamin D[21]	increase	8.6 µg/day	15 ug	*57%*
vitamin E[10]	reduce	2.32–2.9mg	15mg	*15%-0.19%*
Vitamin E[93]	reduce	86.7 mg/day	15mg	**578%**
Zinc[81]	reduce	10.81, 13.4, 22.27 mg/day	11 mg	95%, 117% 194%
Calcium[21]	reduce	677.6 mg/day	1000 mg	*67.8%*
Omega - 6[90]	increase	14.1	13 g	**107%**
Alpha-Linolenic acid[90]	increase	10.4-11.3 g	1.4 g	743% - 807%
Omega 6[91]	increase	10.6g/d	13 g/day	*81.5%*
Total fat[91]	increase	58.6/d	80g/d (range 53 –	*3.25%*

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			93 g)	
Alpha Linolenic acid[91]	increase	1.9	1.4 g/day	**136%**
Vegetables[93]	reduce	Total Veg 144.4g,	3 x 125 g	*39%*
Total dairy products[92]	reduce	120.8 g/day	500 ml/g per day	*24%*
Total dairy products[21]	reduce	255.3 g.day	500 ml/g per day	*50%*
Total fish[83]	reduce	>= 1x/week vs no intake	2-3 times per week	*33- 50%*
Food Allergy				
Vitamin C[112]	increase	*102-201*(mg/day)^2	85 mg	*120%-236%*
Copper[112]	increase	>2.6 (mg/day)^2	1mg	**260%**
Vegetable[109]	reduce	>324g/d (21/2 cups) vs 153-324 g/d) (1 – 2.5 cups)	3 cups	*75% - >100%*
Cereal[109]	reduce	Both having less than 143g/d (5 x 1 oz) and more than 230 g/d (8 x 1 oz)	240 g	*Decrease if <60% and >95%.*
Sensitization				
Vitamin C[112]	increase	130	85 mg	**216.7%**
Copper[112]	increase	1.6	1 g	**160%**
Free sugar[11]	increase	82.4-345.1g/d	<12 g	**687%-2875.8%**

Italic = below recommended intake; bold = above recommended intake; normal – stretch across lower than higher than recommended intake.

*listing only significant OR/RR/HR

Table 3: Summary table for systematic review

	Decreased				**Increased**			
Observational trials	**Vit/Min**	**Fats/fatty fish**	**Foods**	**Diet Pattern**	**Vit/Min**	**Fats/fatty fish**	**Foods**	**Diet Pattern**
Food allergy	*Copper* Vitamin C	NA	NA	NA	Vitamin D	NA	Vegetables	NA
Atopic Dermatitis	*Vitamin E* *Copper* *Calcium* *Zinc* *Beta-carotene* *Magnesium*	*Cholesterol* Arachidonic acid	Green vegetables *Dairy* Fruit (apples) Fish *Probiotic milk*	NA	Vitamin D Vitamin C	Vegetable oil Fatty fish Margarine Linoleic acid Omega-6 fatty acid Ratio omega3/omega6 Alpha-linolenic acid Total fat Monounsaturated fatty acids	Alcohol Shell fish Meat Fast Food Natto	NA
Asthma/wheeze	*Vitamin E*	DHA	Vegetables	*Mediterranean*	Folic acid	Omega-3 fatty	Fruit	NA

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	Zinc *Copper* *Manganese* Folic acid Vitamin D Vitamin C Alpha-tocopherol *Calcium* Vitamin K	Fatty fish Palmitic acid Arachidonic acid Alpha-linolenic acid Saturated fatty acid Olive oil Omega-3 fatty acid	Fruit (apples)	*Western*	Vitamin D Vitamin A Vitamin K Alpha-tocopherol Vitamin C	acid Alpha-linolenic acid	Vegetables	
Rhinoconjuctivitis	Vitamin D Vitamin A	Fatty fish Poly-unsaturated fatty acid Alpha linolenic acid	Alcohol Fish *Probiotic foods* *Peanut and pistachio*	NA	Vitamin D	Butter Omega 6/omega 3 ratio	Fruit	NA
Sensitization	*Vitamin C* *Copper* Vitamin D	Butter Omega-6 fatty acids Poly-unsaturated fatty acid	fish	*Mediterranean* *Soy,Fish, nuts*	NA	Vegetable fat Oily fish	Fruit Vegetable (celery and sweet pepper) Free sugar	Health conscious Vegetarian
	Decreased				**Increased**			
RCTs	**Vit/Min**	**Fats/fatty fish**	**Foods**	**Diet Pattern**	**Vit/Min**	**Fats/fatty fish**	**Foods**	**Diet Pattern**
Food allergy	NA	No effect	NA	NA	NA	No effect	NA	NA
Atopic Dermatitis	No effect	No effect	NA	NA	No effect	No effect	NA	NA
Asthma/wheeze	Vitamin D	No effect	NA	NA	NA	No effect	NA	NA
Rhinoconjuctivitis	NA	No effect	NA	NA	NA	NA	NA	NA
Sensitization	No effect	No effect	NA	NA	No effect	No effect	NA	NA

*Italic = only associated with reduced outcomes

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Figures for Systematic review on maternal diet

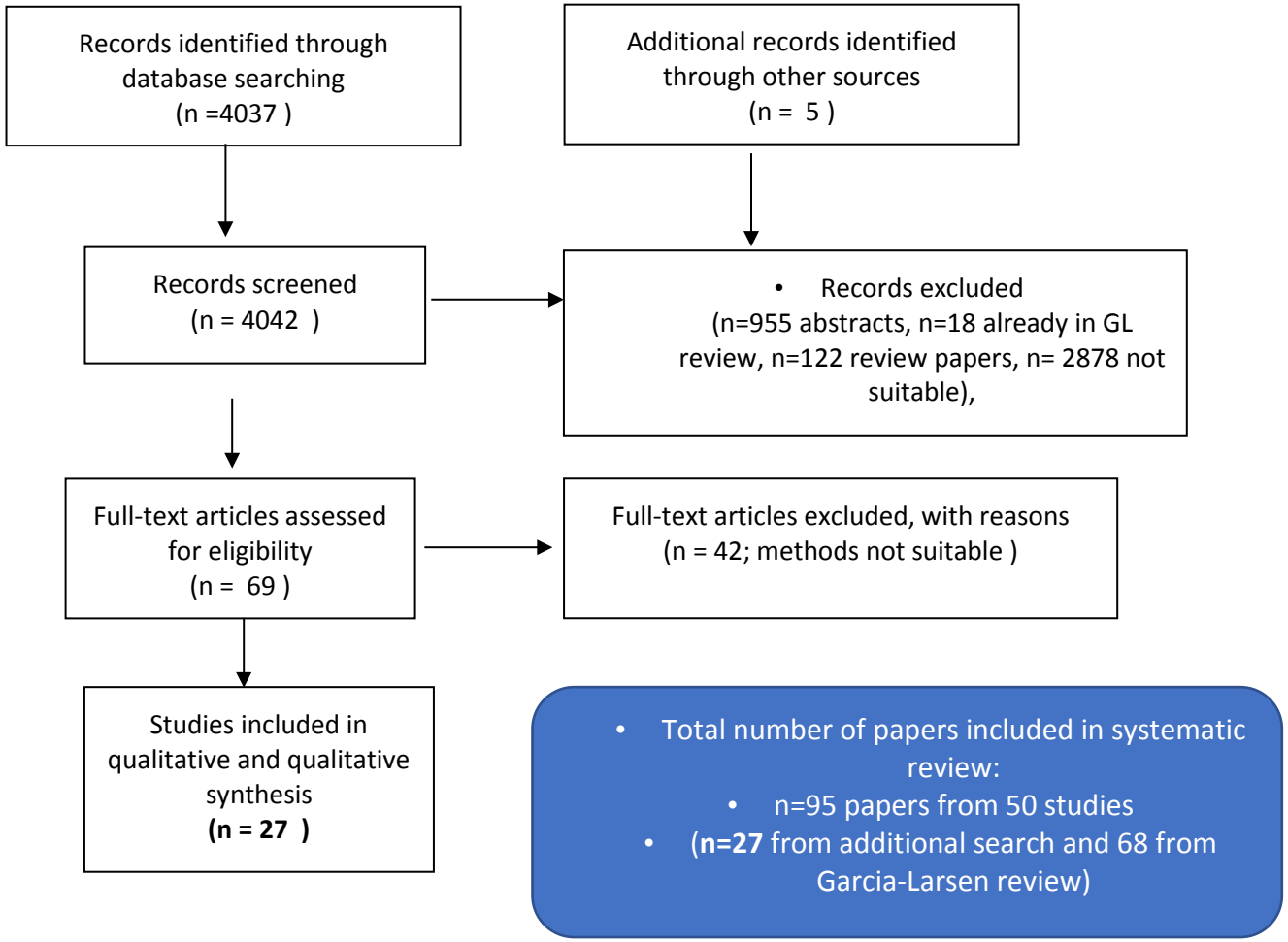


Figure 1: Flow chart for study inclusion

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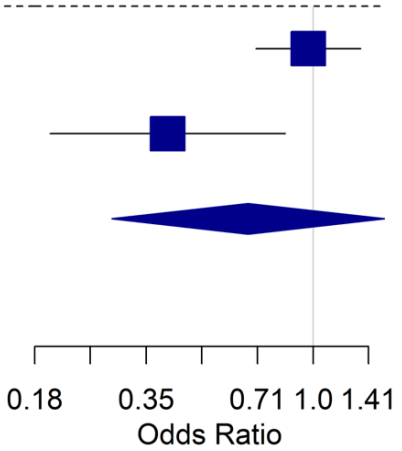
Anti-oxidants: Vitamin C and Vitamin E (2a)

Study	Exposure	Treatment events / total	Control events / total
Greenough 2010	Vitamins C and E	100/386	97/366
McEvoy 2014	Vitamin C	15/70	31/77

Random Effects Model

Test for Heterogeneity: $\chi^2 = 4.59$, df = 1, p-value = 0.032, $I^2 = 78.2\%$

Overall Effect: 0.67, 95% CI (0.29, 1.56)



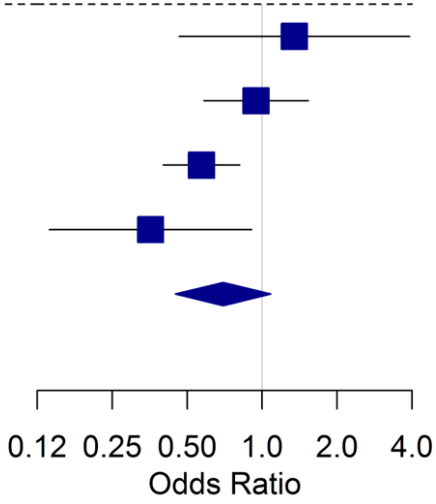
Omega-3 fatty acids *2 b)

Study	Exposure	Treatment events / total	Control events / total
Noakes 2012	Salmon	11/46	7/37
Best 2018	n-3 LCPUFA	38/290	38/276
Bisgaard 2016	n-3 LCPUFA	66/346	102/349
Olsen 2008	n-3 PUFA fish oil	8/263	11/136

Random Effects Model

Test for Heterogeneity: $\chi^2 = 6.12$, df = 3, p-value = 0.106, $I^2 = 51.0\%$

Overall Effect: 0.70, 95% CI (0.45, 1.08)



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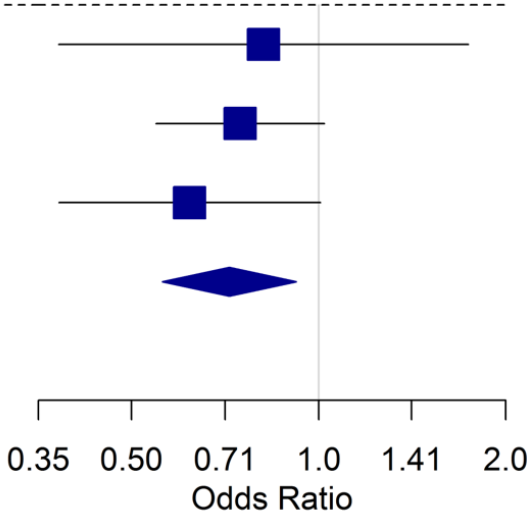
Vitamin D (2c)

Study	Exposure	Treatment events / total	Control events / total
Goldring 2013	Vitamin D	26/108	14/50
Litonjua 2016	Vitamin D	98/405	120/401
Chawes 2016	Vitamin D	32/278	47/271

Random Effects Model

Test for Heterogeneity: $\chi^2 = 0.52$, df = 2, p-value = 0.769, $I^2 = 0.0\%$

Overall Effect: 0.72, 95% CI (0.56, 0.92)

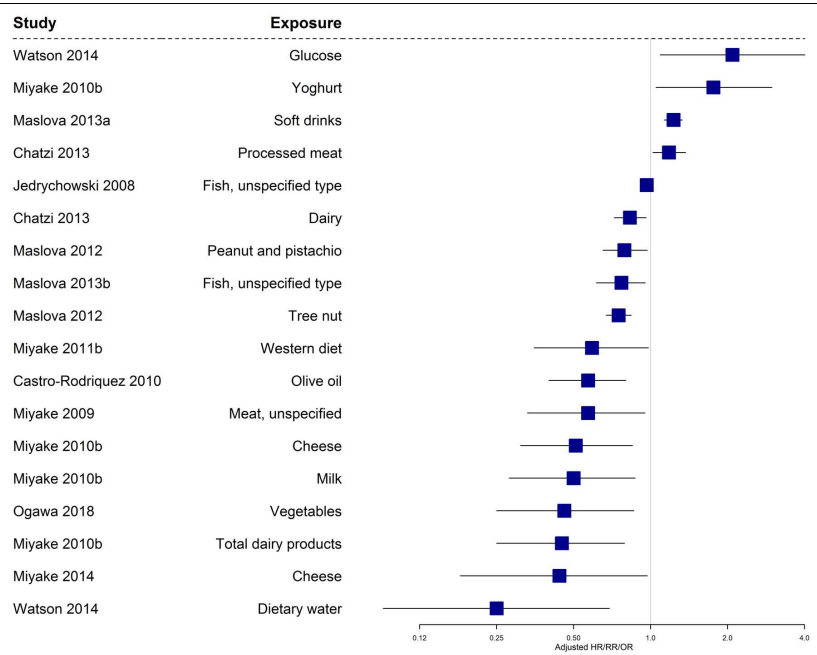


Figures 2a, b, c: Randomized controlled trials with asthma/wheeze as an outcome

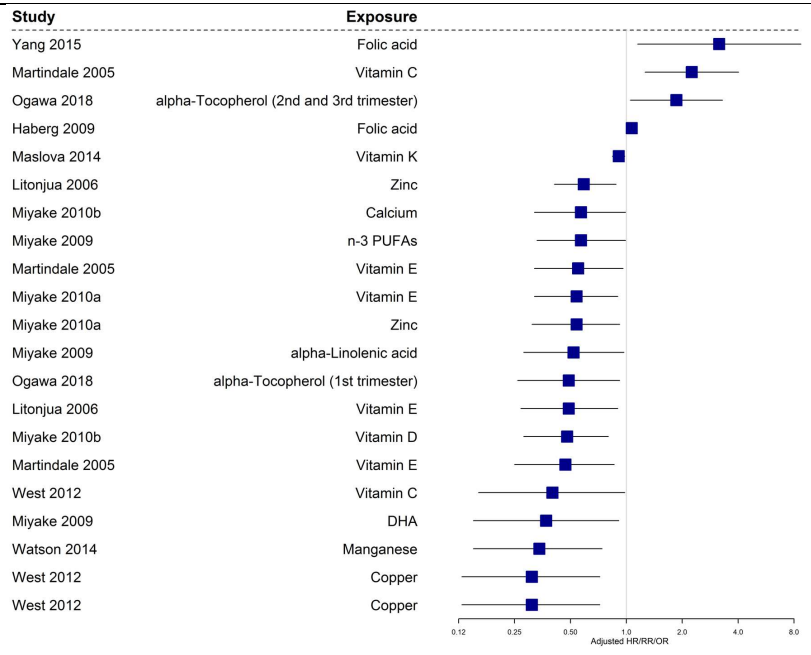
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3 a: Foods, food groups and food patterns



3 b: Vitamins, minerals and fatty acids

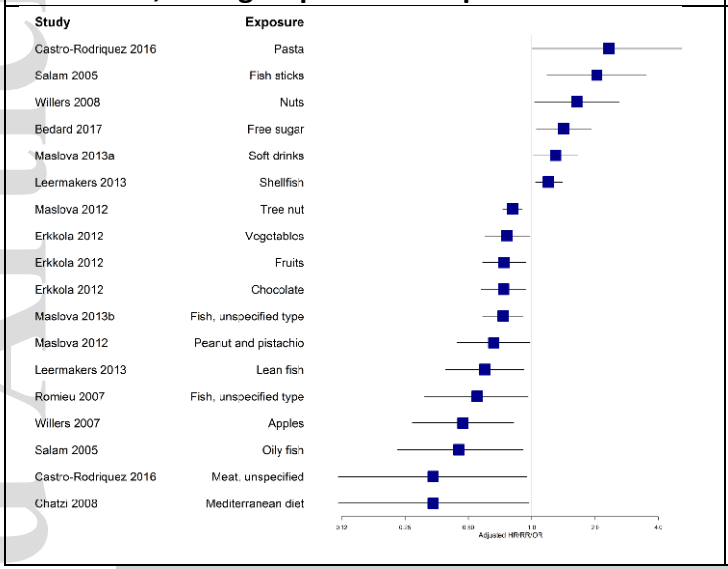


Figures 3 a and b : Observational studies with asthma/wheeze (age 0- <3 years) as an outcome

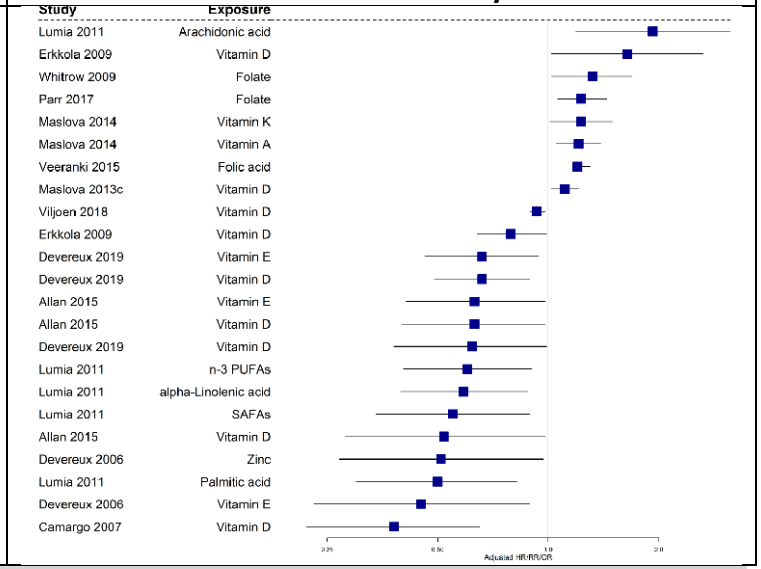
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4 a: Foods, food groups and food patterns



4 b: Vitamins and Minerals and fatty acids



Figures 4 a and b : Observational studies with asthma/wheeze (age 3 years and above) as an outcome

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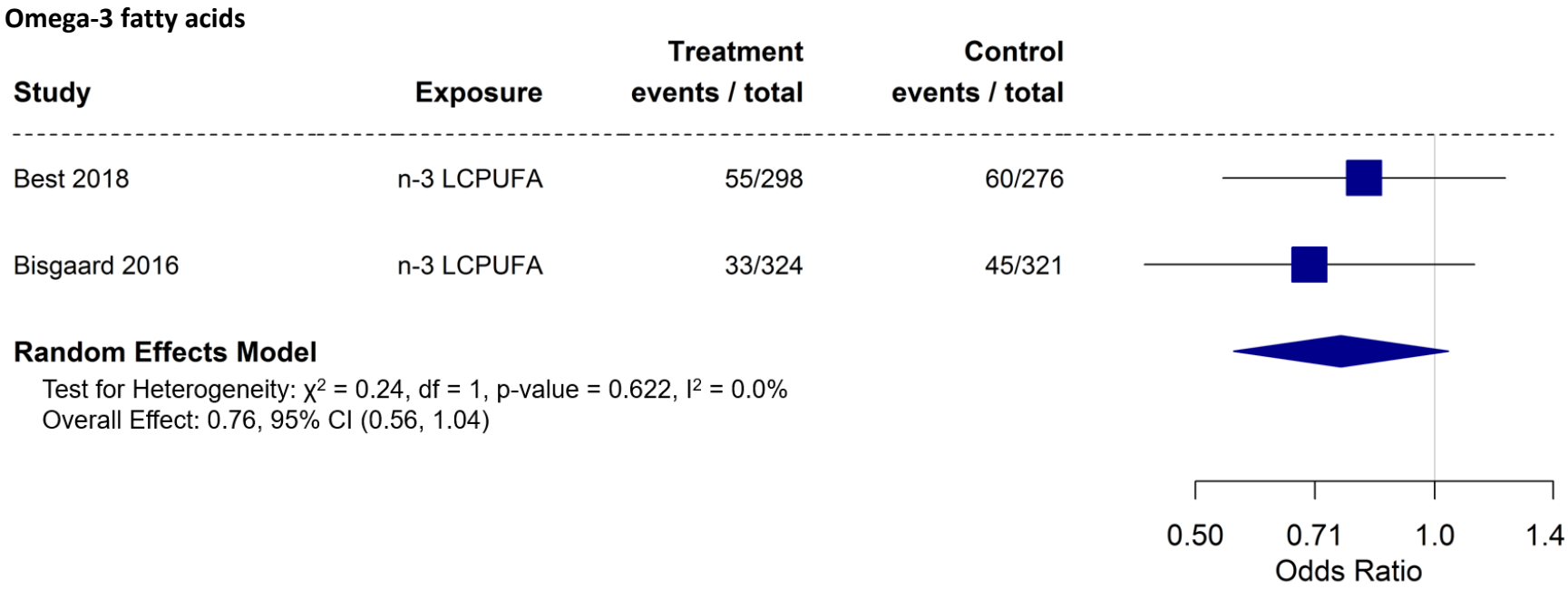
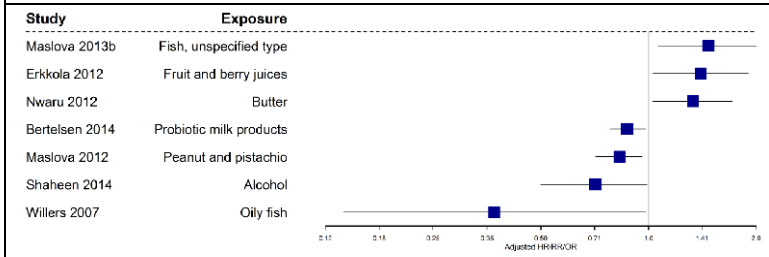
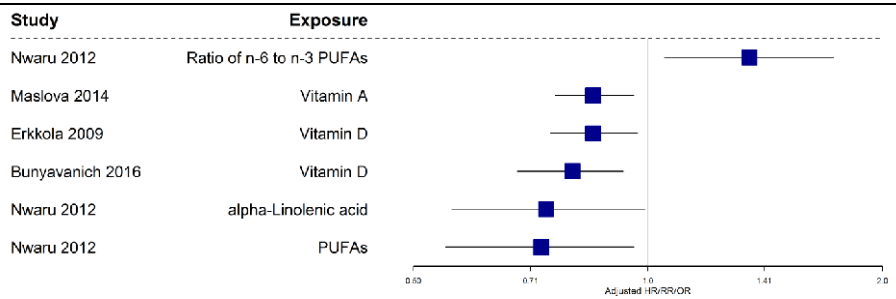


Figure 5: Randomized controlled trials with allergic rhinitis/hay fever as an outcome

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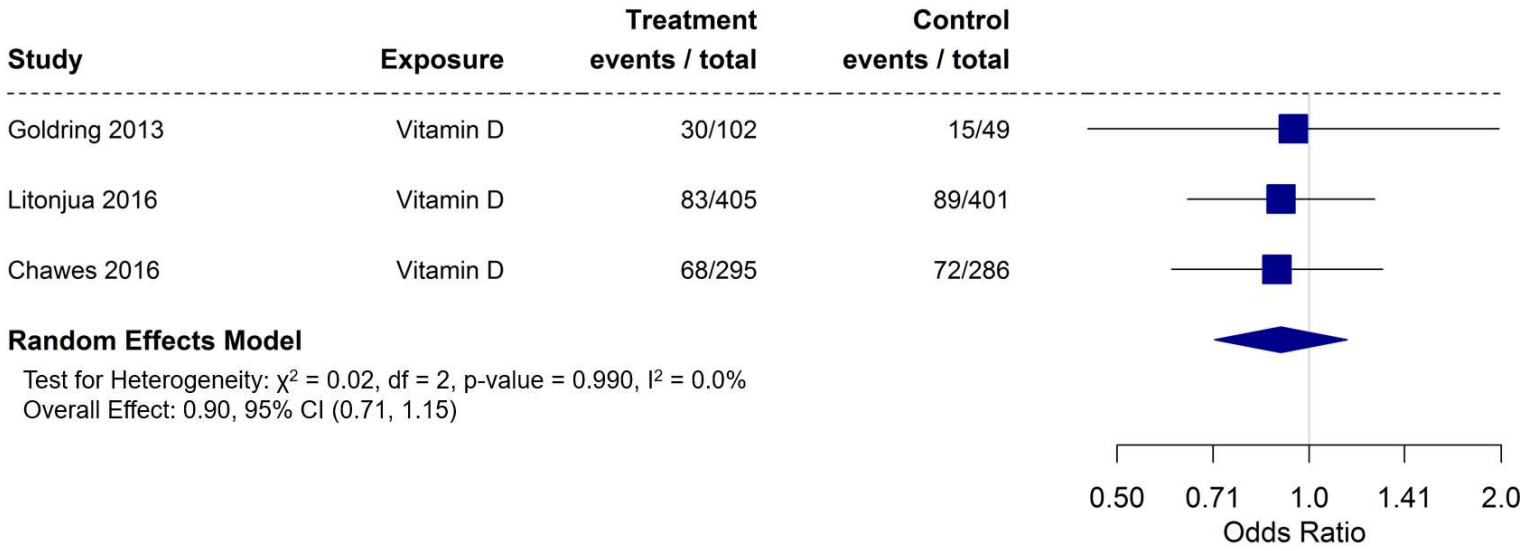
6 a: Foods, food groups and food patterns	6 b: Vitamins, minerals and fatty acids
	

Figures 6 a and b: Observational studies with allergic rhinitis/hay fever as an outcome

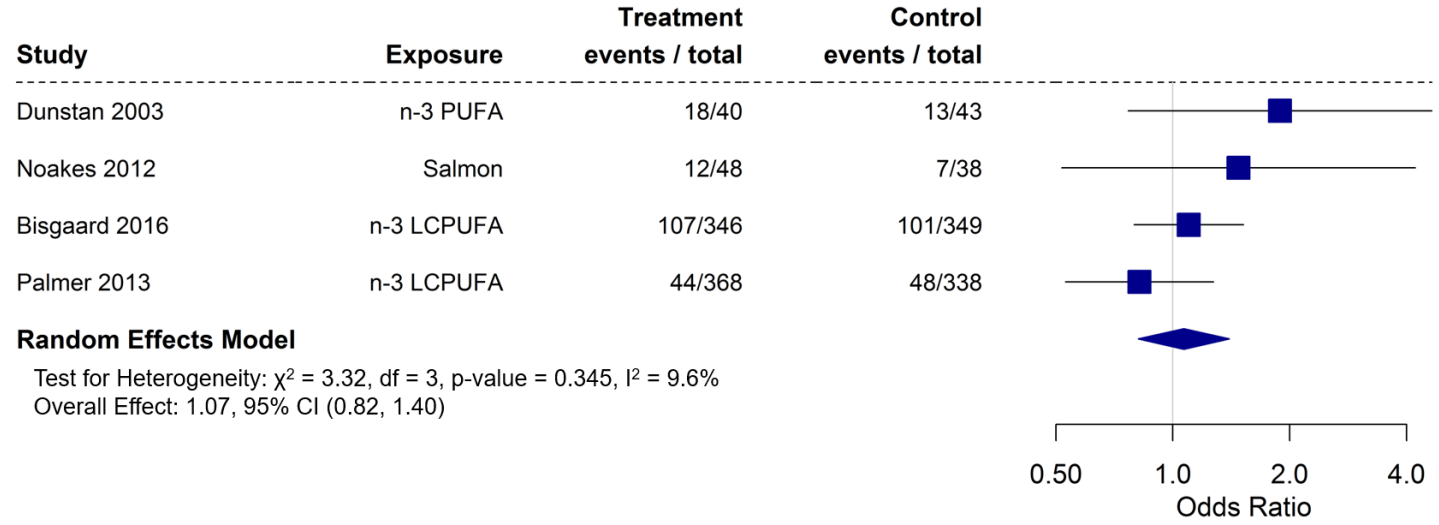
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Vitamin D (7a)



Omega- 3 fatty acids (7b)

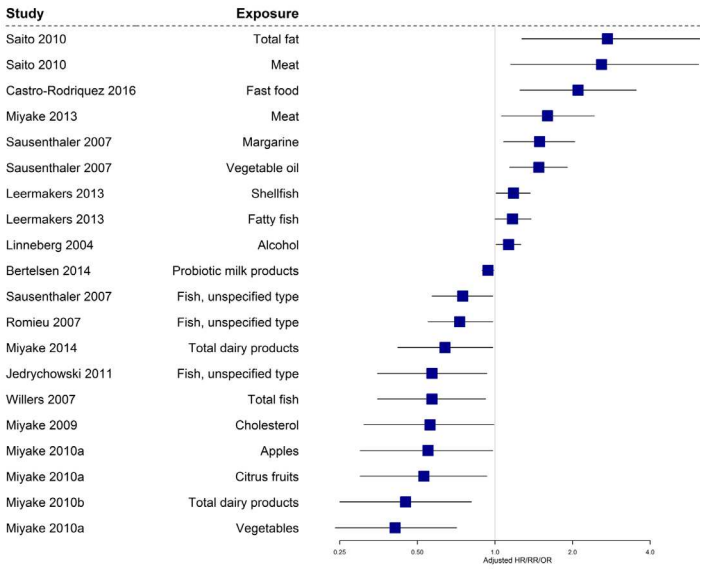


Figures 7a and b: Randomized controlled trials with atopic dermatitis as an outcome

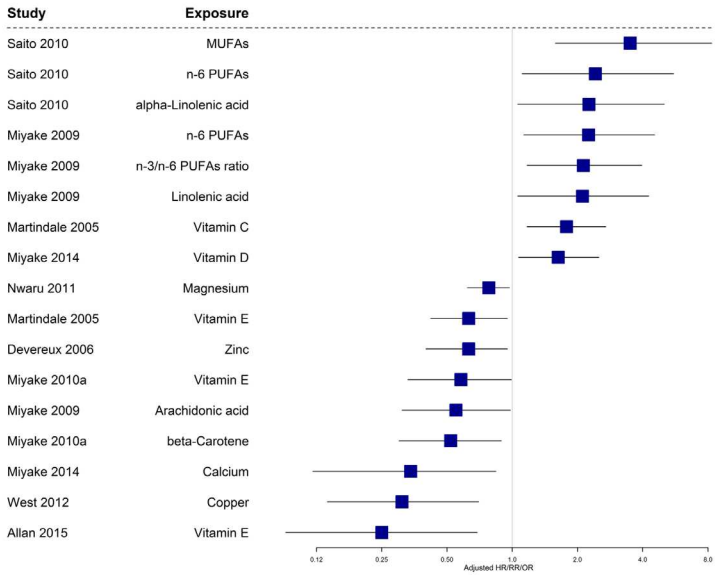
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8 a: Foods, food groups and food patterns



8 b: Vitamins, minerals and fatty acids



Figures 8a and 8 b: Observational studies with atopic dermatitis as an outcome

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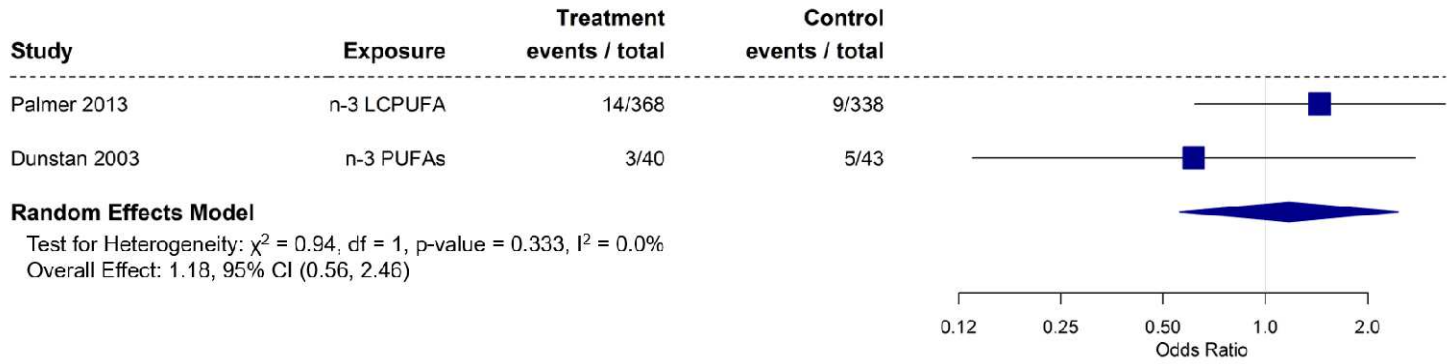


Figure 9: Randomized controlled trials with food allergy as an outcome

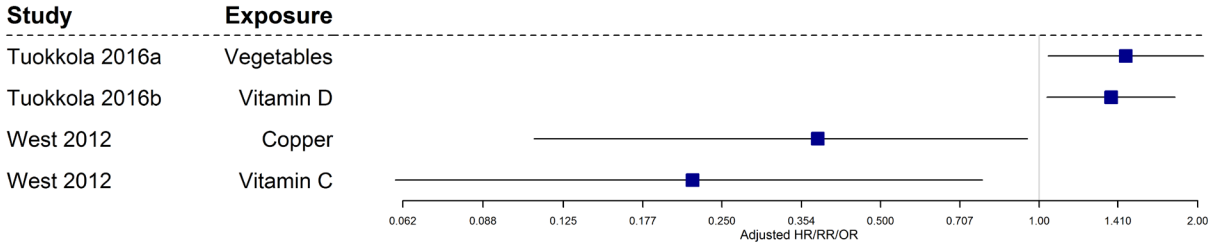
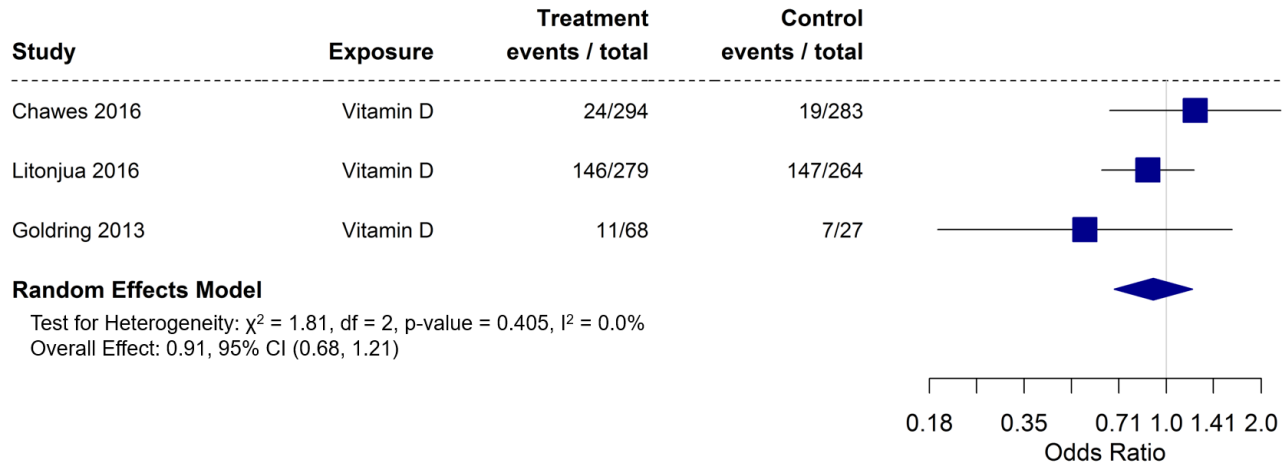


Figure 10: Observational studies with food allergy as an outcome

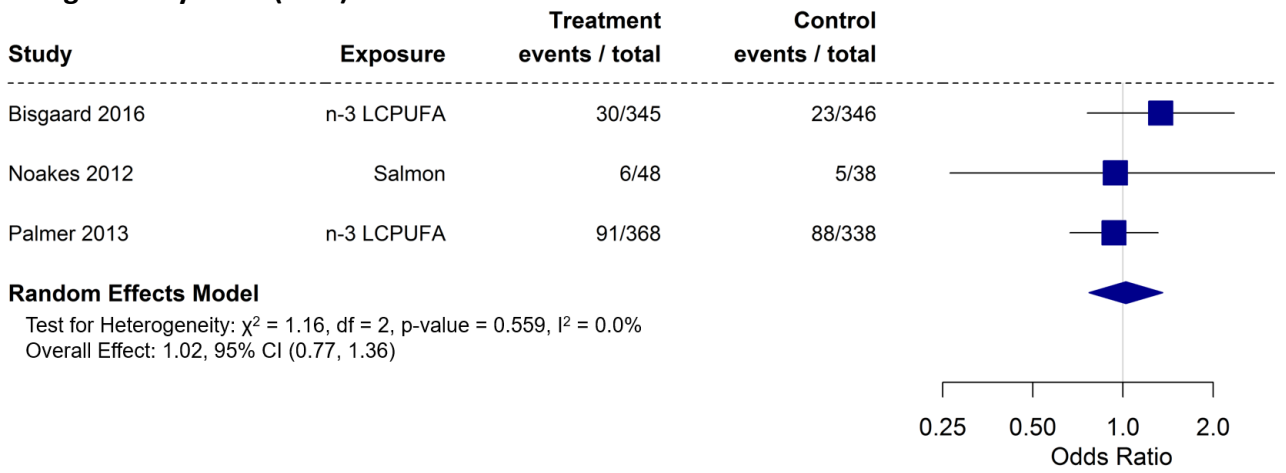
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Vitamin D (11 a)



Omega-3 fatty acids (11 b)

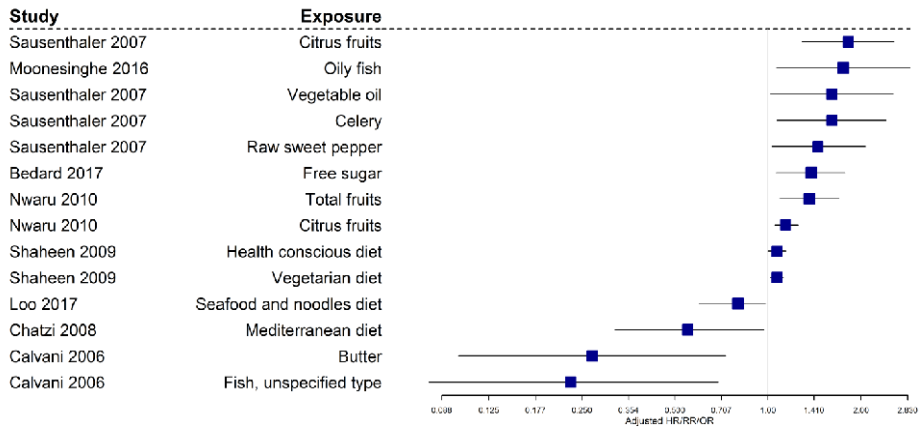


Figures 11a and b: Randomized controlled trials with "any" sensitization as an outcome

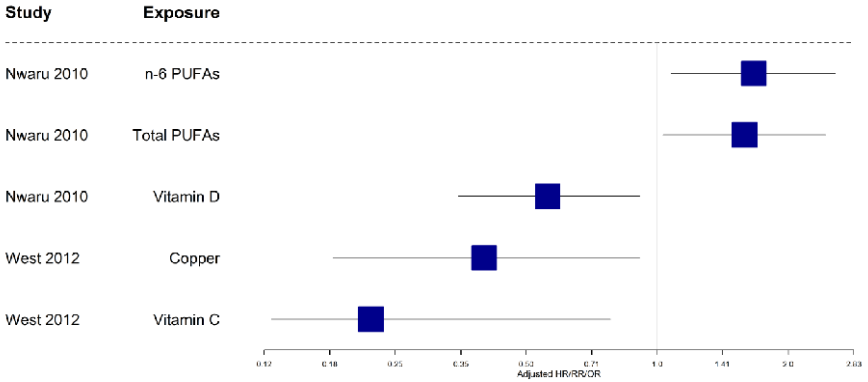
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12 a. Foods, food groups and food patterns



12 b. Vitamins, minerals and fatty acids



Figures 12 a and b: Observational studies with "any" sensitization as an outcome

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