Original article

Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis

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Background: Epidemiologic studies suggest that deficiencies of the nutrients selenium; zinc; vitamins A, C, D, and E; and low fruit and vegetable intake may be associated with the development of asthma and allergic disorders.
Objectives: To investigate the evidence that nutrient and food intake modifies the risk of children developing allergy.
Methods: We systematically searched 11 databases. Studies were critically appraised, and meta-analyses were undertaken.
Results: We identified 62 eligible reports. There were no randomized controlled trials. Studies used cohort (n = 21), case-control (n = 15), or cross-sectional (n = 26) designs. All studies were judged to be at moderate to substantial risk of bias. Meta-analysis revealed that serum vitamin A was lower in children with asthma compared with controls (odds ratio [OR], 0.25; 95% CI, 0.10-0.40). Meta-analyses also showed that high maternal dietary vitamin D and E intakes during pregnancy were protective for the development of wheezing outcomes (OR, 0.56, 95% CI, 0.42-0.73; and OR, 0.68, 95% CI, 0.52-0.88, respectively). Adherence to a Mediterranean diet was protective for persistent wheeze (OR, 0.22; 95% CI, 0.08-0.58) and atopy (OR, 0.55; 95% CI, 0.31-0.97). Seventeen of 22 fruit and vegetable studies reported beneficial associations with asthma and allergic outcomes. Results were not supportive for other allergic outcomes for these vitamins or nutrients, or for any outcomes in relation to vitamin C and selenium.
ConclusionThe available epidemiologic evidence is weak but nonetheless supportive with respect to vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet for the prevention of asthma. Experimental studies of these exposures are now warranted. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: *Allergy, antioxidants, asthma, atopy, diet, foods, nutrients*

Abbreviations used
ISAAC: International Survey of Allergies and Asthma in Childhood
OR: Odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT: Randomized controlled trial

In westernized countries, asthma and atopic disease are public health concerns because of their high prevalence, associated morbidity, and substantial health care and societal costs. In the United States, 8.5% of children and 6.7% of adults have asthma, equating to about 14 million adults and 6 million children with asthma.[1] It has been estimated that the direct and indirect costs of asthma to the US economy are about $18 billion annually.[2] In westernized countries, atopic dermatitis is also common, affecting up to 30% of preschool children, 15% to 20% of school-age children, and 7% of adults,[3] with an economic impact similar to that of asthma.[4]

The prevalence of asthma and atopic disease has markedly increased in the westernized countries since the 1970s.[1,5-7] It has been hypothesized that these increases are a consequence of changing diet and/or nutrient status. Two contradictory hypotheses relate the increase in asthma/atopy to decreasing,[8] and increasing, intake of antioxidant-rich foods.[9] Similarly, the increase in asthma and atopic disease has been attributed to widespread vitamin D supplementation for rickets prophylaxis[10] and widespread vitamin D insufficiency.[11] In recent years, studies have reported associations between childhood asthma/atopic disease and either maternal nutrient status during pregnancy and/or childhood nutrient status. These observational data have led to calls for randomized controlled trials (RCTs) of early-life dietary interventions, particularly in pregnant women.[12] Although there have been a number of reviews of the literature relating diet and nutrient status in adults and children, to date there has been no systematic review of the epidemiologic and experimental literature that critically assesses the potential role of diet in the primary prevention of asthma and atopic disease. Although a number of excellent review articles are available, these have not been subject to the rigor and critical assessment of a systematic review and have furthermore not included the more recent data on maternal/early-life diet.[13]

In the absence of any existing systematic critique of the epidemiologic and experimental literature, we undertook a systematic review with a view to assessing critically the potential role of diet in the primary prevention of asthma and atopic disease in children up to the age of 16 years. This systematic review does not cover the field of dietary fats because systematic reviews of this literature have recently been conducted.[14,15]

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METHODS

This work was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[16,17] Included studies were all those relevant to children (ie, pregnant women, infants, and children ≤16 years) that investigated the role of nutrients and foods for the primary prevention of asthma and atopic disorders in children—that is, cohort, case-control, and cross-sectional studies with modeling; and all intervention studies—that is, RCTs, quasi-RCTs and controlled clinical trials. Also included were studies investigating nutrient deficiency and/or increased nutrient consumption (diet or supplementation).

The main outcome of interest was the primary prevention of asthma/wheezing outcomes and atopic disorders as assessed by any validated measure. Secondary outcomes were measures of increased/decreased disease severity, health economics, and data on adverse effects. The outcome terminologies presented in this report (eg, recurrent wheeze) are those used in the original publications.

Eleven international databases were searched for the period January 1988 to May 2009 by using a detailed search strategy (see this article's Appendix E1 in the Online Repository at www.jacionline.org). The bibliographies of eligible studies were scrutinized to identify additional possible studies.

Titles and abstracts of identified studies were checked and independently reviewed by 2 of the researchers (U.N., G.D.). The full text of all potentially eligible studies was assessed for eligibility against the predefined inclusion criteria. Unpublished research and research in progress was identified by using key Internet-based databases—http://www.clinicaltrials.gov and http://www.controlled-trails.com—and by contacting international experts in the field (see this article's Appendix E2 in the Online Repository at www.jacionline.org).

The methodologic quality of included observational studies was assessed by using the Critical Appraisal Skills Programme. Each parameter of study quality was independently graded by a panel of 3 reviewers (A.S., G.D., U.N.): A, low risk of bias; B, moderate risk of bias; and C, high risk of bias. An overall assessment for each article using the same 3 criteria was made after discussion and by consensus. Because G.D. was an author of some of the reviewed publications, he did not participate in the review of these studies.

Statistical methods

The clinical and the statistical appropriateness of meta-analysis were considered for all exposures/outcomes. In keeping with published guidance,[17] we chose to pool data from cohort and case-control studies into separate meta-analyses. Appreciable heterogeneity was assumed if I^2 >40%. Meta-analysis was undertaken by using fixed effect modeling if I^2 <40%, and random effects modeling was used if I^2 ≥40%. In contrast with fixed effect modeling, random effects modeling does not assume a single underlying effect size and therefore generates more conservative estimates of precision. The net effect is that these 2 modeling techniques result in essentially identical point estimates of effect, but that the width of the 95% CIs around these estimates is wider with the random effects–derived models. We calculated pooled means for continuous outcomes and odds ratios (ORs) with 95% CIs for categorical outcomes.

RESULTS

Our searches identified 14,747 potentially relevant published papers; 62 of these satisfied our inclusion criteria and were included in the systematic review (Fig 1).

We found no published RCTs; included studies used cohort (n = 21),[18-38] case-control (n = 15),[39-53] cross-sectional (n = 25),[54-78] or ecologic designs (n = 1)[79] (see this article's Table E1 in the Online Repository at www.jacionline.org).

Overall, we undertook 9 meta-analyses. Three used fixed effect modeling, and for the remaining 6, we used random effects modeling.

Vitamin A

Description of studies. Seventeen studies reported on the association between vitamin A and its constituents (retinol, carotenoids) and asthma or atopic outcomes (see this article's Table E2 in the Online Repository at www.jacionline.org).[23,28,29,33,39,43,44,46,48,49,52,65-67,69,73,79] The main limitations in this body of evidence were the poor matching of cases and controls, investigators' inability to assess vitamin A intake comprehensively, and a failure to adjust for potentially important confounding factors.

Main findings. Results were inconsistent, with nearly equal numbers of studies reporting either no association or potentially beneficial associations; meta-analysis of 2 comparable case-control studies[39,48] in children with asthma revealed that higher vitamin A levels were associated with a reduced risk of developing asthma (OR, 0.25; 95% CI, 0.10-0.40; Fig 2). There was, however, no clear relationship between maternal intake of β-carotene and risk of wheezing in children at age 2 years from pooling the results of the 2 comparable cohort studies (OR, 1.05; 95% CI, 0.76-1.44)[28,29] (see this article's Fig E1 in the Online Repository at www.jacionline.org). Because of the heterogeneity of study designs and findings for other atopic outcomes, additional meta-analyses were not possible.

Summary of evidence. Overall, the body of evidence from these studies was judged to be methodologically weak, but possibly suggestive of an association between reduced vitamin A and childhood asthma, but not between maternal vitamin A intake during pregnancy and childhood wheeze. Because the majority of the studies reporting beneficial outcomes used either cross-sectional or case-control designs, it is not possible to conclude whether the association with vitamin A represented causality or was the consequence of the oxidative stress associated with asthma/atopic disease.[80]

Vitamin C studies

Description of studies. Fourteen articles reported on the association between vitamin C and asthma or atopic outcomes in children[23,28,29,43,46,49,52,59,65-67,69,72,73] (see this article's Table E3 in the Online Repository at www.jacionline.org).

Main findings. Two birth cohort studies were sufficiently similar to allow meta-analysis; this demonstrated that there was no association between wheezing in 2-year-old children and vitamin C intake by pregnant mothers (OR highest vs lowest intake, 1.30; 95% CI 0.47-3.63; see this article's Fig E2 in the Online Repository at www.jacionline.org).[28,29]

Four case-control studies investigated the relationship between vitamin C and atopic sensitization, wheeze, or asthma-related outcomes, with most reporting no association[43,49,52]; 1, however, reported a potentially beneficial association between serum ascorbate and childhood asthma, but the effect sizes were small and of questionable clinical relevance.[46] All 4 case-control studies were graded C for quality. Meta-analyses of these studies were not considered appropriate.

Seven cross-sectional studies[59,65-67,69,72,73] also reported no association between vitamin C and atopy, self-reported current wheezing, or lung function,[59,67,69,72] or potentially beneficial associations between vitamin C and asthma or lung function.[26,67,73] Meta-analyses of the cross-sectional studies were not possible because of inconsistencies of design, exposure, and outcome measurement.

Summary of evidence. Overall, the body of evidence was judged to be methodologically weak and unsupportive of the possible effectiveness of vitamin C to prevent atopic outcomes.

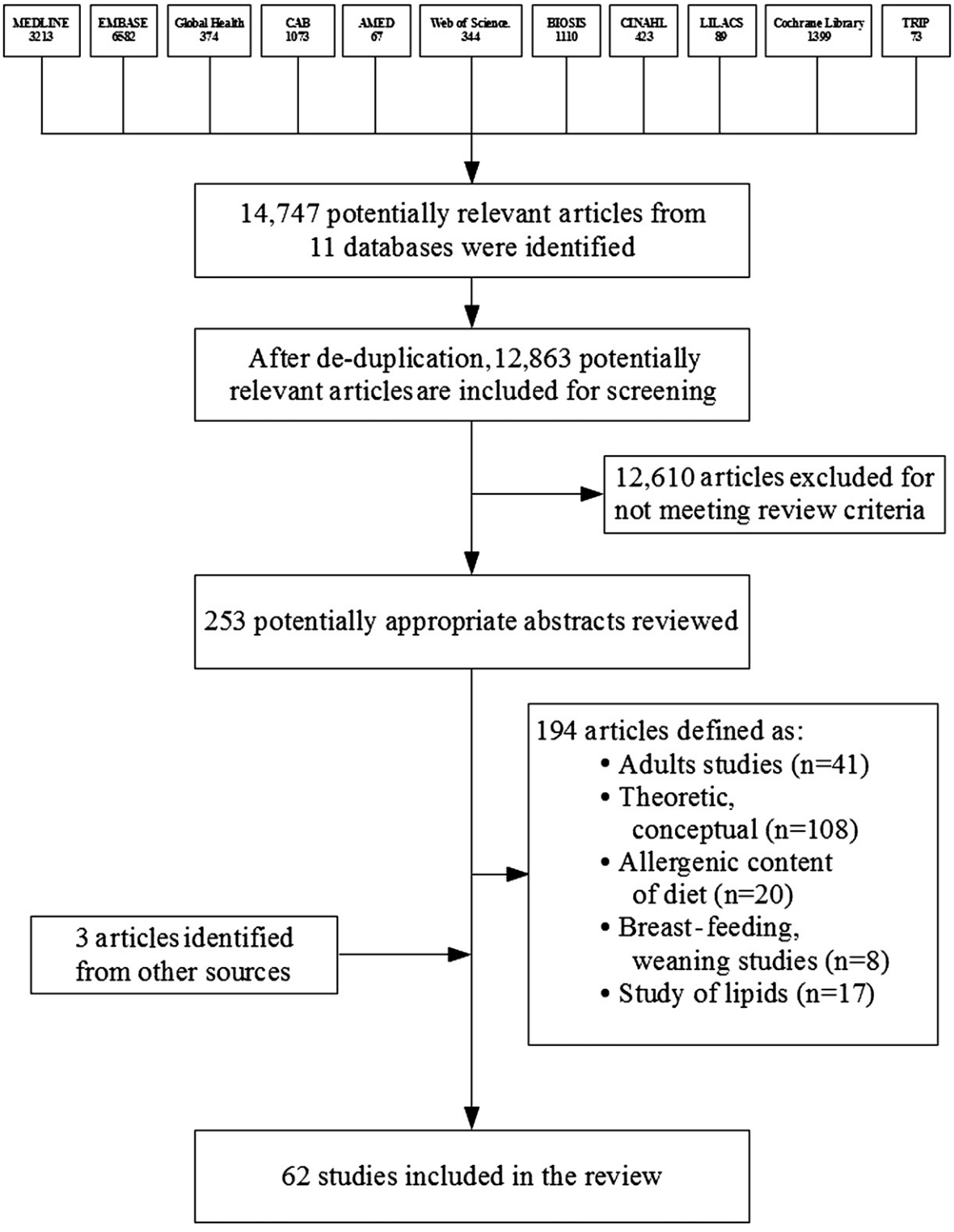

FIG 1. PRISMA flow diagram. *AMED*, Allied and Complementary Medicine Database; *BIOSIS*, BioSciences Information Service of Biological Abstracts; *CAB Direct*, Commonwealth Agricultural Bureau; *CINAHL*, Cumulative Index to Nursing and Allied Health Literature; *Cochrane Library*, Cochrane Library's medical and healthcare database; *EMBASE*, Excerpta Medica Database; *LILACS*, Latin American and Caribbean Health Sciences; *MEDLINE*, Medical Literature Analysis and Retrieval System Online; *TRIP*, Turning Research Into Practice; *Web of Science*, Thomson Reuters academic citation index.

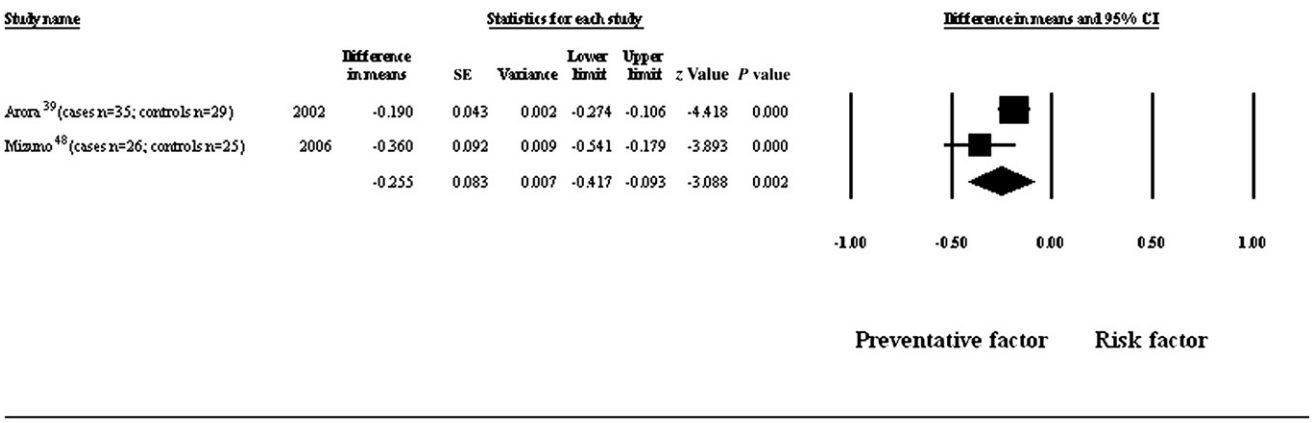

FIG 2. Association between serum vitamin A and asthma in children (case-control).

Vitamin E studies

Description of studies. Fifteen studies reported the association between asthma/atopy–related outcomes and mothers' vitamin E intake or serum/cord blood vitamin E levels or children's vitamin E status (see this article's Table E4 in the Online Repository at www.jacionline.org).[23,28,29,32,43,44,46,49,52,65-67,69,73,79]

Main findings. Four reports from 3 birth cohort studies consistently reported beneficial associations between maternal vitamin E intake and childhood asthma/wheeze outcomes.[23,28,29,32] Critical appraisal of these cohort studies raised concerns regarding the risk of information bias and loss to follow-up rates, and these studies were therefore graded C for quality. These cohort studies did, however, have the strengths of using objective measures of exposure and clinically relevant subjective and objective measurements of outcomes. Meta-analysis of the data from the 3 cohort studies showed higher maternal vitamin E intake during pregnancy to be associated with a significant decrease in the odds of wheezing in children at age 2 years (OR, 0.68; 95% CI, 0.52-0.88; $P = .004$; Fig 3).[28,29,32]

All 5 case-control studies were considered weak in design and hence were graded C for quality.[43,44,46,49,52] Four of the 5 studies were flawed in that they failed to adjust for potential confounding factors.[44,46,49,52] Three of the studies reported potentially beneficial associations,[43,44,46] and 2 reported no associations.[49,52] Meta-analyses of the case-control studies were not conducted because of clinical heterogeneity of studies.

Six cross-sectional studies investigated the associations between intake or serum levels of vitamin E in children and sensitization, atopic eczema, current wheeze, allergic rhinoconjunctivitis, lung function, and asthma outcomes.[65-67,69,73,79] In 1 study, lower vitamin E intake was associated with reduced ventilatory function[65]; the remaining 5 studies reported no associations between vitamin E and ventilatory function, atopic sensitization, allergic rhinoconjunctivitis, or asthma.[66,67,69,73,79] Meta-analysis was not possible because of variations in study design.

Summary of evidence. Overall, the body of evidence from these studies was judged to be methodologically weak, but in view of the positive associations identified in the large and more robust cohort studies, sufficiently encouraging to warrant experimental studies of the possible effectiveness of vitamin E.

Vitamin D studies

Description of studies. Eight studies reported associations with vitamin D[18,19,21,24,26,27,31,70] (see this article's Table E5 in the Online Repository at www.jacionline.org). We found 7 cohort studies. Four cohort studies reported that higher maternal vitamin D intake during pregnancy may decrease the risk of wheezing in early childhood.[19,21] Two cohort studies reported on the association between maternal vitamin D intake and childhood asthma at age 5 years, with 1 study reporting no association[21] and 1 reporting a beneficial inverse association.[24] In contrast, 2 other cohort studies reported adverse associations between maternal blood vitamin D levels during pregnancy or high-dose vitamin D supplementation during infancy and childhood asthma, atopic dermatitis, and/or allergic rhinitis.[26,27]

Main findings. Pooled analysis of 4 large cohort studies[19,21,24,31] showed that higher maternal vitamin D intake was associated with reduced odds of wheezing (ie, either recurrent wheezing/wheeze in the previous year (OR, 0.56; 95% CI, 0.42-0.73; $P < .001$; Fig 4). Pooled analysis from 2 studies showed[21,24] that maternal vitamin D intake was not associated with asthma in children age 5 years (see this article's Fig E3 in the Online Repository at www.jacionline.org). We could not undertake meta-analyses for other outcomes.

One cross-sectional study found that early-life cod liver oil supplementation was associated with increased atopic sensitization (adjusted OR, 1.78; 95% CI, 1.03-3.07).[70] However, this study was problematic in that it did not fully adjust for all relevant confounding factors.

Summary of evidence. Overall, the body of evidence from these observational studies was judged to be methodologically weak but supportive of an association between maternal vitamin D intake and childhood wheeze.

Selenium studies

Description of studies. Ten studies assessed association with selenium[22,34,36,40,43,47,49,50,69,73] (see this article's Table E6 in the Online Repository at www.jacionline.org).

Main findings. Three reports, including 2 large birth cohort studies, assessed associations between selenium concentrations

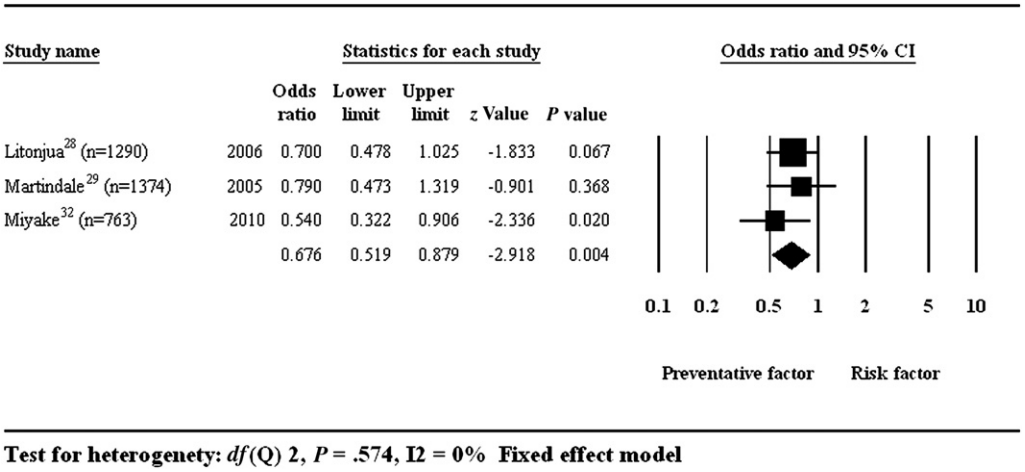

FIG 3. Association between mothers' intake of vitamin E and wheezing in the second year of life (cohort).

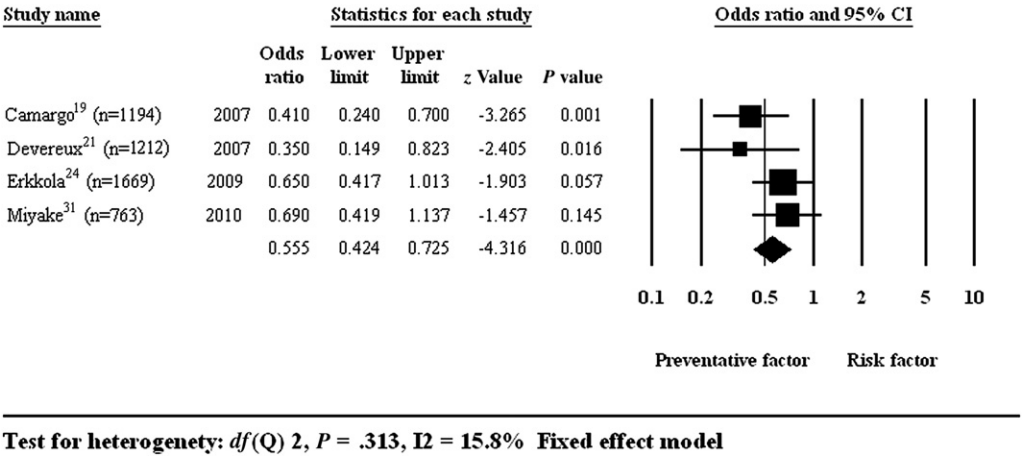

FIG 4. Association between mothers' intake of vitamin D and recurrent wheeze or wheeze in previous year in children (cohort).

measured in maternal blood, umbilical cord, and early childhood and related these to childhood wheezing, asthma, or atopic sensitization.[22,34,36] One large cohort study concluded that higher selenium levels in maternal plasma during early pregnancy and cord blood were associated with a reduced risk of early (at 2 years) childhood wheezing, but not asthma, because the associations were absent at age 5 years.[22] Another cohort study also found higher cord selenium to be associated with a reduced risk of persistent wheeze (OR, 0.67; 95% CI, 0.45-0.99).[34] Pooled analysis of original data from umbilical cord levels in these 2 studies revealed nonsignificant associations with wheezing outcome measures in early childhood (OR, 0.83; 95% CI, 0.57-1.21; see this article's Fig E4 in the Online Repository at www.jacionline.org).[22,34] Critical appraisal of articles revealed that these studies had weaknesses in relation to lack of power, in part resulting from losses to follow-up.

Four of the 5 case-control studies reported no associations between serum/urine selenium levels or selenium intake and atopic dermatitis or asthma-related outcomes.[40,43,49,50] One study reported higher serum selenium levels to be associated with less frequent wheezing in young children (<5 years).[47] The limitations of this body of evidence included small sample sizes, a failure to measure and/or adjust for potentially important confounding factors, and, more fundamentally, the risk of reverse causation. Meta-analyses were not performed because of heterogeneity.

Two cross-sectional studies assessed the relationship with atopic sensitization, parental reports of physician-diagnosed asthma, and asthma with wheeze.[69,73] There were nonsignificant associations between serum selenium in children and the aforementioned outcome measures. No meta-analyses of the cross-sectional studies were possible because of study heterogeneity.

Summary of evidence. Overall, the body of evidence in relation to selenium was judged to be methodologically weak and unsupportive of an association between childhood asthma and allergy and selenium status during pregnancy or childhood.

Zinc studies

Description of studies. Eight studies investigated the associations between maternal serum or children's umbilical cord blood, serum or hair zinc status, and atopic outcomes (see this article's Table E7 in the Online Repository at www.jacionline.org).[23,28,34,41-43,49,53]

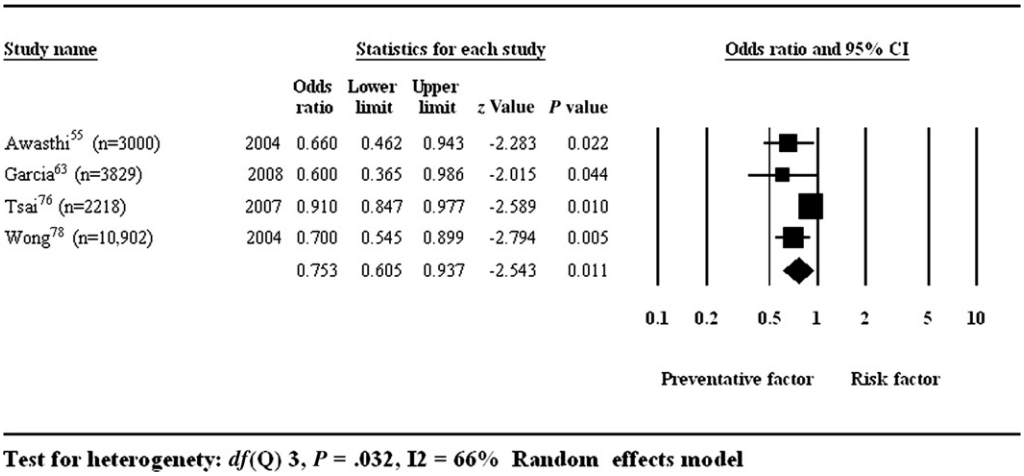

FIG 5. Association between fruit intake (highest vs lowest) and wheeze in children 10 to 14 years old (cross-sectional).

Main findings. Three large cohort studies assessed the relationships between dietary or maternal plasma/umbilical cord zinc and early wheeze and asthma-related outcomes.[23,28,34] These reported potentially beneficial associations between maternal zinc intake during pregnancy and childhood asthma, wheeze, and atopic dermatitis.[23,28] There was no association between zinc biomarker measurements and early wheeze or asthma-related outcomes.[23,34] All cohort studies were graded C for quality. Meta-analysis of 2 cohort studies revealed no association between umbilical cord zinc levels and wheezing in early childhood (OR, 1.02; 95% CI 0.98-1.05).[23,34]

Three small case-control studies assessed either serum or hair levels of zinc in children.[41,42,53] The authors reported serum or hair zinc levels to be significantly lower in children with asthma and/or children who wheezed. The risk of selection bias, the failure to adjust adequately for potential confounders, and concerns with the analytic techniques used were the main limitations of these studies. All case-control studies were graded C for quality. Because of clinical heterogeneity between studies, meta-analyses were not performed.

Summary of evidence. Overall, the body of evidence from these studies was judged to be methodologically weak but weakly suggestive of the possible effectiveness of zinc in relation to the prevention of asthma.

Fruit and vegetable studies

Description of studies. These 22 studies were 3 cohort,[25,37,38] 2 case-control,[43,51] and 17 cross-sectional studies[54,55,58,59,61-63,65,68,70,71,74-79] (see this article's Table E8 in the Online Repository at www.jacionline.org).

Main findings. In 1 prospective cohort study, higher fruit and vegetable intake by mothers during pregnancy (Q1, the lowest quartile of intake vs Q4, the highest quartile of intake) was associated with lower risk of children developing asthma at the age of 3 years (OR, 0.42; 95% CI, 0.18-0.99).[25] In the second large birth cohort study, the authors found that higher maternal apple intake (highest vs lowest tertile) was associated a reduced likelihood of "ever wheeze" (OR, 0.63; 95% CI, 0.42-0.95), "ever asthma" (OR, 0.54; 95% CI, 0.32-0.92), and "doctor-diagnosed asthma" (OR, 0.47; 95% CI, 0.27-0.82) in 5-year-old children.[37] However, the third large cohort study showed that maternal fruit and vegetable consumption during pregnancy was not associated with childhood asthma outcomes.[38]

In 1 case-control study, higher vegetable intake (>3 portions/d vs <2 portions/d) by 12-year-old children was associated with a reduced risk of having the condition (OR, 0.35; 95% CI, 0.12-1.02).[43] The second case-control study also found that the consumption of cooked vegetables by children age 13 to 14 years old was a protective factor for wheezing and asthma (OR, 0.37; 95% CI, 0.18-0.79).[51]

The majority of the cross-sectional studies were International Survey of Allergies and Asthma in Childhood (ISAAC) surveys and relied on a relatively limited food frequency questionnaire that permitted quantification of major food groups but not individual nutrients. Nevertheless, 17 studies report some beneficial associations of fruit and vegetable intakes with atopy, eczema, allergic rhinoconjunctivitis, and wheezing/asthma-related outcomes. Pooled analysis of 4 cross-sectional studies showed that high dietary intake of fruits by children age 10 to 14 years was associated with reduced odds of wheezing (ie, either wheezing/wheezing without cold or current asthma symptoms; OR, 0.75; 95% CI, 0.60-0.94; Fig 5).[55,63,76,78] Another meta-analysis of 3 studies showed that higher dietary intake of vegetables by children age 10 to 14 years was not associated with reduced odds of wheezing (OR, 0.84; 95% CI, 0.64-1.10; Fig 6).[55,76,78] Only 1 study found that higher dietary vegetable intake by pregnant women increased the likelihood of asthma in infants (OR, 1.84; 95% CI, 1.06-3.18).[77] Because of studies being conducted in children of different ages, crude and inconsistent exposure assessment, and variability in outcome measures, other meta-analyses were not possible.

The majority of fruit and vegetable studies (2 of 3 cohort, 2 case-control, and 13 cross-sectional) were indicative of a protective effect. Even though the analytical body of evidence was limited, this overall body of evidence is large, and the highest consumption of fruits versus lowest by mothers during pregnancy or children at early childhood had a suggestive protective effect in the primary prevention of asthma and asthma-related symptoms.

Summary of evidence. The majority of fruit and vegetable studies were indicative of higher consumptions by mothers during pregnancy and children in early life resulting in reductions in the

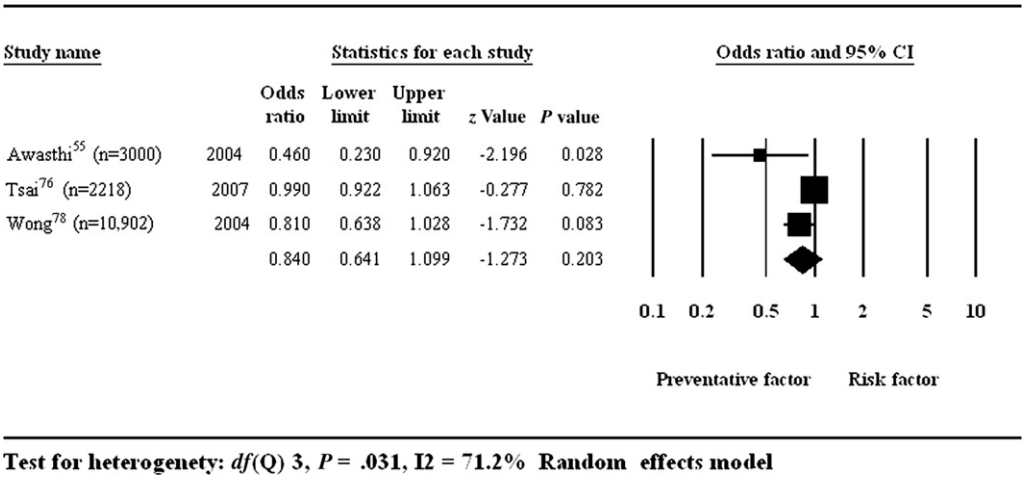

FIG 6. Association between vegetable intake (highest vs lowest) and wheeze in children 10 to 14 years old (cross-sectional).

risk of children developing asthma and asthma-related symptoms. Overall, the body of data was more convincing for fruit than vegetables.

Mediterranean diet studies

Description of studies. In this category, only 1 of the 5 studies used a cohort design.[20] The other studies were all cross-sectional[56,57,60,64] (see this article's Table E9 in the Online Repository at www.jacionline.org). All but 1 was graded C for quality; the large prospective cohort study was graded B because it had the strengths of studying clinically relevant outcomes, long duration of follow-up (from pregnancy to 6.5 years), good completeness of follow-up, and appropriate adjustment for potential confounding.[20]

Main findings. The cohort study found that a high adherence to a Mediterranean diet by pregnant women was found to be protective for childhood atopy (OR, 0.55; 95% CI, 0.31-0.97), atopic wheeze (OR, 0.30; 95% CI, 0.10-0.90), and persistent wheeze (OR, 0.22; 95% CI, 0.08-0.58) at age 6.5 years after adjusting for potential confounders.[20]

Meta-analyses of a Mediterranean diet studies were not possible because of differences in exposure and outcome assessment.

Summary of evidence. Overall, the body of evidence from these studies was judged to be methodologically weak to inform prevention decisions but suggestive of the possible effectiveness of a Mediterranean diet during pregnancy for the prevention of sensitization and asthma.

Unpublished and ongoing studies

We are aware of 2 epidemiologic studies investigating the relationship between vitamin D and allergic outcomes. We have also learned of 2 RCTs of vitamin D supplementation during pregnancy with childhood wheeze/asthma as primary outcomes in the United States (4400 IU/d vs 400 IU/d) and in Denmark (2800 IU/d vs 400 IU/d). Finally, we are aware of 2 unpublished trials investigating the relationship between vitamin A supplementation in early life and lung function and asthma outcomes.

DISCUSSION

This systematic review and meta-analysis has investigated the role of nutrients and foods for the primary prevention of asthma and atopic disorders in children age ≤16 years. Critical appraisal of studies suggested that there was a substantial risk of bias in this overall body of knowledge. The results were nonetheless somewhat suggestive of potentially beneficial associations of vitamins A, D, and E; zinc; fruits and vegetables; and Mediterranean diet, particularly in relation to asthma. In contrast, the overall body of evidence was not particularly supportive for any outcomes in relation to vitamin C and selenium.

Strengths and limitations of this review

The searches were comprehensive, and we believe our work has greater methodologic rigor than 2 recent reviews.[81,82] We were careful to preserve the outcome terminology used in the original publications, and it is notable that some studies did report on associations with "asthma" in children age 2 years and under.[39,41,48,52,72] The quality assessment of these studies acknowledged the well recognized difficulties in diagnosing asthma in such young children, and these studies were not included in any meta-analyses. By contacting authors for primary data not presented in original articles, we were able to conduct several meta-analyses not possible using published data alone.

The limitations of this work stem primarily from the lack of intervention studies, heterogeneity of study design, small study sample sizes, lack of data on the race/ethnicity of participants, inconsistent exposure assessment (dietary intake vs biomarkers in blood, umbilical cord, hair, and urine), different time points (antenatal, various postnatal ages) and differing outcome parameters (eg, wheeze, asthma, and ventilatory function). Consequently, we were able to conduct only a relatively limited number of meta-analyses of a small number of studies. Thus, although most pooled analyses were of 2 studies only, we were able to combine the results of 4 vitamin D studies and 3 vitamin E studies. We are unable to comment on the possible influences of genetics and race/ethnicity on any associations between diet, asthma, and allergy. Further birth cohort studies in populations that differ with respect to dietary habit, socioeconomic profile,

ethnicity/race, and genetic susceptibility are required. We planned to investigate heterogeneity and explore for publication bias by using funnel plots, but because of the insufficient numbers of studies, this was not possible.

In contrast with our work, a recently published systematic review reported no beneficial associations between dietary antioxidant intake and asthma or lung function.[81] However, the authors searched only 1 electronic database for studies of adults in English-language journals; furthermore, for outcome measurements, they combined asthma and wheeze. Our searches were in comparison much more comprehensive.

Our findings also differ somewhat from a recently published systematic review and meta-analysis of the literature on antioxidant vitamins (A, C, E) and asthma outcomes.[82] First, we included studies of a Mediterranean diet and dietary intakes of fruit, vegetables, and vitamin D; second, the study by Allen et al,[82] although it included studies of both children and adults, did not include studies of maternal diet during pregnancy. The review by Allen et al[82] reported that serum vitamin A levels were significantly lower in children with asthma than controls, and the meta-analysis of the same studies replicated in our systematic review produced identical results. However, as highlighted by Allen et al,[82] because the 2 studies were case-control studies, they were unable to differentiate whether reduced vitamin A levels were a consequence of asthma or a contributory factor. In the current study, we concluded that there was little evidence of associations between maternal and childhood vitamin C status and childhood asthma. This contrasts with Allen et al,[82] who reported that lower quintile dietary intakes and serum levels of vitamin C were associated with increased odds of asthma; however, the majority (n = 22) of these studies were in adults. There is the risk of reverse causation because asthma/atopic disorders are associated with oxidant stress, and there is some evidence suggesting that dietary habits may change as asthma develops.[83] Allen et al[82] also reported that vitamin E intake was generally unrelated to asthma status but was significantly lower in severe asthma than in mild asthma; however, for their meta-analysis, they combined studies in children and adults. In the current review, there was suggestive evidence of a potentially beneficial association between maternal vitamin E intake during pregnancy and childhood wheeze and probably asthma, suggesting that the timing of dietary exposures may be important.

We believe this to be the first systematic review and meta-analysis simultaneously assessing the evidence in relation to several dietary exposures.

Although the available epidemiologic evidence is limited and weak, it is nonetheless supportive with respect to vitamins A, D, and E; zinc; fruits and vegetables; and Mediterranean diet for the prevention of childhood wheeze and possibly asthma. More epidemiologic data are available for maternal vitamin D and E intake during pregnancy, and the pooled analyses of these studies support the setting up of trials to investigate whether manipulation of maternal intakes of these nutrients during pregnancy reduces the likelihood of childhood wheeze and asthma. The results of this review provide further justification for the trials of vitamin D intervention during pregnancy that are now underway. Until the results of intervention trials are available of the kind that are now being undertaken in those with established allergic disease,[84] it is important that the dietary advice given to expectant women and the parents of young children remains unchanged, because meta-analyses of observational studies do not necessarily reliably predict the results of clinical trials.[85]

We thank Marshall Dozier for her advice on the literature searches. We acknowledge the contribution of an international panel of experts and thank them for providing information on unpublished/ongoing studies and additional analyses of primary data to include in this study. Also, we thank Anna Wierzoch for administrative support.

Key messages

- **There are no published experimental studies investigating the role of nutrients and foods for the primary prevention of asthma and allergic disorders in children.**
- **The body of epidemiologic evidence in relation to nutrients and dietary factors for the prevention of asthma and allergic disorders is overall weak but nonetheless suggestive in relation to vitamins A, D, and E; zinc; fruits and vegetables; and Mediterranean diet, particularly in relation to asthma outcomes.**
- **The evidence was less encouraging in relation to vitamin C and selenium.**
- **There is a need for well designed randomized controlled trials of vitamins A, D, and E; zinc; fruits and vegetables; and Mediterranean diet. There is a need to prioritize vitamin D and E trials for the primary prevention of asthma in children.**
- **The existing level of evidence adds to the existing public health messages on a balanced healthy diet in relation to a Mediterranean diet and fruits and vegetables.**

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APPENDIX E1. Search strategies

Search strategy 1 for MEDLINE, EMBASE, GLOBAL HEALTH, AMED, and CAB

1. exp Diet/
2. exp Mediterranean diet/
3. Mediterranean Diet Score.mp.
4. mediterranean diet.mp.
5. nutrition.mp.
6. exp Fruit/
7. exp seafood/
8. exp vegetables/
9. nutrient*.mp.
10. apple.mp.
11. orange.mp.
12. citrus.mp.
13. fruit juice.mp.
14. olive oil.mp.
15. wine.mp.
16. onion.mp.
17. flavonoid.mp.
18. flavonol.mp.
19. flavone.mp.
20. isoflavone.mp.
21. catechin.mp.
22. chalcone.mp.
23. oxidative stress.mp.
24. antioxidant*.mp.
25. vitamin C.mp.
26. exp Ascorbic acid/
27. ascorbic acid.mp.
28. exp vitamin D/
29. vitamin D.mp.
30. hydroxy vitamin D.mp.
31. hydroxy cholecalciferol.mp.
32. exp vitamin E/
33. vitamin E.mp.
34. tocopherol.mp.
35. tocotrienol.mp.
36. exp vitamin A/
37. vitamin A.mp.
38. exp beta carotene/
39. beta carotene.mp.
40. carotenoid.mp.
41. carotene.mp.
42. cryptoxanthin.mp.
43. lycopene.mp.
44. lutein.mp.
45. zeaxanthin.mp.
46. exp zinc/
47. zinc.mp.
48. exp selenium/
49. selenium.mp.
50. or/1-49
51. analytical stud*.mp.
52. exp Epidemiologic Studies/
53. exp Intervention Studies/
54. exp Evaluation Studies/
55. exp Comparative Studies/
56. exp Follow-up Studies/
57. exp Prospective Studies/
58. prospectiv*.mp.
59. exp Cohort Studies/
60. exp Case-Control Studies/
61. control.mp.
62. healthy control children.mp.
63. exp Cross-sectional Studies/
64. cohort stud*.mp.
65. cohort.mp.
66. birth cohort.mp.
67. case-control stud*.mp.
68. cross-sectional stud*.mp.
69. etiology.mp.
70. trial.mp.
71. Clinical trial/
72. clinical trial.mp.
73. Controlled Clinical Trial/
74. controlled clinical trial.mp.
75. Randomized Controlled Trial/
76. exp Placebos/
77. exp Random Allocation/
78. exp Double-Blind Method/
79. double-blind design.mp.
80. exp Single-Blind Method/
81. single-blind design.mp.
82. randomi?ed controlled trial.mp.
83. random*.mp.
84. exp Survey/
85. survey.mp.
86. questionnaire*.mp.
87. Food frequency questionnaire*.mp.
88. Nutrition Examination Survey.mp.
89. ISAAC.mp.
90. exp Primary prevention/
91. primary prevention.mp.
92. or/51-91
93. exp Hypersensitivity/
94. allerg*.mp.
95. react*, allergic.mp.
96. reaction, allerg*.mp.
97. atop*.mp.
98. or/93-97
99. exp Asthma/
100. asthma.mp.
101. asthmatic children.mp.
102. acute asthmatic attack.mp.
103. wheez*.mp.
104. Respiratory hypersensitivity/
105. bronchial disorder.mp.
106. hyper-responsiveness wheez*.mp.
107. lung function.mp.
108. ventilatory function.mp.
109. FEV.mp.
110. FEF.mp.
111. FVC.mp.
112. PEF.mp.
113. bronchial hyperreactivity.mp.
114. airway hyperreactivity.mp.
115. bronchial responsiveness.mp.
116. airway responsiveness.mp.
117. or/99-116

118. exp Food hypersensitivity/
119. food allerg*.mp.
120. food hypersensitivity.mp.
121. food hypersensitivities.mp.
122. allergy, food.mp.
123. or/118-122
124. exp Dermatitis, Atopic/
125. exp Eczema/
126. Neurodermatitis/
127. eczema.mp.
128. dermatitis.mp.
129. dermatitides.mp.
130. atopic dermatitis.mp.
131. atopic eczema.mp.
132. eczematous dermatiti*.mp.
133. dermatiti*, eczematous.mp.
134. neurodermatitis.mp.
135. dermatitis, atopic.mp.
136. eczema, atopic.mp.
137. or/124-136
138. exp Rhinitis/
139. Rhinitis Allergic Perennial/
140. Rhinitis, allergic, seasonal/
141. hayfever.mp.
142. hay fever.mp.
143. fever, hay.mp.
144. seasonal allergic rhinitis.mp.
145. allergic rhinitides.mp.
146. allergic rhinitis.mp.
147. rhiniti*.mp.
148. poll?nosis.mp.
149. pollenosis.mp.
150. Conjunctivitis, Allergic/
151. conjunctivit*.mp.
152. rhino-conjunctivit*.mp.
153. or/138-152
154. exp Anaphylaxis/
155. anaphylaxis react*.mp.
156. anaphylactic react*.mp.
157. anaphylactic shock*.mp.
158. anaphylactoid syndrome*.mp.
159. anaphylactoid react*.mp.
160. anaphylactic syndrome*.mp.
161. anaphylactoid shock*.mp.
162. acute systemic allergic react*.mp.
163. idiopathic anaphylaxis.mp.
164. systemic anaphylaxis.mp.
165. or/154-164
166. 98 or 117 or 123 or 137 or 153 or 165
167. 50 and 92 and 166
168. limit 167 to (humans and yr="1988 - 2008")

AMED, Allied and Complementary Medicine Database; *CAB Direct*, Commonwealth Agricultural Bureau; *EMBASE*, Excerpta Medica Database; *MEDLINE*, Medical Literature Analysis and Retrieval System Online.

SEARCH STRATEGY 2 FOR COCHRANE LIBRARY, LILACS, TRIP, CINAHL, ISI WEB OF SCIENCE, AND BIOSIS

(Hypersensitivity OR allergy OR asthma OR atopy OR "atopic dermatitis" OR eczema OR "hay fever" OR "allergic rhinitis" OR pollinosis OR "food allergy" OR anaphylaxis OR "anaphylactic shock" OR "systematic allergic reaction")

AND

(Nutrition OR diet OR "Mediterranean diet" OR foods OR fruit OR vegetables OR antioxidant* OR "vitamin C" OR "vitamin D" OR "vitamin A" OR "vitamin E" OR "beta carotene" OR zinc OR selenium)

AND

(Prevention OR "primary prevention" OR etiology OR "risk of developing" OR effect* OR cause* OR protect* OR risk*)

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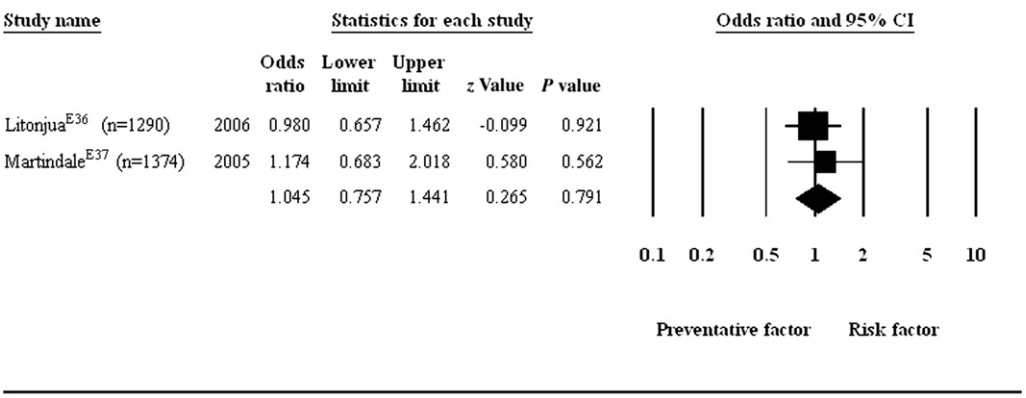
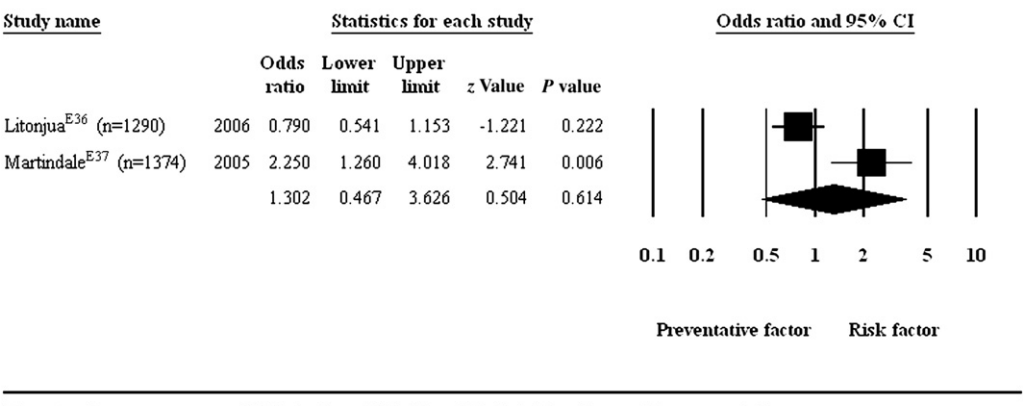
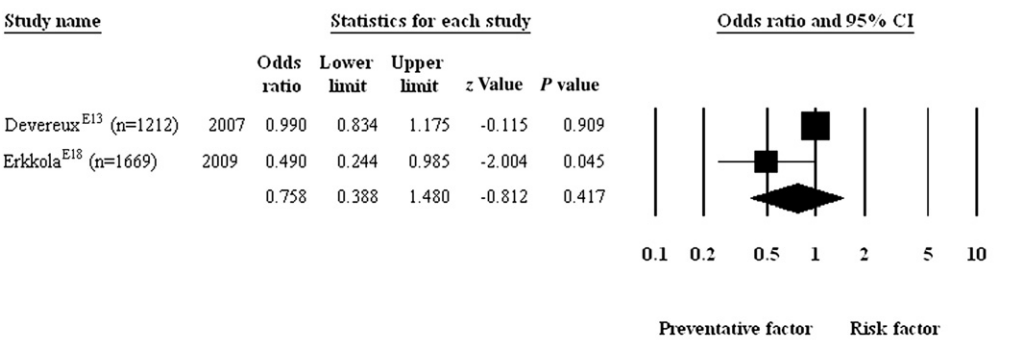


FIG E1. Association between mothers' intake of β-carotene and wheezing in the second year of life (cohort).



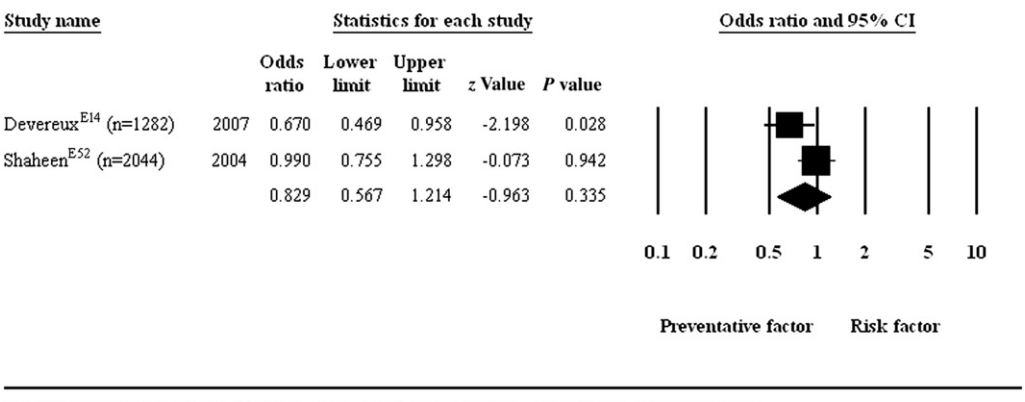
Test for heterogeneity: *df*(Q) 1, *P* = .003, I2 = 88.6% Random effects model

FIG E2. Association between mothers' intake of vitamin C and wheezing in the second year of life (cohort).



Test for heterogeneity: *df*(Q) 1, *P* = .055, I2 = 72.8% Random effects model

FIG E3. Association between mothers' intake of vitamin D and asthma in children (cohort).



Test for heterogeneity: *df*(Q) 1, *P* = .088, I2 = 65.7% Random effects model

FIG E4. Association between neonatal cord selenium and wheezing in children (cohort).

TABLE E1. Description of included studies (n = 62)

Authors	Geographic area	Design	Statistical methods for potential confounder factor adjustments	Dietary component measured§								Outcomes							Quality assessment score
				A	C	E	D	Zn	Se	F&V	MD	Atopy	AD	ARC	W/A/LF	FA	U	A	
Antova[E1]	Six countries in Central and Eastern Europe	Cross-sectional/	Logistic regression							✓					✓				C
Arora[E2]	India	Case-control	Age-matched, sex-matched controls; no adjustment for potential confounders	✓											✓				C
Awasthi[E3]	India	Cross-sectional	Logistic regression							✓					✓				C
Bäck[E4]	Sweden	Cohort	Univariate and multivariate logistic regression				✓						✓	✓	✓				C
Burney[E5]	Greece, Norway	Case-control	Logistic regression						✓						✓				C
Camargo[E6]	United States	Cohort	Multiple logistic regression				✓						✓		✓				C
Castro-Rodriges[E7]	Spain	Cross-sectional	Logistic regression							✓				✓	✓				C
Chatzi[E8]	Greece	Cross-sectional	Logistic regression							✓	✓	✓		✓	✓				C
Chatzi[E9]	Spain	Cross-sectional	Logistic regression							✓		✓			✓				C
Chatzi[E10]	Spain	Cohort	Multiple logistic regression								✓	✓			✓				B
Cook[E11]	England, Wales	Cross-sectional	Multiple logistic regression							✓					✓				C
De Batle[E12]	Mexico	Cross-sectional	Logistic regression							✓	✓			✓	✓				C
Devereux[E13]	Scotland	Cohort	Univariate and multivariate logistic regression				✓					✓			✓				C
Devereux[E14]	Scotland	Cohort	Univariate and multivariate logistic regression						✓			✓			✓				C
Devereux[E15]	Scotland	Cohort	Univariate and multivariate logistic regression	✓	✓	✓		✓				✓			✓				C
El-Kholy[E16]	Egypt	Case-control	Age-matched, sex-matched, socioeconomic status–matched controls; no adjustment for potential confounders					✓					✓		✓				C
Ellwood[E17]	53 countries	Cross-sectional	Univariate and multivariate logistic regression							✓			✓	✓	✓				C
Erkkola[E18]	Finland	Cohort	Logistic regression				✓							✓	✓				C
Ermis[E19]	Turkey	Case-control	Age-matched, sex-matched controls; no adjustment for potential confounders					✓							✓				C
Farchi[E20]	Italy	Cross-sectional	Logistic regression							✓				✓	✓				C
Fitzsimon[E21]	Ireland	Cohort	Univariate and multivariate logistic regression							✓					✓				C
Forastiere[E22]	Italy	Cross-sectional	Logistic regression		✓					✓				✓	✓				C
Gale[E23]	England	Cohort	Logistic regression				✓						✓		✓				C
Garcia[E24]	Colombia	Cross-sectional	Logistic regression							✓					✓				C
Garcia-Marcos[E25]	Spain	Cross-sectional	Logistic regression								✓			✓	✓				C
Gilliland[E26]	United States	Cross-sectional	Logistic regression		✓					✓					✓				C
Harik-Khan[E27]	United States	Cross-sectional	Logistic regression	✓	✓	✓									✓				C
Hijazi[E28]	Saudi Arabia	Case-control	Logistic regression	✓	✓	✓		✓	✓	✓		✓			✓				C
Hozyasz[E29]	Poland	Case-control	No adjustments			✓							✓						C
Hozyasz[E30]	Poland	Case-control	Method of statistical analysis not stated	✓									✓						C

(Continued)

TABLE E1. *(Continued)*

Authors	Geographic area	Design	Statistical methods for potential confounder factor adjustments	Dietary component measured§								Outcomes							Quality assessment score
				A	C	E	D	Zn	Se	F&V	MD	Atopy	AD	ARC	W/A/LF	FA	U	A	
Huang[E31]	Taiwan	Cross-sectional	Logistic regression	✓	✓	✓								✓	✓				C
Hypponen[E32]	Finland	Cohort	Logistic regression				✓					✓		✓	✓				C
Kalayci[E33]	Turkey	Case-control	Age-matched controls; no adjustment for potential confounders	✓	✓	✓									✓				C
Kocabas[E34]	Turkey	Case-control	Age-matched, sex-matched, nutritional status–matched controls; no adjustment for matched design in analysis					✓							✓				C
Lewis[E35]	England	Cross-sectional	Logistic regression							✓			✓		✓				C
Litonjua[E36]	United States	Cohort	Bivariate and multivariate logistic regression	✓	✓	✓		✓					✓		✓				C
Martindale[E37]	Scotland	Cohort	Univariate and multivariate logistic regression	✓	✓	✓							✓		✓				C
McKeever[E38]	United States	Cross-sectional	Initial exploratory analysis	✓	✓	✓			✓			✓							C
Milner[E39]	United States	Cohort	Multiply logistic regression												✓	✓			C
Mizuno[E40]	Japan	Case-control	Age-sex matched controls; no adjustment for potential confounders	✓		✓									✓				C
Miyake[E41]	Japan	Cohort	Logistic regression				✓						✓		✓				C
Miyake[E42]	Japan	Cohort	Logistic regression		✓	✓		✓		✓			✓		✓				C
Murray[E43]	England	Case-control	Age-matched, sex-matched nested case-control study; no adjustment for energy intake	✓	✓	✓		✓	✓			✓			✓				C
Nja[E44]	Norway	Cross-sectional	Logistic regression							✓		✓			✓				C
Okoko[E45]	England	Cross-sectional	Logistic regression							✓					✓				C
Omata[E46]	Japan	Case-control	Unmatched case-control study; no adjustment for potential confounders						✓				✓						C
Pastorino[E47]	Brazil	Case-control	Logistic regression							✓		✓			✓				C
Pesonen[E48]	Finland	Cohort	Logistic regression	✓								✓	✓	✓	✓				C
Powell[E49]	England	Case-control	Age-matched, sex-matched controls; no adjustment for potential confounders	✓	✓	✓			✓						✓				C
Romieu[E50]	United States	Cross-sectional	Logistic regression		✓							✓			✓				C
Rubin[E51]	United States	Cross-sectional	Logistic regression	✓	✓	✓			✓						✓				C
Shaheen[E52]	England	Cohort	Logistic regression					✓	✓				✓		✓				C
Shaheen[E53]	England	Cohort	Logistic regression									✓	✓	✓	✓				C
Shaw[E54]	New Zealand	Cohort	Logistic regression; no adjustment for potential confounders						✓						✓				C
Tabak[E55]	The Netherlands	Cross-sectional	Logistic regression							✓		✓			✓				C
Tahan[E56]	Turkey	Case-control	Age-matched, sex-matched controls; no adjustment for potential confounders					✓							✓				C

(Continued)

TABLE E1. *(Continued)*

Authors	Geographic area	Design	Statistical methods for potential confounder factor adjustments	Dietary component measured§								Outcomes							Quality assessment score
				A	C	E	D	Zn	Se	F&V	MD	Atopy	AD	ARC	W/A/LF	FA	U	A	
Tamay[E57]	Turkey	Cross-sectional	Logistic regression							✓				✓					C
Tsai[E58]	Taiwan	Cross-sectional	Logistic regression							✓					✓				C
Ushiama[E59]	Japan	Cross-sectional	Logistic regression							✓			✓		✓	✓			C
Willers[E60]	Scotland	Cohort	Multiple logistic regression							✓		✓	✓	✓	✓				C
Willers[E61]	The Netherlands	Cohort	Multiple logistic regression							✓					✓				C

A, Anaphylaxis; *AD,* atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *F&V,* fruits and vegetables; *MD,* Mediterranean diet; *U,* urticaria; *W/A/LF,* wheeze/asthma/lung function.
*Constituents of vitamins A, C, E, and D.

TABLE E2. Detailed characteristics of vitamin A studies

Exposure			Outcomes						
Vitamin A	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Devereux[E15]	Cohort (same cohort as Martindale[E37])	5 yo; FFQ; α-carotene; β-carotene by normal-phase HPLC; exposure during pregnancy	Narrative report of no associations			Narrative report of no associations	Narrative report of no associations	Narrative report of no associations	
Litonjua[E36]	Cohort	2 yo; α-carotene and β -carotene; diet with/without supplement; exposure during pregnancy		Narrative report of no associations		Narrative report of no associations			
Martindale[E37]	Cohort	2 yo; maternal β-carotene intake; FFQ and maternal plasma and cord blood β-carotene by normal-phase HPLC; exposure during pregnancy		Narrative report of no associations		Narrative report of no associations			
Pesonen[E48]	Cohort	200 infants followed up 20 y; plasma retinol by HPLC in cord blood, plasma retinol at 2, 4, 12 mo, 5 y, and 11 y; SPT, IgE	Allergic symptoms (n = 46), positive SPT (n = 46), and verified atopy (n = 35) at age 20 y associated with low retinol concentration at 2 mo (P = .01, .004, and .01, respectively)	At age 5 y, children with AD (n = 26) had a lower retinol concentration, 297 μg/L, than symptom-free subjects, 322 μg/L (P = .03) At 20 y, AD associated with reduced retinol at 2 mo, 207 μg/L vs 236 μg/L, P = .01	ARC (n = 59) at age 20 y significantly lower retinol concentration at age 11 y (P = .03)				Not applicable
Arora[E2]	Case-control	2-12 yo (mean, 5.89); serum A by HPLC					Vitamin A levels in children with asthma (mean ± SD, 22.14 ± 5.38 μg/dL) lower than controls (27.54 ± 4.83 μg/dL; P = .0001)		
Hijazi[E28]	Case-control	12 yo; FFQ vitamin A, C, E, β-carotene Zn, Se, vegetables					Narrative report of no associations with asthma + wheeze		

(Continued)

TABLE E2. *(Continued)*

Exposure			Outcomes						
Vitamin A	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Hozyasz[E29]	Case-control	1-9 yo; AD + tocopherol deficiency vs AD-free controls, plasma retinol by HPLC		Retinol cases, 1.2 ± 0.3 μmol/L, vs controls, 1.5 ± 0.3 μmol/L, $P < .01$					
Kalayci[E33]	Case-control	13-15 yo; serum β-carotene by calorimetric method					Children with asthma have significantly lower blood β-carotene, $P < .001$, graphic representation of results		
Mizuno[E40]	Case-control	Cases: 5.5 ± 4.21 yo; controls: 6.4 ± 4.32 yo; serum vitamin A					Vitamin A levels in children with asthma (mean ± SD, 19.41 ± 7.45 μg/dL) lower than controls (29.52 ± 11.34 μg/dL; $P = .0001$)		
Murray[E43]	Case-control	Mean age, 4.4 y; FFQ dietary intake of vitamin A, C, E, zinc, selenium Atopic wheezers vs nonatopic never wheezed				Wheeze vs controls, 264.0 (160.5) vs 264.0 (128.0) μg/d; $P = .79$			
Powell[E49]	Case-control	Range, 18 mo to 16 y (mean, 9 y); plasma retinol					Plasma retinol in children with asthma, 1.29 (1.04-1.59) μmol/L; controls, 1.42 (1.28-1.71) μmol/L; P = not significant		
Ellwood[E17]	Cross-sectional	6-7 yo and 13-14 yo ISAAC phase 1 (1994-95) vitamin A from vegetables (μg/24 h) measured at population level; FAOSTAT data Food and Agriculture Organisation food-balance sheets; measured in % of total energy consumption		Vitamin A from vegetables, $\mu g.d^{-1}$, coefficient, –0.01 (95% CI, –0.02 to –0.0045); $P = .001$	Vitamin A from vegetables, $\mu g.d^{-1}$, coefficient, –0.01 (95% CI, –0.02 to –0.0012); $P = .085$	Vitamin A from vegetables, $\mu g.d^{-1}$, coefficient, –0.01 (95% CI, –0.03 to –0.001); $P = .040$			

(Continued)

TABLE E2. *(Continued)*

Exposure			Outcomes						
Vitamin A	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Gilliland[E26]	Cross-sectional	11-19 yo; vitamin A intake; total diet and supplement; validated FFQ						Vitamin A in girls (FEF_{25-75}, –7.9%; 95% CI, –12.7 to –2.8), boys NS; vitamin A in boys with asthma (FEF_{25-75}, –15.6%; 95% CI, –27.6 to –1.6)	
Harik-Khan[E27]	Cross-sectional	6-17 yo; NHANES III; dietary (24-h recall); questionnaires; serum vitamin A; α-carotene; β-carotene; cryptoxanthin; lutein/zeaxanthin; lycopene					Serum α-carotene, 0.945 (0.899, 0.993); $P < .05$.		
Huang[E31]	Cross-sectional	13-17 yo; mean, 14.7 y; dietary intake; 24-h food recall			No associations, vitamin A and ARC		No associations, vitamin A and asthma		
McKeever[E38]	Cross-sectional	10.7 yo (SD, 3.10); NHANES III; serum A; α-carotene; β-carotene; SPT	Vitamin A, 1.11 (1.04-1.78); no associations with α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene						
Rubin[E51]	Cross-sectional	4-16 yo; NHANES III; serum β-carotene					β-carotene, OR, 0.87 (95% CI, 0.7-1.0)		

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FAOSTAT*, Food and Agriculture Organization of the United Nations; FEF_{25-75}, forced expiratory flow at 25% to 75% of forced vital capacity; *FFQ,* Food Frequency Questionnaire; *NHANES,* National Health and Nutritional Examination Survey; *SPT*, skin prick test; *yo,* years old. A blank cell indicates that this outcome was not studied.

TABLE E3. Detailed characteristics of vitamin C studies

Exposure			Outcomes						
Vitamin C	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Devereux[E15]	Cohort (same cohort as Martindale[E37])	5 y.; plasma vitamin C by enzymatic colorimetric assays; maternal and child C intake; FFQ; exposure during pregnancy				No associations	No associations	No associations	
Litonjua[E36]	Cohort	2 yo; vitamin C with/without supplement; exposure during pregnancy		No associations		No associations			
Martindale[E37]	Cohort	2 yo; maternal vitamin C intake by FFQ Maternal plasma and cord blood vitamin C by enzymatic colorimetric assays; exposure during pregnancy		No associations		Maternal vitamin C intake: ever wheeze 5th vs 1st quintile, 3.00 (1.47, 6.12), *P* (trend) .010			
Hijazi[E28]	Case-control	12 yo; FFQ vitamin A, C, E, β-carotene, Zn, Se, vegetables					No associations		
Kalayci[E33]	Case-control	13-15 yo; serum vitamin C by calorimetric method					Children with asthma significantly lower blood ascorbate, $P < .001$, graphic representation of results		
Murray[E43]	Case-control	Mean age, 4.4 y; FFQ dietary intake of vitamin A, C, E, zinc, selenium Atopic wheezers vs nonatopic never wheezed				Wheeze vs controls 121.0 (104.2, 140.6) vs 116.3 (9602, 140.7) mg/d, $P = .74$			
Powell[E49]	Case-control	Range, 18 mo to 16 y (mean, 9 y); plasma vitamin C by HPLC					Vitamin C in children with asthma, 57.96 (40.32-70.00) μmol/L; in controls, 59.92 (42.98-77.98) μmol/L; P = not significant		
Cook[E11]	Cross-sectional	8-11 yo; FFQ; plasma vitamin C by HPLC				Plasma vitamin C slightly higher in wheezers, 64.1 vs 60.1 μmol/L ($P = .31$; 95% CI of difference, –4.7 to 12.6 μmol/L)			
Gilliland[E26]	Cross-sectional	11-19 yo; vitamin C intake; total diet and supplement; validated FFQ						Low vitamin C intake (<10th percentile) associated with reduced FVC in boys, –2.6 (–5.1, –0.2) and girls, –2.7 (–5.2, –0.1)	

(Continued)

TABLE E3. *(Continued)*

Exposure			Outcomes						
Vitamin C	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Harik-Khan[E27]	Cross-sectional	6-17 yo; NHANES III; dietary (24-h recall); questionnaires; serum vitamin C					Serum vitamin C, 0.720 (0.546, 0.949); $P < .05$; no association with dietary vitamin C intake		
Huang[E31]	Cross-sectional	13-17 yo; dietary intake; 24-h food recall		No association between vitamin C and allergic rhinitis			No association between vitamin C and asthma		
McKeever[E38]	Cross-sectional	10.7 yo (SD, 3.10); NHANES III; serum A; α-carotene; β-carotene; SPT	Vitamin C, 0.95 (0.88-1.03)						
Romieu[E50]	Cross-sectional	2-16 yo; NHANES III; dietary vitamin C intake (24-h recall), <60 vs ≥60 mg/d				No associations between vitamin C intake and wheezing, 1.38 (0.92-2.08)	No associations between vitamin C intake and asthma, 1.04 (0.69-1.59)		
Rubin[E51]	Cross-sectional	4-16 yo; NHANES III; serum vitamin C					Serum vitamin C, 0.81 (0.7, 0.9)		

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ,* Food Frequency Questionnaire; *FVC,* forced vital capacity; *GP,* general practitioner; *yo,* years old.

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TABLE E4. Detailed characteristics of vitamin E studies

Exposure			Outcomes						
Vitamin E	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Devereux[E15]	Cohort (same cohort as Martindale[E37])	5 yo; maternal and child vitamin E intake—FFQ; maternal and cord plasma α-tocopherol by normal phase HPLC, adjusted for cholesterol; exposure during pregnancy	Maternal plasma α-tocopherol OR, 0.60 (95% CI, 0.40-0.91); $P = .02$			OR highest vs lowest quintiles of maternal vitamin E intake, P trend Ever wheeze, 0.75 (0.44-1.28); $P = .07$ Wheeze previous year, 0.46 (0.24-0.90); $P = .01$ Wheeze no cold, previous year, 0.22 (0.08-0.62); $P = .01$ Seen GP with wheeze previous year, 0.38 (0.17-0.87); $P = .02$	OR, highest vs lowest quintiles of maternal vitamin E, P trend Parental report of ever asthma, 0.47 (0.24-0.92); $P = .04$ Doctor-diagnosed asthma, 0.45 (0.23-0.89); $P = .02$ Asthma with wheeze, previous year, 0.28 (0.11-0.69); $P = .02$	FEV_1 of children with mothers in lowest third α-tocopherol reduced by 77 mL (95% CI, 26-128; $P < .01$)	
Litonjua[E36]	Cohort	2 yo; vitamin E with/without supplement; exposure during pregnancy				Vitamin E, highest vs lowest quartile Ever wheeze, 0.70 (0.48, 1.03); P trend = .06 Recurrent wheeze, 0.49 (0.27, 0.90); P trend = .05			
Martindale[E37]	Cohort	2 yo: maternal and child E intake—FFQ; maternal and cord plasma α-tocopherol by normal phase HPLC, adjusted for cholesterol; exposure during pregnancy				Maternal vitamin E intake 5th vs 1st quintiles Ever wheeze, 0.53 (0.27-1.01); P (trend) .183 Wheeze in the absence of a "cold" 3rd vs 1st third 0.49 (0.26-0.93); P (trend) .009			
Miyake[E42]	Cohort	763 Japanese mother-child pairs; dietary intake; dietary history questionnaire based on the Standard Tables of Food Composition in Japan		No associations		Maternal intake of vitamin E is a protective factor against infantile wheeze, 0.54 (0.32-0.90)			
Hijazi[E28]	Case-control	12 yo; FFQ vitamin A, C, E, β-carotene, Zn, Se, vegetables					Vitamin E Lowest third vs highest, OR, 3.00; 95% CI, 1.38- 6.50 P trend <.02		

(Continued)

TABLE E4. *(Continued)*

Exposure			Outcomes						
Vitamin E	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Hozyasz[E29]	Case-control	1-9 yo; serum and erythrocyte α-tocopherol adjusted for cholesterol		Erythrocyte α-tocopherol lower in AD (2.14 ± 0.69 mmol/L vs 3.17 ± 0.49 mmol/L, $P < .001$)					
Kalayci[E33]	Case-control	13-15 yo; serum α-tocopherol					Children with asthma, lower α-tocopherol, $P < .001$, graphic representation of results		
Murray[E43]	Case-control	Mean age, 4.4 y; FFQ dietary intake of vitamin A, C, E, zinc, selenium Atopic wheezers vs nonatopic never wheezed				Wheeze vs controls, 5.7 (5.0, 6.6) vs 4.9 (4.4, 5.4) mg/d, $P = .06$			
Powell[E49]	Case-control	Range, 18 mo to 16 y (mean, 9 y); plasma α-tocopherol					Vitamin E: in children with asthma, 20.87μmol/L (14.74-22.97); in controls, 21.6 μmol/L (17.02-25.93) not significant		
Ellwood[E17]	Cross-sectional	6-7 yo and 13-14 yo ISAAC phase 1 (1994-95); vitamin E from vegetables (microg/24 h) measured at population level; FAOSTAT data Food and Agriculture Organization food-balance sheets; measured in: % of total energy consumption		Vegetable derived vitamin E not associated with AD	Vegetable derived vitamin E not associated with ARC		Vegetable-derived vitamin E not associated with asthma		
Gilliland[E26]	Cross-sectional	11-19 yo; vitamin E intake; total diet and supplement; validated FFQ						In boys, low dietary vitamin E, lower $FEF_{25–75}$ –8.9%, (–14.2, –3.3)	
Harik-Khan[E27]	Cross-sectional	6-17 yo; NHANES III; dietary (24-h recall); questionnaires; serum vitamin E					Serum vitamin E not associated with asthma		
Huang[E31]	Cross-sectional	13-17 yo; dietary intake; 24-h food recall			Vitamin E not associated with ARC		Vitamin E not associated with asthma		
McKeever[E38]	Cross-sectional	10.7 yo (SD, 3.10); NHANES III; serum vitamin E; SPT	Vitamin E, 1.01 (0.93-1.09)						
Rubin[E51]	Cross-sectional	Serum vitamin E, 4-16 yo; NHANES III; serum vitamin E					Serum vitamin E, 0.95 (0.8, 1.1)		

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ*, Food Frequency Questionnaire; *FEF_{25-75},* forced expiratory flow at 25% to 75% of forced vital capacity; *SPT,* skin prick test; *yo,* years old.

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TABLE E5. Detailed characteristics of vitamin D studies

Exposure			Outcomes						
Vitamin D	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Bäck[E4]	Cohort	6 yo; vitamin D intake during the first year of life; validated postal questionnaire (ISAAC study questions used)		Vitamin D intake and AD, OR, 3.63 (95% CI, 1.49-8.87)	No associations		No associations		
Camargo[E6]	Cohort	3 yo; dietary and supplemental vitamin D; validated FFQ; exposure during pregnancy		Highest vs lowest quartile of maternal intake, 0.92 (0.63, 1.35); $P = .75$		Recurrent wheeze highest vs lowest quartile of vitamin D intake; OR, 0.38 (0.22, 0.65); $P < .001$			
Devereux[E13]	Cohort	5 yo; maternal vitamin D intake by FFQ				Highest vs lowest quintile of vitamin D Ever wheeze, OR, 0.48 (0.25-0.91); $P = .01$ Current wheeze, OR, 0.35 (0.15-0.83); $P = .009$ Persistent wheeze 2 and 5 y, OR, 0.33 (0.11-0.98); $P = .01$			
Erkkola[E18]	Cohort	5 yo; 1669 children from a birth cohort; outcome measures by ISAAC questionnaire; maternal total vitamin D intake by FFQ			Maternal intake of vitamin D was protective against allergic rhinitis (hazard ratio, 0.85; 0.75-0.97)		Maternal intake of vitamin D was protective against asthma (hazard ratio, 0.80; 0.64-0.99)		
Gale[E23]	Cohort	9 mo and 9 y; maternal blood vitamin D at 33 gestation, FFQ for dietary vitamin D		Eczema at 9 mo, highest quarter blood vitamin D vs lowest (<30), 3.26 (1.15-9.29); $P = .025$			Asthma at 9 y highest quarter maternal blood vitamin D, 5.40 (1.09-26.65); $P = .038$, middle 2 quarters nonsignificant		
Hypponen[E32]	Cohort	Vitamin D supplementation in infancy; followed up at 31 y: SPT; infant vitamin D supplements: regular, irregular, or none; subject report	Vitamin D regular vs non/irregular, 1.33 (1.07-1.64); $P = .01$ >2000 IU vitamin D, 0.77 (0.32-1.84); $P < .001$		Vitamin D regular, 1.33 (1.12-1.58); $P < .001$		Vitamin D regular, 1.33 (0.97-1.82); $P = .08$		

(Continued)

TABLE E5. *(Continued)*

Exposure			Outcomes						
Vitamin D	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Miyake[E41]	Cohort	763 Japanese mother-child pairs; children age 16-24 mo; higher intake vs lower (a cut-off point at the 25th percentile) intake of vitamin D by mothers		Consumption of vitamin D 4.309 mg/d was protective against eczema in children (OR, 0.63; 0.41-0.98)		Consumption of vitamin D 4.309 mg/d was protective against wheeze in children (OR, 0.64; 0.43-0.97)			
Nja[E44]	Cross-sectional	6-16 yo; 0-11 mo intake of cod liver oil; a second parentally completed questionnaire	Infant cod liver oil and atopic sensitization (OR, 1.78; 95% CI, 1.03-3.07)			No association of infant cod liver oil and wheeze	No association of infant cod liver oil and asthma		

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ,* Food Frequency Questionnaire; *SPT,* skin prick test; *yo,* years old.
Frequency of vitamin D supplementation during the first year of life was reported by the mother as regular intake, irregular intake, or no intake.

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TABLE E6. Detailed characteristics of selenium studies

Exposure			Outcomes						
Selenium	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Devereux[E14]	Cohort	Cohort followed up 1,2, 5 y; maternal blood and neonatal cord blood Se and glutathione peroxidase; exposure during pregnancy	No associations between selenium and atopy at 5 y			OR, 10 mg/kg maternal plasma selenium 2 y Wheeze previous y, 0.86 (0.76-0.97); $P = .011$ Wheeze in the absence of a cold previous y, 0.91 (0.76-1.09); $P = .32$ OR, 10 mg/kg cord plasma selenium 2 y Wheeze previous y, 0.67 (0.47-0.96); $P = .030$ Wheeze in the absence of a cold previous y, 0.978 (0.47-1.30); $P = .35$ No associations between selenium at 5 y	OR, 10 mg/kg maternal plasma selenium 2 y Doctor-confirmed asthma, 0.92 (0.76-1.12); $P = .41$ OR, 10 mg/kg cord plasma selenium 2 y Doctor-confirmed asthma, 0.95 (0.57-1.58); $P = .85$ No associations between selenium and asthma at 5 y	No associations between selenium and spirometry at 5 y	
Shaheen[E52]	Cohort	ALSPAC cohort; umbilical cord Se, 2 methods used (ICP-OES and ICP-MS) Persistent wheeze 0-6 and 30-42 mo		No associations of selenium and eczema		OR Se (per doubling concentration) persistent wheeze, 0.67 (0.45-0.99); $P = .043$ OR highest vs lowest Se quintile, 0.58 (0.36-0.91); $P = .019$			
Shaw[E54]	Cohort	8-13 yo; wheeze related to serum Se in stored samples collected 8 y prior; Se assessed by a semiautomated fluorometric method; written questionnaire to parents.				Current wheeze low vs highest Se, OR, 3.1 (95% CI, 0.9-11.8)			
Burney[E5]	Case-control	7-14 yo; the GA2LEN network organized; questionnaire; plasma Se by atomic absorption spectroscopy using a Perkin Elmer 4110 ZL spectrometer					Athens: Asthma vs controls plasma Se, mean, 82.7 (SD, 10.9) vs 80.3 (13.1); $P = .46$ Oslo: Asthma vs controls plasma Se, 56.4 (9.4) vs 56.1 (9.6); $P = .87$		
Hijazi[E28]	Case-control	12 yo; Se dietary intake; FFQ					Asthma vs controls, 0.24 (0.05) vs 0.25 (0.06); $P = .56$		

(Continued)

TABLE E6. *(Continued)*

Exposure			Outcomes						
Selenium	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Kocabas[E34]	Case-control	0.3-5 yo; serum Se by spectrofluorometric method; SPT, IgE				Frequent wheeze vs controls mean (SD) serum Se, 61.95 ± 1.20 and 72.71 ± 1.280; $P < .001$			
Murray[E43]	Case-control	Mean age, 4.4 y; FFQ dietary intake of vitamin A, C, E, zinc, selenium Atopic wheezers vs nonatopic never wheezed				Wheeze vs controls, 46.7 (41.6-52.4) vs 45.4 (40.4-51.0) μg/d; $P = .76$			
Omata[E46]	Case-control	Age 2.8-15.0 y; urinary Se by diaminonaphthalene fluorometric method; early morning samples; unmatched case-control study		Mean urinary Se AD vs controls, 60.1 ng/mg (SD, 26.7) vs 61.4 (23.9) No P value given					
McKeever[E38]	Cross-sectional	10.7 (SD, 3.10); NHANES III: serum Se; SPT	Selenium, 0.99 (0.84-1.02)						
Rubin[E51]	Cross-sectional	4-16 yo; NHANES III; serum Se					Serum Se, 0.88 (95% CI, 0.7-1.1)		

AD, Atopic dermatitis; *ALSPAC*, The Avon Longitudinal Study of Parents and Children; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ*, Food Frequency Questionnaire; *ICP-OES*, inductively coupled plasma-optical emission spectrometry; *ICP-MS*, inductively coupled plasma-mass spectrometry; *GA2LEN*, Global Allergy and Asthma European Network; *SPT,* skin prick test; *yo,* years old.
All analysis reagents and modifiers were purchased from Merck, the standards used were Selenium Atomic Standard Solution (Stigma-Aldrich, St Louis, Mo).

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TABLE E7. Detailed characteristics of zinc studies

Exposure			Outcomes						
Zinc	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Devereux[E15]	Cohort (same cohort as Martindale[E37])	5 yo; maternal blood Zn enzymatic colorimetric assays; maternal and child FFQ exposure during pregnancy	No association with SPT	Ever eczema, 0.63 (0.40-0.95); $P = .03$ Doctor-confirmed eczema, 0.67 (0.43-1.07); $P = .05$ Current treatment for eczema, 0.51 (0.29-0.90); $P = .04$			OR, highest vs lowest quintiles of maternal zinc, P trend Parental report of ever asthma, 0.51 (0.27-0.97); $P = .04$ Treatment for asthma, 0.61 (0.32-1.17); $P = .08$ Asthma with wheeze previous year, 0.28 (0.12-0.67); $P = .003$	No association with lung function	
Litonjua[E36]	Cohort	2 yo; Zn with/without supplement; exposure during pregnancy				Ever wheeze, 0.59 (0.41- 0.88); P (trend) .01 Recurrent wheeze, 0.49 (0.27-0.87); P (trend) .06			
Shaheen[E52]	Cohort	ALSPAC cohort; umbilical cord Se, 2 methods used (ICP-OES and ICP-MS) Persistent wheeze 0-6 and 30-42 mo		Eczema 18-30 mo OR, 1.10 (95% CI, 0.94-1.28); P $P = .25$		Wheeze 30-42 mo, OR, 1.16 (95% CI, 0.93-1.44); $P = .18$			
El-Kholy[E16]	Case-control	2-12 yo; serum and hair Zn by atomic absorption spectrophotometry		Mean serum Zn vs control, 65.9 ± 11.7 vs 88.4 ± 11.0 μg/100 mL Mean hair Zn vs control, 164.8 ± 23.6 vs 194.5 ± 18.6 μg/gm; $P < .001$			Mean serum Zn vs control and hairs were respectively 70.3 ± 13.2 μg vs 88.4 ± 11.0 μg/100 mL Mean hair Zn vs control, 167.5 ± 23.0 vs 194.5 ± 18.6 μg/gm; $P < .001$		
Ermis[E19]	Case-control	7.6 ± 1.8 yo; serum Zn by atomic absorption spectrometry					Mean serum Zn asthma vs controls, 70.6 μg/dL (SD, 8.3) vs controls, 78.3 (9.2); $P < .01$		
Hijazi[E28]	Case-control	12 yo; Zn dietary intake; FFQ					Asthma vs controls, 14.2 (2.2) vs 14.7 (2.3) mg/d; $P = .09$		
Murray[E43]	Case-control	In abstract, mean age 4.4 y; methods: 3 y (±4 wk); dietary intake Zn; FFQ, nutrient analysis program				Wheeze vs controls, 7.8 (7.0- 8.5) vs 7.4 (6.8-7.9) mg/d; $P = .39$			
Tahan[E56]	Case-control	1-3 yo; hair Zn by atomic absorption spectrophotometry				Hair zinc levels wheezy infants vs controls, wheezy infants, 34 (4-85) vs 136.5 (111-175) μg/g; $P < .001$)			

AD, Atopic dermatitis; *ALSPAC*, The Avon Longitudinal Study of Parents and Children; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ*, Food Frequency Questionnaire; *ICP-OES*, inductively coupled plasma-optical emission spectrometry; *ICP-MS*, inductively coupled plasma-mass spectrometry; *SPT,* skin prick test; *yo,* years old.

TABLE E8. Detailed characteristics of fruits and vegetables studies

Exposure			Outcomes						
Fruits and vegetables	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Fitzsimon[E21]	Cohort	3 yo; Life-ways Cross-Generation Cohort Study; diagnosis of asthma by GP; maternal dietary fruit and vegetable intake; FFQ; exposure during pregnancy					Comparing highest vs lowest quartiles of maternal fruit and vegetable intake, OR, 0.42 (0.18-0.99)		
Willers[E60]	Cohort (same cohort as Devereux[E15], 2007, Martindale Martindale[E37])	5 yo; Aberdeen cohort; maternal dietary fruit and vegetable intake; FFQ; exposure during pregnancy	No associations	No associations	No associations	OR, highest vs lowest tertiles of maternal apple intake Ever wheeze, 0.63 (0.42-0.95); *P* trend .029	OR, highest vs lowest tertiles of maternal apple intake Doctor-confirmed asthma, 0.47 (0.27-0.82); *P* trend = .008 Ever asthma, 0.54 (0.32-0.92); *P* trend = .026		
Willers[E61]	Cohort	PIAMA birth cohort followed up 8 y; maternal dietary fruit and vegetable intake; FFQ; exposure during pregnancy				Daily vs rare nut products (peanut butter), wheeze, OR, 1.42 (1.06-1.89); no association with regular vs rare	Daily vs rare nut products (peanut butter), asthma symptoms, 1.47 (1.08-1.99), no association with regular vs rare		
Hijazi[E28]	Case-control	12 yo; fruit and vegetable intake; FFQ					Vegetables: portion/d >3, OR, 1.0; 2-3/d, OR, 2.45 (95% CI, 1.30-4.65); <2/d, 2.83 (0.98-8.09); *P* trend .01		
Pastorino[E47]	Case-control	From ISAAC study (phase III); 13-14 yo; SPT; dietary intake of fresh fruit and cooked vegetables					Consumption of fresh fruit, yes vs no, OR, 0.31 (0.08-1.21); *P* = .091 Consumption of cooked vegetables, 0.37 (0.18-0.79); *P* = .010		

(Continued)

TABLE E8. *(Continued)*

Exposure			Outcomes						
Fruits and vegetables	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Antova[E1]	Cross-sectional	From Central European Study on Air Pollution and Respiratory Health (CESAR) cross-sectional study; 7-11 yo were surveyed in 6 European countries (Bulgaria, Hungary, Czech Republic, The Netherlands, Poland, Slovak Republic); winter and summer fruit and vegetable intake by children; questionnaire				Current wheeze, high vs low summer fruit intake, OR, 1.25 (95% CI, 0.91-1.73); $P = .10$ High vs low winter fruit intake, OR, 0.89 (0.71-1.10); $P = .21$			
Awasthi[E3]	Cross-sectional	6-7 yo and 13-14 yo; ISAAC III screening questionnaire; wheeze not specified; fruit and vegetable intake				For wheeze in 13-14 yo: vegetables ≥1/wk, OR, 0.46 (0.23-0.92) Fruits ≥3/wk, OR, 1.77 (1.28-2.43)	No relationship between fruit/vegetables and asthma/wheeze presented in 6-7 yo or for asthma in 13-14 yo		
Chatzi[E9]	Cross-sectional	6.5 yo; fruit and vegetable intake; parental report; parental FFQ; SPT	Fruits, high vs lowest thirds, OR, 0.90 (0.48-1.70); $P = .74$. Vegetables, high vs low thirds, OR, 0.94 (0.48-1.83); $P = .860$			Fruit and vegetable intake, high vs low thirds Current wheeze, OR, 0.38 (CI, 0.15-0.95); $P = .044$ Atopic wheeze, OR, 0.19 (CI, 0.04-0.95); P for trend = .04 No associations with fruits or vegetables			
Cook[E11]	Cross-sectional	8-11 yo; fresh fruit, salads and green vegetables intake, parental FFQ				Wheeze not related to fresh fruit consumption; $P = .63$		Fresh fruit intake, highest vs lowest, mean FEV_1 (SE), 1.850 (0.012); P trend = .031	
Ellwood[E17]	Cross-sectional	6-7 yo and 13-14 yo ISAAC phase 1 (1994-1995) vegetable intakes g/d or percentage		Vegetables, g/d: coefficient, –0.02 (95% CI, –0.03 to –0.01); $P = .001$	Vegetables, g/d: coefficient, –0.02 (–0.04 to –0.002); $P = .083$	Vegetables, g/d: coefficient, –0.02 (–0.04 to –0.001); $P = .041$			

(Continued)

TABLE E8. *(Continued)*

Exposure			Outcomes						
Fruits and vegetables	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Farchi[E20]	Cross-sectional	6-7 yo; ISAAC; Italy; intake of cooked vegetables, tomatoes, fruit, citrus fruit; parental FFQ			No associations between food consumption (cooked vegetables, fresh salads, summer tomatoes, and fruit) and 12-mo occurrence of allergic rhinitis	No associations with cooked vegetables, peppers, potatoes, fruit, citrus fruit, kiwi fruit Fresh salads: high vs low, OR, 0.66 (0.41-1.04); *P* trend .047 Summer tomatoes: high vs low, 0.49 (0.31-0.80); *P* trend .003			
Forastiere[E22]	Cross-sectional	6-7 yo; Italian Studies on Respiratory Disorders in Children and the Environment (SIDRIA) within ISAAC; winter intake of citrus fruit and kiwi fruit; parental ISAAC questionnaire			Winter citrus/kiwi fruit intake, high vs low, OR, 0.72 (0.63-0.83); *P* trend < .001	Winter citrus/kiwi fruit intake high vs low, wheeze: OR, 0.66 (0.55-0.78); *P* trend < .001 Exercise-induced wheeze: OR, 0.74 (0.53-1.04); *P* trend .160			
Garcia[E24]	Cross-sectional	7 yo and 13-14 yo; ISAAC phase 1; Colombia; fruit intakes; self-administered written questionnaire and video questionnaire for 13-14 yo children				No data presented on 6-7 yo, just reported as not a strong association In 13-14 yo, high fruit intake vs low, OR, 0.6 (95% CI, 0.4-1.0); *P* = .031			
Gilliland[E26]	Cross-sectional	11-19 yo; oranges and fruit juices, vegetable intake; validated FFQ						Low intakes of fruit juices, $\%FEV_1$ in boys, –2.7 (95% CI, –5.0 to –0.4)	
Lewis[E35]	Cross-sectional	4-6 yo; East Midland and East of England Regions (UK); dietary fruit intake; a short questionnaire to parents		Fruit intake not associated with eczema (data not presented)		No relationship between fruit and wheezing outcomes	No relationship between fruit and asthma (*P* for trend = .2)		

(Continued)

TABLE E8. *(Continued)*

Exposure			Outcomes						
Fruits and vegetables	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Nja[E44]	Cross-sectional	6-16 yo; infant intake of fruit and vegetables; SPT; parental questionnaire	Infant fruit/vegetable not associated				Infant fruit/vegetable intake, OR for asthma, 0.57 (95% CI, 0.37-0.88)		
Okoko[E45]	Cross-sectional	5-10 yo; South London, UK; fresh apple, apple juice, orange juice, banana, pears, miscellaneous fruit assessed by ISAAC screening questionnaire				OR (95% CI), high vs low intakes Apples Current wheeze, 0.83 (0.50-1.36); *P* trend = .91 Ever wheeze, 0.78 (0.53-1.15); *P* = .37 Apple juice from concentrate Ever wheeze, 0.63 (0.47-0.85); *P* = .002 Current wheeze, 0.53 (0.34-0.83); *P* = .003 Bananas Current wheeze, 0.66 (0.44-1.00) Ever wheeze, 0.69 (0.50-0.95)	OR (95% CI), high vs low intakes Apples Ever asthma, 0.79 (0.52-1.20); *P* = .39 Apple juice from concentrate 0.90 (0.63-1.28); *P* = .40 Bananas 0.80 (0.56-1.14)		
Tabak[E55]	Cross-sectional	8-13 yo; ISAAC 2; fruit, citrus fruit, vegetable intake; FFQ	No associations between fruit and vegetable intake and sensitization			High vs low intakes Current wheeze Vegetables, OR, 1.24 (0.69-2.23) Citrus, 0.96 (0.56-1.66)	High vs low intakes Current asthma Vegetables OR, 0.69 (0.33-1.45) Citrus 0.65 (0.37-1.14)		
Tamay[E57]	Cross-sectional	6-12 yo; ISAAC; Istanbul, Turkey; fruit and vegetable intake; ISAAC questionnaire completed by parents			High vs low intake of fruit, allergic rhinitis, OR, 0.64 (95% CI, 0.45-0.91) No association with vegetables				
Tsai[E58]	Cross-sectional	11-12 yo; Taiwan; consumption of fruit and vegetable intake; interview survey				Wheeze in absence of a cold Vegetable intake, OR, 0.99 (0.92-1.06) Fruit, 0.91 (0.85-0.98); *P* < .01	Asthma Vegetables, OR, 1.00 (0.93-1.07) Fruit, 0.96 (0.89-1.02)		

(Continued)

TABLE E8. *(Continued)*

Exposure			Outcomes						
Fruits and vegetables	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Ushiama[E59]	Cross-sectional	Infants age 7.9 ± 2.8 mo; Japan; fruit and vegetable intake during pregnancy; questionnaire and FFQ; exposure during pregnancy		AD not associated with fruit or vegetable intake			Vegetable intake by mother's childhood asthma, OR, 1.84 (1.06-3.18); *P* .03	Lung function not associated with fruit or vegetable intake	
Wong[E62]	Cross-sectional	10 yo; China; consumption of fruit, cooked green vegetables, raw vegetables; SPT; parental questionnaire				Current wheeze, fruit >1/d vs ≤1, OR, 0.70 (0.54-0.89); *P* .004; raw vegetables >1/wk vs ≤1, 0.81 (0.64-1.03); *P* = .082			

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *FFQ*; Food Frequency Questionnaire; *GP*, general practitioner; *PIAMA*, Prevention and Incidence of Asthma and Mite Allergy; *SPT,* skin prick test; *UK,* United Kingdom; *yo,* years old.

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TABLE E9. Detailed characteristics of Mediterranean diet studies

Exposure			Outcomes						
Mediterranean diet	**Design**	**Notes**	**Atopy**	**AD**	**ARC**	**Wheeze**	**Asthma**	**Lung function**	**FA**
Chatzi[E10]	Cohort	6.5 yo; Menorca, Spain; MD was evaluated by *a priori* defined scores; maternal and child's by FFQ; exposure during pregnancy	Childhood sensitization Maternal vegetables, OR, 0.40 (0.22-0.72); $P < .05$ Maternal MD, OR, 0.55 (0.31-0.97) Child's MD, OR, 0.49 (0.18-1.32); $P = .213$			Persistent wheeze Maternal vegetables, OR, 0.36 (0.14-0.92); $P < .05$ Maternal MD, 0.22 (0.08-0.58) Child's MD, OR, 0.46 (0.10-2.17); $P = .523$			
Castro-Rodriges[E7]	Cross-sectional	Mean age, 4.08 ± 0.8 y; Spain; MD score; the questionnaire used based on the ISAAC phase III core and environment questionnaires; parental completion of dietary questions		Not reported	Not reported	Highest vs lowest quartile of MD intake, OR, 0.54 (0.33-0.88); $P = .014$			
Chatzi[E8]	Cross-sectional	7-18 yo; Crete, Greece; adherence to MD was measured using a scale with 12 dietary items; ISAAC questionnaire			Ever allergic rhinitis High vs low intake Grapes, OR, 0.31 (0.14-0.64); P trend = .21 Oranges, OR, 0.29 (0.11-0.80); P trend = .047 Kiwi, OR, 0.37 (0.16-0.86); P trend = .018 High MD, OR, 0.34 (0.18-0.64); $P = .004$	Ever wheeze, OR, >1/d vs 0 High vs low intake Grapes, OR, 0.19 (0.09 -0.42); P trend = .001 Oranges, OR, 0.30 (0.11-0.90); P trend = .804 Apples, OR, 0.14 (0.04-0.48); P trend = .225 Fresh tomatoes, OR, 0.32 (0.15-0.67); P trend = .01 MD, OR, 0.67 (0.34-1.32); P trend = .229.			
De Batle[E12]	Cross-sectional	6-7 yo; Mexico; ISAAC methodology; adherence to MD (score); children's intake and mothers intake during pregnancy; parental FFQ; exposure during pregnancy			Children's diet in last year Higher 2 tertiles of MD score Allergic rhinitis ever, OR, 0.41 (0.22-0.77); P trend = .046	Children's diet in last year, higher 2 tertiles of MD score, wheezing ever, OR, 0.64 (0.47-0.87); P trend = .001	Children's diet in last year higher 2 tertiles of MD score, asthma ever, OR, 0.60 (0.40-0.91); P trend = .034		

(Continued)

TABLE E9. *(Continued)*

Exposure			Outcomes						
Mediterranean diet	Design	Notes	Atopy	AD	ARC	Wheeze	Asthma	Lung function	FA
Garcia-Marcos[E25]	Cross-sectional	6-7 yo; Spain; ISAAC phase III questionnaire; MD score			Rhinoconjunctivitis, high vs low intake Fruit, OR, 0.71 (0.57-0.88); *P* trend < .001 No association with MD		Occasional asthma High vs low intakes Fruit, OR, 0.89 (0.70-1.12); *P* trend .01 Vegetables, 0.87 (0.72-1.04); *P* trend .03 Severe asthma Fruit, OR, 0.74 (0.50-1.10); *P* trend < .001 Vegetables, OR, 0.78 (0.56-1.11); *P* trend < .001 Severe asthma in girls, MD score, OR, 0.90 (0.82-0.98)		

AD, Atopic dermatitis; *ARC,* allergic rhinoconjunctivitis; *FA,* food allergy; *MD,* Mediterranean diet; *yo,* years old.

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