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Maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood: a systematic review and meta-analysis

A. A. Beckhaus[1], L. Garcia-Marcos[2,3], E. Forno[4], R. M. Pacheco-Gonzalez[2,3], J. C. Celedón[4] & J. A. Castro-Rodriguez[1]

[1]Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; [2]Respiratory and Allergy Units, Arrixaca University Children's Hospital, University of Murcia; [3]IMIB Bio-research Institute, Murcia, Spain; [4]Division of Pediatric Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA, USA

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Correspondence
Jose A. Castro-Rodriguez, MD, PhD, Departments of Pediatrics and Public Health, School of Medicine, Pontificia Universidad Católica de Chile, Lira 44, 1er Piso, casilla 114-D, Santiago, Chile.
Tel.: (56) 2 354 8189
Fax: (56) 2 354 8122
E-mail: jacastro17@homail.com

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Abstract

Background: Epidemiologic studies suggest a relationship between maternal nutrition during pregnancy and the occurrence of asthma and atopic conditions during childhood. However, individual study results are conflicting. The objective of this meta-analysis was to critically examine the current evidence for an association between nutrition (dietary patterns, food groups, vitamins, or oligo-elements) ingestion during pregnancy and asthma, wheeze, or atopic conditions in childhood.

Methods: The inclusion criteria were as follows: (i) systematic recording of diet during the gestational period and (ii) documentation of asthma, wheezing, eczema, or other atopic disease in the offspring. The primary outcomes were prevalence of asthma or wheeze among the offspring during childhood; and secondary outcomes were prevalence of eczema, allergic rhinitis, or other atopic conditions.

Results: We found 120 titles, abstracts, and citations, and 32 studies (29 cohorts) were included in this analysis. Data on vitamins, oligo-elements, food groups, and dietary patterns during pregnancy were collected. A meta-analysis revealed that higher maternal intake of vitamin D [odds ratio (OR) = 0.58, 95% confidence interval (CI) = 0.38–0.88], vitamin E (OR = 0.6, 95% CI = 0.46–0.78), and zinc (OR = 0.62, 95% CI = 0.40–0.97) was associated with lower odds of wheeze during childhood. However, none of these or other nutrients was consistently associated with asthma *per se* or other atopic conditions.

Conclusions: Current evidence suggests a protective effect of maternal intake of each of three vitamins or nutrients (vitamin D, vitamin E, and zinc) against childhood wheeze but is inconclusive for an effect on asthma or other atopic conditions.

Asthma and allergies are a major public health burden worldwide. Over the last few decades, the prevalence of childhood asthma has noticeably increased (1). In the United States, such prevalence increased from 7.3% in 2001 to 8.4% in 2010 (and from 3.5% in the 1970s). In 2010, an estimated 25.7 million people had current or active asthma in the United States, comprising 18.7 million adults and 7 million children (2). This 'asthma epidemic' is likely related to changes in environment or lifestyle, such as those in diet and nutrition (3).

Changes in dietary patterns preceded the increased occurrence of allergic diseases in the United Kingdom and other industrialized countries (4). In particular, consumption of a 'westernized' diet with low intake of antioxidants (and thus increased oxidative stress) may explain this temporal trend (5).

In utero exposures may markedly increase the risk of asthma or allergies in childhood (6), and thus, identifying such exposures is relevant to primary prevention of these common conditions. Findings from experimental and epidemiologic studies suggest that one such exposure—maternal diet or maternal nutrient status during pregnancy—affects the incidence of asthma and/or other allergic diseases (food allergy, eczema, and allergic rhinitis) in childhood (7, 8), perhaps through effects on the development of the fetal airways or immune responses (5, 9). However, the available evidence is inconclusive and of variable quality, depending on the dietary pattern or nutrient of interest, and considering current evidence, no recommendations about increasing or avoiding the consumption of these nutrients to prevent or ameliorate allergic disease in their offspring can be made (8).

The objective of this meta-analysis was to systematically evaluate prior published studies in addition to recently published evidence on whether the ingestion of dietary patterns, food groups, and vitamins or oligo-elements during pregnancy is associated with increased risk of asthma, wheeze, or atopic conditions during childhood.

Methods

Search and selection criteria

We searched electronic databases (March and November 2014) Medline, CENTRAL (Cochrane Collaboration Clinical Trials Register), LILACS, and CINAHL. The search process was conducted using the following keywords: (asthma OR wheeze* OR dermatitis OR eczema OR rhinitis) AND [maternal diet OR pregnancy diet OR (pregnancy AND diet)] AND (offspring OR infant OR child*). We also searched in other nonbibliographic data sources, such as web searching, references of included publications, and pharmaceutical industry websites. If the information was incomplete, we attempted to contact the authors. The inclusion criteria were as follows: (i) systematic recording of diet during the gestational period (daily register or food frequency questionnaire); (ii) assessment of asthma, wheezing, eczema, or other atopic disease in the offspring; and (iii) no language restriction. The exclusion criteria were as follows: (i) vitamin or oligo-element supplementation to the pregnant mother or her offspring, (ii) measurement of nutrients in blood (e.g., serum or plasma) samples with no recording of diet during pregnancy, and (iii) reviews or letters or abstracts, to have full information and results of all included studies. The primary outcomes of the study were asthma and wheeze during childhood. Secondary outcomes included eczema, allergic rhinitis, or other atopic condition during childhood.

Data abstraction and assessment of risk of bias

This systematic review was performed according to the Cochrane methodology and the recommendations for reporting proposed by the Meta-analysis of Observational Studies in Epidemiology group (10) and to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) (11). Titles, abstracts, and citations were independently analyzed by two independent investigators (JACR and LGM). From the full texts, the reviewers independently assessed all studies for inclusion, based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. Disagreements were resolved through a mediator (EF). The risk of bias from including certain studies was assessed according to the Newcastle–Ottawa Scale (12).

Data analysis

We calculated pooled odds ratios (ORs), relative risk ratios (RRs), and hazard ratios (HRs) with 95% confidence interval (CI) for categorical outcomes. Heterogeneity was assessed using the I^2 test and chi-square. For all of the outcomes measured, a fixed-effects meta-analysis was used when low heterogeneity was present ($I^2 < 40\%$), and a random-effects meta-analysis was performed to address the variation across the included studies when high heterogeneity was detected ($I^2 \geq 40\%$). Data from cohort and retrospective studies were pooled into separate meta-analyses. For each food group or oligo-element, high consumption was compared with low consumption. Some studies reported the same associations with several outcomes at different time of follow-up. When this happened, we used only one given estimate of effect (e.g., OR) to perform the meta-analysis, to avoid considering the same data twice. The meta-analysis was performed using Review Manager 5.1.6 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011, Copenhagen, Denmark).

Results

A total of 122 studies were initially identified from databases and other sources: 32 of these studies met our inclusion criteria and were included in the review, as listed in Fig. 1. All of the 32 studies included in the analysis were published between 2002 and 2014: 29 were prospective cohort studies and three were retrospective cohort studies. A detailed description of these 32 studies is shown in Table 1, and a description of our quality assessment is presented in Table 2. Our main results are summarized in Table 3.

Vitamin A

Seven studies reported on maternal intake of vitamin A or its constituent carotenoids and asthma or atopic outcomes (13–19). Two studies (17, 19) found no significant association between maternal vitamin A intake during pregnancy and childhood asthma. Alpha-carotene consumption was not associated with wheezing (15, 16) or eczema (16, 17), and β-carotene was not associated with wheezing (13–16,18) (pooled OR = 0.97, 95% CI = 0.68–1.37, I^2 0%), eczema

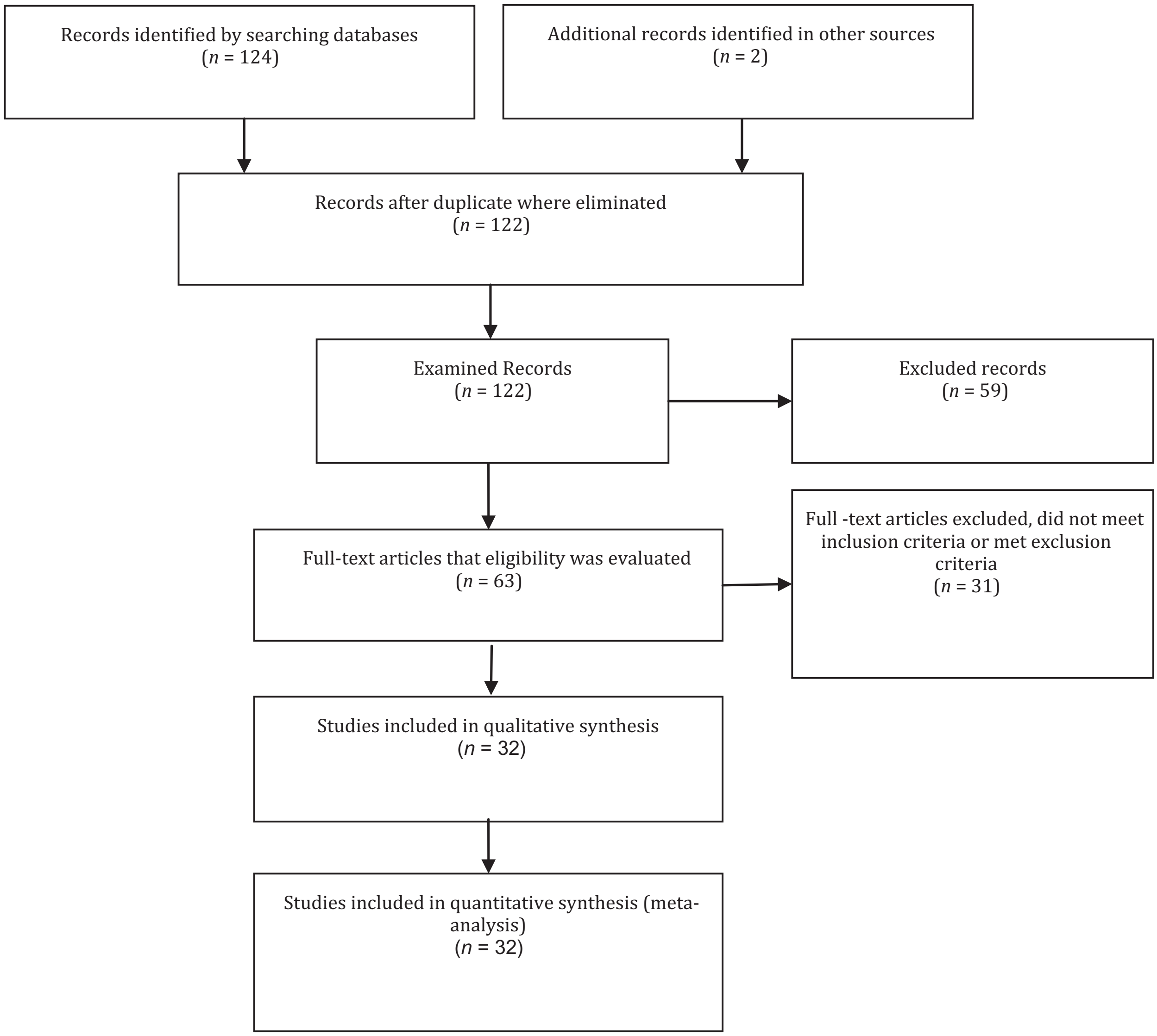

Figure 1 Flowchart for identification of studies used.

(16–18) (pooled OR = 0.76, 95% CI = 0.46–1.26, I^2 72%), food allergy (18), or skin test reactivity (STR) to allergens (18).

Vitamin B complex

Four cohort studies reported on maternal intake of folic acid (vitamin B9) during pregnancy and asthma or atopic outcomes (15, 17, 20, 21). One study (17) found no significant association between maternal intake of folic acid during pregnancy and asthma or allergic rhinitis in childhood. Two studies showed no significant association between maternal intake of folic acid and wheeze (15, 20) (pooled OR = 0.91, 95% CI = 0.49–1.68, I^2 48%), and three studies showed no relation with eczema (17, 20, 21) (pooled OR = 0.91, 95% CI = 0.76–1.09, I^2 0%). Two studies (17, 20) showed no significant association between maternal intake of vitamin B2 during pregnancy and childhood eczema (pooled OR = 0.86, 95% CI 0.74–1.01, I^2 0%). In another cohort study (20), there was no significant association between maternal dietary intake of vitamin B12 or vitamin B6 during pregnancy and childhood wheeze or eczema.

Vitamin C

Six cohort studies examined maternal dietary intake of vitamin C and asthma or atopic conditions (13–18). Four studies (13, 15, 16, 18) found no significant association between maternal intake of vitamin C during pregnancy and childhood wheeze (pooled OR = 0.99, 95% CI = 0.48–2.04, I^2 = 79%). Five studies (13, 14, 16–18) found no significant association between prenatal dietary intake of vitamin C and

Table 1 Summary of Included Studies

Author	Geographic area	Design	Included participants	Dietary component measured	Outcomes	Statistical methods for potential confounder factor adjustments
Ushiyama et al. (34)	Japan	Retrospective cohort	2070 mother–offspring pairs	FFQ of intake of multiple nutrients including fish, meat, egg, dairy, vegetables, fruits, sugar, fatty food, total energy during pregnancy (obtained at recruitment time)	Atopic eczema, food allergies, and asthma during recruitment time (Mean 7.6 ± 2.8 months after birth)	Logistic regression
Martindale et al. (13)	United Kingdom	Prospective Cohort	1924 mother–offspring pairs 1300 pairs at the end of follow-up (68%)	FFQ of antioxidant intake including vitamin E and C, β-carotene, selenium, magnesium, manganese, copper, and zinc (obtained during pregnancy)	Wheeze and eczema, at 6, 12, and 24 months after birth	Logistic regression
Devereux et al. (14)	United Kingdom	Prospective Cohort	1924 mother–offspring pairs 1253 pairs at the end of follow-up (65%)	FFQ of intake of vitamins E and C, β-carotene, selenium, magnesium, copper, iron, and zinc (obtained during pregnancy)	Wheeze, eczema, and asthma at 5 years of age	Logistic regression
Litonjua et al. (15)	United States	Prospective Cohort	1863 mother–offspring pairs 1290 pairs at the end of follow-up (69%)	FFQ of antioxidant intake including vitamin C and E, folic acid, α- and β-carotene, copper and zinc (obtained during pregnancy)	Recurrent wheeze and eczema at 6, 12, and 24 months after birth	Bivariate and multivariate logistic regression
Camargo et al. (22)	United States	Prospective Cohort	1863 mother–offspring binomials 1194 pairs at the end of follow-up (64%)	FFQ of vitamin D intake (obtained during pregnancy)	Recurrent wheeze and eczema at 6, 12, 24, and 36 months after birth	Multivariate logistic regression
Devereux et al. (23)	United Kingdom	Prospective Cohort	1924 mother–offspring pairs 1253 pairs at the end of follow-up (65%)	FFQ of vitamin D intake (obtained during pregnancy)	Wheeze and asthma at 2 and 5 years of age Atopic sensitization, spirometry and FE_{NO} at 5 years of age	Multivariate logistic regression
Romieu et al. (35)	Spain	Prospective Cohort	483 mother–offspring pairs 462 pairs at the end of follow-up (96%)	FFQ of dietary fish intake (obtained 3 months after delivery)	Eczema, atopy and persistent wheeze at 6.5 years of age	Multivariate logistic regression

Table 1 (continued)

Author	Geographic area	Design	Included participants	Dietary component measured	Outcomes	Statistical methods for potential confounder factor adjustments
Sausenthaler et al. (27)	Germany	Prospective Cohort	3097 mother–offspring pairs 2641 pairs at the end of follow-up (85%)	FFQ of multiple nutrients intake including fish, egg, dairy, and sorts of vegetables and fruits (obtained few days after delivery)	Eczema at 6, 12, 18, and 24 months after birth Allergic sensitization at 2 years of age	Logistic regression
Willers et al. (28)	United Kingdom	Prospective Cohort	1924 mother–offspring pairs 1253 pairs at the end of follow-up (65%)	FFQ of multiple nutrients intake including fish, meat, egg, dairy, vegetables, fruits, sugar, fatty food, total energy (obtained during pregnancy)	Asthma, wheeze, eczema, and hay fever at 5 years of age Atopic sensitization, spirometry and FE_{NO} at 5 years of age	Multivariate logistic regression
Chatzi et al. (29)	Spain	Prospective Cohort	482 mother–offspring pairs 468 pairs at the end of follow-up (97%)	FFQ evaluating mediterranean diet consumption (MD) and MD components (obtained 3 months after delivery)	Atopy and persistent wheeze at 6.5 years of age	Multivariate logistic regression
de Batlle et al.(40)	Mexico	Retrospective cohort	1476 mother–offspring pairs	FFQ evaluating mediterranean diet consumption (MD) during pregnancy (obtained at recruitment time)	Asthma, wheeze and allergic rhinitis, during recruitment time (6–7 years of age)	Logistic regression
Willers et al. (30)	The Netherlands	Prospective Cohort	4146 mother–offspring pairs 3320 pairs at the end of follow-up (80%)	FFQ of intake of multiple nutrients including fish, egg, dairy, vegetables, fruits, sugar, fatty food, and total energy during pregnancy (obtained during pregnancy)	Wheeze and asthma symptoms at 3 months after birth and then yearly from 1 to 8 years of age	Multiple logistic regression
Miyake Y et al. (36)	Japan	Prospective Cohort	1002 mother–offspring pairs 763 pairs at the end of follow-up (76%)	FFQ of fat intake including fish and meat (obtained during pregnancy)	Wheeze and eczema at 2–9 and 16–24 months after birth	Multiple logistic regression
Erkkola et al. (24)	Finland	Prospective Cohort	1669 pairs at the end of follow-up	FFQ evaluating vitamin D intake (obtained until 3 months after delivery)	Asthma, allergic rhinitis, and eczema at 5 years of age (children with HLA-DQB1 susceptibility for type 1 diabetes)	Logistic regression

Table 1 (continued)

Author	Geographic area	Design	Included participants	Dietary component measured	Outcomes	Statistical methods for potential confounder factor adjustments
Shaheen et al. (42)	United Kingdom	Prospective Cohort	14062 mother–offspring pairs at beginning, no description of number of pairs at the end of follow-up	FFQ evaluating five dietary patterns (obtained during pregnancy)	Wheeze, asthma, allergic rhinitis, eczema, and atopy at 7–8 years of age	Logistic regression
Castro-Rodriguez et al. (41)	Spain	Retrospective cohort	1409 mother–offspring binomials	FFQ of mediterranean diet and olive oil intake during pregnancy (obtained at recruitment time)	Wheeze during first year of live (15–18 months of age at recruitment)	Multivariate logistic regression
Miyake et al. (25)	Japan	Prospective Cohort	1002 mother–offspring pairs 763 pairs at the end of follow-up (76%)	FFQ of dairy, calcium and vitamin D intake (obtained during pregnancy)	Wheeze and eczema at 16–24 months after birth	Multiple logistic regression
Miyake et al. (16)	Japan	Prospective Cohort	1002 mother–offspring pairs 763 pairs at the end of follow-up (76%)	FFQ of vegetables, fruits and several antioxidants, including vitamin C, vitamin E, α- and β-carotene, and zinc (obtained during pregnancy)	Wheeze and eczema at 16–24 months after birth	Multiple logistic regression
Oien et al. (31)	Norway	Prospective Cohort	3086 pairs at the end of follow-up	FFQ of vegetables, fish, and cod liver oil (obtained 12 months after delivery)	Asthma and eczema at 24 months after birth	Multivariate logistic regression
Saito et al. (37)	Japan	Prospective Cohort	1002 mother–offspring pairs 771 pairs at the end of follow-up (77%)	FFQ of fat intake including fish and meat (obtained during pregnancy)	Eczema at 3–4 months of age	Multiple logistic regression
Miyake et al. (43)	Japan	Prospective Cohort	1002 mother–offspring pairs 763 pairs at the end of follow-up (76%)	FFQ evaluating three dietary patterns (obtained during pregnancy)	Wheeze and eczema at 16–24 months after birth	Multiple logistic regression
Miyake et al. (20)	Japan	Prospective Cohort	1002 mother–offspring pairs 763 pairs at the end of follow-up (76%)	FFQ evaluating folic acid and vitamins B12, B6, and B2 (obtained during pregnancy)	Wheeze and eczema at 16 to 24 months after birth	Multiple logistic regression

Table 1 (continued)

Author	Geographic area	Design	Included participants	Dietary component measured	Outcomes	Statistical methods for potential confounder factor adjustments
Nwaru et al. (17)	Finland	Prospective Cohort	2441 pairs at the end of follow-up	FFQ of antioxidant intake including vitamins A, C, and E, zinc, cooper, selenium, magnesium, manganese, calcium, folate, and riboflavin (B2) (obtained until 3 months after delivery)	Asthma, allergic rhinitis, and eczema at 5 years of age (children with HLA-DQB1 susceptibility for type 1 diabetes)	Logistic regression
Dunstan et al. (21)	Australia	Prospective Cohort	628 mother–offspring pairs 484 pairs at the end of follow-up (77%)	FFQ of folate intake (obtained during pregnancy)	Eczema, food allergy, and allergic sensitization at 12 months of age	Logistic regression
Erkkola et al. (32)	Finland	Prospective Cohort	2441 pairs at the end of follow-up	FFQ of intake of multiple nutrients including fats, fish, meat, dairy, vegetables, and fruits during pregnancy (obtained until 3 months after delivery)	Asthma, allergic rhinitis and wheezing at 5 years of age (children with HLA-DQB1 susceptibility for type 1 diabetes)	Logistic regression
Nwaru et al. (39)	Finland	Prospective Cohort	2441 pairs at the end of follow-up	FFQ of dietary fats during pregnancy (obtained until 3 months after delivery)	Wheezing, allergic rhinitis and eczema at 5 years of age (children with HLA-DQB1 susceptibility for type 1 diabetes)	Logistic regression
West et al. (18)	Australia	Prospective Cohort	450 mother–offspring pairs 300 pairs at the end of follow-up (67%)	FFQ of vitamin C, vitamin E, β-carotene, copper, and zinc (obtained during pregnancy)	Wheeze, eczema, food allergy, and allergic sensitization at 12 months of age	Multivariate logistic regression
Maslova et al. (44)	Denmark	Prospective Cohort	60466 mother–offspring pairs 38149 pairs at the end of follow-up (63%)	FFQ of artificially sweetened soft drinks (obtained during pregnancy)	Asthma at 18 months of age and asthma and allergic rhinitis at 7 years of age	Logistic regression
Chatzi et al. (33)	Spain and Greece	Prospective Cohort	Spain: 1784 pairs at the end of follow-up Greece: 1317 mother–offspring pairs 798 pairs at the end of follow-up (45%)	FFQ about mediterranean diet, vegetables, fruits, fish, meat, and dairy product intake (obtained during pregnancy)	Wheeze and eczema at 12 months of age	Multivariate log-binominal regression

Table 1 (continued)

Author	Geographic area	Design	Included participants	Dietary component measured	Outcomes	Statistical methods for potential confounder factor adjustments
Miyake et al. (38)	Japan	Prospective Cohort	1590 mother–offspring pairs 1362 pairs at the end of follow-up (86%)	FFQ of fat intake including fish and meat (obtained during pregnancy)	Wheeze and eczema at 4, 12, and 24 months after birth	Multiple logistic regression
Maslova et al. (19)	Denmark	Prospective Cohort	60466 mother–offspring pairs 28 678 pairs at the end of follow-up (47%)	FFQ about vitamin A, E, and K intake (obtained during pregnancy)	Asthma at 18 months of age and asthma and allergic rhinitis at 7 years of age	Multivariate logistic regression
Miyake et al. (26)	Japan	Prospective Cohort	1590 mother–offspring pairs 1362 pairs at the end of follow-up (86%)	FFQ of dairy, calcium and vitamin D intake (obtained during pregnancy)	Wheeze and eczema at 4, 12, and 24 months after birth	Multiple logistic regression

FFQ, food frequency questionnaire; HLA: human leukocyte antigen.

childhood eczema (pooled OR = 0.95, 95% CI = 0.69–1.31, I^2 = 56%). Two studies (14, 17) showed no significant association between maternal dietary intake of vitamin C during pregnancy and asthma or other atopic outcomes (allergic rhinitis, food allergy, or STR to allergens) (18).

Vitamin D

Five cohort studies reported on maternal dietary intake of vitamin D during pregnancy and asthma or atopic diseases (22–26). Maternal vitamin D intake during pregnancy was associated with a reduction in the odds of childhood wheeze (22, 23, 25, 26) (pooled OR = 0.58, 95% CI = 0.38–0.88, I^2 = 59%; Fig. 2). We found no significant association between maternal dietary intake of vitamin D during pregnancy and asthma (24, 25), eczema (22, 24–26) (pooled OR = 0.76, 95% CI = 0.46–1.26, I^2 = 72%), or allergic rhinitis (24). Our findings thus support an inverse association between maternal vitamin D intake during pregnancy and childhood wheeze. However, our results do not support an association between maternal vitamin D intake during pregnancy and asthma or other atopic diseases during childhood.

Vitamin E

Seven cohort studies examined maternal dietary intake of vitamin E and atopic conditions during childhood (13–19). Maternal vitamin E intake was associated with a 46% reduction in the odds of childhood wheeze (13–16, 18) [pooled OR = 0.54, 95% CI = 0.41–0.71, I^2 = 0% (Fig. 3)]. There were no significant results for asthma (14, 17, 19), eczema (13, 16–18) (pooled OR = 0.87, 95% CI = 0.65–1.18, I^2 = 48%), allergic rhinitis (17), food allergy (18), or STR to allergens (18). Hence, our results are consistent with an inverse association between maternal dietary intake of vitamin E during pregnancy and childhood wheeze. We found no supportive evidence of an association between maternal vitamin E intake during pregnancy and asthma or any atopic condition during childhood.

Zinc

Six cohort studies examined the relation between maternal dietary intake of zinc during pregnancy and the outcomes of interest (13–18). Maternal zinc intake during pregnancy was associated with a reduction in the odds of childhood wheeze (15, 16, 18) [pooled OR = 0.57, 95% CI = 0.40–0.81, I^2 = 0% (Fig. 4)]. There were no significant results for asthma (14, 17), eczema (13, 14, 16–18) (pooled OR = 1.00, 95% CI = 0.69–1.45, I^2 = 63%), allergic rhinitis (17), food allergy (18), or STR to allergens (18). Thus, our results support an inverse association between maternal zinc intake during pregnancy and childhood wheeze. On the other hand, our findings do not support an association between prenatal intake of zinc and asthma or allergies in childhood.

Copper

Of the five cohort studies that examined maternal dietary intake of copper during pregnancy and asthma or allergic diseases during childhood (13–15, 17, 18), one (18) found an inverse association between maternal copper intake and food allergy in their offspring (OR 0.38, 95% CI = 0.15–0.95), but none found a significant association with asthma (14, 17)

Table 2 Risk of Bias of the Included Studies

	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up
Ushiyama et al. (34)	*	*		*	*		*	
Martindale et al. (13)	*	*	*	*	*		*	
Devereux et al. (14)	*	*	*	*	*		*	
Litonjua et al. (15)	*	*	*	*	*		*	
Camargo et al. (22)	*	*	*	*	*		*	
Devereux et al. (23)	*	*	*	*	*		*	
Romieu et al. (35)	*	*	*	*	*		*	*
Sausenthaler et al. (27)	*	*	*	*	*		*	*
Willers et al. (28)	*	*	*	*	*		*	
Chatzi 2008(29)	*	*	*	*	*		*	*
de Batlle et al. (40)	*	*		*	*		*	
Willers 2008(30)	*	*	*	*	*		*	*
Miyake Y et al. (36)	*	*	*	*	*		*	*
Erkkola et al. (24)	*	*	*	*	*		*	
Shaheen et al. (42)	*	*	*	*	*		*	
Castro-Rodriguez et al. (41)	*	*		*	*		*	
Miyake et al. (25)	*	*	*	*	*		*	*
Miyake et al. (16)	*	*	*	*	*		*	*
Oien et al. (31)	*	*	*	*	*		*	
Saito et al. (37)	*	*	*	*	*		*	*
Miyake et al. (43)	*	*	*	*	*		*	*
Miyake et al. (20)	*	*	*	*	*		*	*
Nwaru et al. (17)	*	*	*	*	*		*	
Dunstan et al. (21)		*	*	*	*		*	*
Erkkola et al. (32)	*	*	*	*	*		*	
Nwaru et al. (39)	*	*	*	*	*		*	
West et al. (18)		*	*	*	*		*	
Maslova et al. (44)	*	*	*	*	*	*	*	
Chatzi et al. (33)	*	*	*	*	*	*	*	
Miyake et al. (38)	*	*	*	*	*		*	*

Table 2 (continued)

	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up
Maslova et al. (19)	*	*	*	*	*	*	*	
Miyake et al. (26)	*	*	*	*	*		*	*

Selection

1 Representativeness of the exposed cohort
- **a** Truly representative*
- **b** Somewhat representative*
- **c** Selected group of users eg nurses, volunteers
- **d** No description of the derivation of the cohort

2 Selection of the nonexposed cohort
- **a** Drawn from the same community as the exposed cohort*
- **b** Drawn from a different source
- **c** No description of the derivation of the nonexposed cohort

3 Ascertainment of exposure
- **a** Secure record (e.g., surgical records)*
- **b** Structured interview*
- **c** Written self-report
- **d** No description

4 Demonstration that outcome of interest was not present at start of study
- **a** Yes*
- **b** No

Comparability

1 Comparability of cohorts on the basis of the design or analysis
- **a** Study controls for the studied conditions*
- **b** Study controls for any additional factor*

Outcome

1 Assessment of outcome
- **a** Independent blind assessment*
- **b** Record linkage*
- **c** Self-report
- **d** No description

2 Was follow-up long enough for outcomes to occur
- **a** Yes*
- **b** No

3 Adequacy of follow-up of cohorts
- **a** Complete follow-up*
- **b** Subjects lost to follow-up unlikely to introduce bias, with follow-up $>75\%$ or description provided of those lost*
- **c** Follow-up rate $<75\%$ and no description of those lost
- **d** No statement

Table 3 Main results of the studies included in the meta-analysis of maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood

	Wheezing		Asthma		Eczema		Allergic Rhinitis		Food Allergy		Atopic Sensitization	
Exposure	Studies	Results	Studies	Results	Studies	Results	Studies	Results	Studies	Results	Studies	Results
Vitamin A												
α-Carotene	2	OR = 1.16 [0.79–1.69]	1	HR = 1.20 [0.92–1.56]	2	OR = 0.95 [0.68–1.35]						
β-Carotene	3	OR = 0.97 [0.68–1.37]	1	RR = 1.02 [0.93–1.11]	3	OR = 0.76 [0.46–1.26]			1	OR = 0.38 [0.11–1.27]	1	OR = 0.73 [0.33–1.61]
Vitamin B2	1	OR = 1.27 [0.64–2.52]			2	OR = 0.86 [0.74–1.01]						
Vitamin B6	1	OR = 0.92 [0.47–1.77]			1	OR = 1.06 [0.52–2.15]						
Vitamin B9	2	OR = 0.91 [0.49–1.68]	1	HR = 1.04 [0.71–1.52]	2	OR = 0.91 [0.76–1.09]	1	HR = 0.95 [0.79–1.15]				
Vitamin B12	1	OR = 1.27 [0.59– 2.73]			1	OR = 0.85 [0.39–1.84]						
Vitamin C	4	OR = 0.99 [0.48–2.04]	1	HR = 0.92 [0.70–1.22]	4	OR = 0.95 [0.69– 1.31]	1	HR = 0.93 [0.82–1.07]	1	OR = 0.46 [0.16–1.36]	1	OR = 0.76 [0.34–1.67]
Vitamin D	4	OR = 0.58 [0.38–0.88]	1	OR = 0.59 [0.27–1.29]	4	OR = 0.99 [0.72–1.35]	1	HR = 0.98 [0.69–1.37]				
			1	HR = 0.81 [0.45–1.47]								
Vitamin E	5	OR = 0.54 [0.41–0.71]	1	OR = 0.47 [0.24–0.92]	4	OR = 0.87 [0.65–1.18]	1	HR = 0.99 [0.83–1.18]	1	OR = 0.57 [0.19–1.72]	1	OR = 0.64 [0.29–1.41]
			1	RR = 1.01 [0.91–1.12]								
			1	HR = 1.02 [0.70–1.47]								
Zinc	3	OR = 0.57 [0.40–0.81]	1	OR = 0.51 [0.27–0.97]	4	OR = 1.00 [0.69–1.45]	1	HR = 1.08 [0.86–1.35]	1	OR = 0.52 [0.16–1.73]	1	OR = 0.87 [0.39–1.96]
			1	HR = 1.15 [0.77–1.72]								
Copper	2	OR = 0.55 [0.19–1.58]	1	HR = 1.00 [0.71–1.41]	2	OR = 0.91 [0.76–1.10]	1	HR = 1.08 [0.89–1.31]	1	OR = 1.08 [0.89–1.31]	1	OR = 0.64 [0.30–1.37]
Calcium	2	OR = 0.90 [0.39–2.08]	1	OR = 0.72 [0.31–1.67]	3	OR = 0.94 [0.82–1.08]	1	OR = 0.97 [0.83–1.14]				
			1	HR = 1.14 [0.89–1.48]								
Magnesium			1	HR = 0.91 [0.59–1.41]	1	OR = 0.78 [0.62–0.97]	1	HR = 0.95 [0.76–1.19]				
Manganese			1	HR = 0.94 [0.73-1.20]	1	OR = 0.87 [0.76-1.00]	1	OR = 1.00 [0.87-1.15]				

Table 3 (continued)

Exposure	Wheezing Studies	Wheezing Results	Asthma Studies	Asthma Results	Eczema Studies	Eczema Results	Allergic Rhinitis Studies	Allergic Rhinitis Results	Food Allergy Studies	Food Allergy Results	Atopic Sensitization Studies	Atopic Sensitization Results
Selenium			1	HR = 1.37 [0.89–2.11]	1	OR = 0.99 [0.81–1.21]	1	HR = 0.99 [0.80–1.22]				
Vegetables	4	OR = 0.90 [0.69–1.18]	2	OR = 1.02 [0.58–1.81]	2	OR = 0.71 [0.53–0.96]	1	HR = 1.07 [0.78–1.47]			1	OR = 1.09 [0.76–1.57]
	1	RR = 0.94 [0.79–1.12]	1	HR = 0.75 [0.46–1.22]	1	RR = 1.21 [0.97–1.51]						
Fruits	3	OR = 1.03 [0.81–1.31]	1	HR = 0.97 [0.60–1.58]	1	OR = 0.78 [0.45–1.35]	1	HR = 0.95 [0.68–1.34]				
	1	RR = 0.94 [0.81–1.09]			1	RR = 0.82 [0.64–1.05]						
Fish	6	OR = 1.00 [0.89–1.13]	2	OR = 0.99 [0.72–1.37]	6	OR = 0.84 [0.68–1.05]	1	OR = 0.28 [0.06–1.19]			2	OR = 0.99 [0.75–1.30]
			1	HR = 1.09 [0.66–1.78]	1	RR = 1.07 [0.86–1.33]	1	HR = 0.92 [0.67–1.28]				
Meat	3	OR = 1.16 [0.97–1.40]	1	HR = 0.79 [0.48–1.32]	2	OR = 1.28 [0.92–1.78]	1	HR = 0.95 [0.67–1.33]				
	1	RR = 1.22 [1.00–1.49]			1	RR = 0.96 [0.76–1.20]						
Dairy	4	OR = 0.88 [0.69–1.13]	1	OR = 0.82 [0.35–1.88]	4	OR = 0.95 [0.81–1.11]	1	HR = 0.85 [0.61–1.19]			1	OR = 0.93 [0.67–1.28]
	1	RR = 0.83 [0.72–0.96]	1	HR = 1.00 [0.59–1.69]	1	RR = 0.95 [0.76–1.18]						
Fats												
Total fats	3	OR = 0.87 [0.71–1.06]	1	HR = 0.92 [0.54–1.56]	3	OR = 0.97 [0.80–1.17]	2	HR = 0.98 [0.79–1.22]				
SFA	3	OR = 0.80 [0.65–0.97]			3	OR = 1.03 [0.86–1.24]	1	HR = 1.06 [0.82–1.37]				
	1	RR = 1.08 [0.93–1.26]			1	RR = 1.13 [0.88–1.45]						
MUFA	3	OR = 0.93 [0.77–1.14]			3	OR = 0.99 [0.82–1.19]	1	HR = 0.96 [0.74–1.24]				
	1	RR = 1.06 [0.79–1.40]			1	RR = 1.25 [0.96–1.62]	1	HR = 0.84 [0.64–1.11]				
n-6 PUFA	3	OR = 1.06 [0.87–1.30]			3	OR = 1.24 [0.87–1.76]	1	HR = 0.82 [0.63–1.08]				
n-3 PUFA	3	OR = 0.86 [0.58–1.26]			3	OR = 0.94 [0.78–1.14]		HR = 0.82 [0.63–1.08]				

HR, hazard ratio; MUFA, monounsaturated fatty acid; OR, odds ratio; PUFA, polyunsaturated fatty acid; RR, risk ratio; SFA, saturated fatty acid

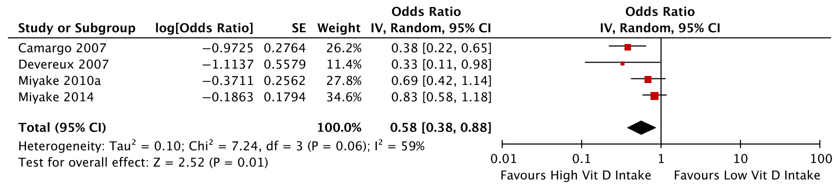

Figure 2 Pooled difference for maternal dietary vitamin D intake during pregnancy and childhood wheeze.

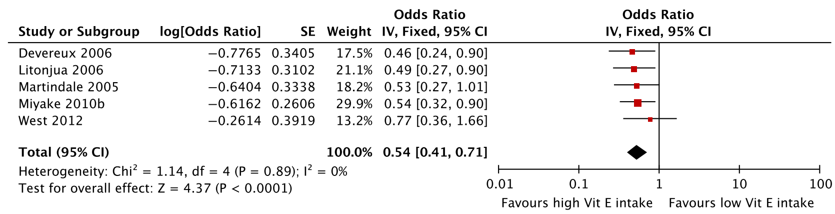

Figure 3 Pooled difference for maternal dietary vitamin E intake during pregnancy and childhood wheeze.

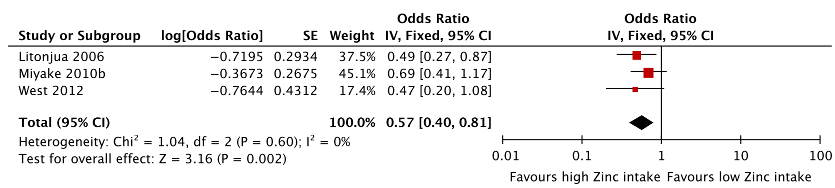

Figure 4 Pooled difference for maternal dietary zinc intake during pregnancy and childhood wheeze.

wheeze (13–15, 18), eczema (13, 14, 17, 18), allergic rhinitis (14, 17), or STR to allergens (14, 18) during childhood. Thus, our findings offer limited support for an inverse association between maternal copper intake during pregnancy and food allergy during childhood.

Calcium

Three cohort studies reported the association between maternal dietary intake of calcium during pregnancy and asthma or other allergic diseases during childhood (17, 25, 26). We found no significant association between maternal calcium intake and asthma (17, 26), wheeze (25, 26), eczema (17, 25, 26) (pooled OR = 0.94, 95% CI = 0.82–1.08, I^2 = 0%), or allergic rhinitis (17) during childhood.

Magnesium

Three cohort studies examined maternal dietary intake of magnesium and atopic conditions during childhood (13, 14, 17). Although maternal magnesium intake during pregnancy was significantly associated with eczema in one study (17) (OR = 0.78, 95% CI = 0.62–0.97), our analysis yielded negative results for asthma (17), wheeze (13), and allergic rhinitis (14, 17). Thus, there is limited evidence of an inverse association between maternal magnesium intake during pregnancy and childhood eczema.

Manganese and Selenium

Two cohort studies found no significant association between maternal dietary intake of manganese during pregnancy and asthma (17) or any atopic condition [including wheeze (13), eczema (17), and allergic rhinitis (17)] during childhood. Two cohort studies found no significant evidence of an association between maternal dietary intake of selenium during pregnancy and asthma (17), wheeze (13), eczema (17), or allergic rhinitis (17) during childhood.

Vegetables

Eight prospective cohort studies (16, 27–33) and one retrospective cohort study (34) assessed maternal consumption of vegetables during pregnancy and atopic conditions in childhood. Maternal vegetable intake during pregnancy was associated with a reduction in the odds of eczema using data from two studies with similar design (16, 31) (pooled OR = 0.71, 95% CI = 0.53–0.96, I^2 = 0%), but not in a third study (33) (RR = 1.21, 95% CI = 0.97–1.51). The latter study did not report OR for any results, so these results were not used to calculate the pooled OR. There were negative findings for wheeze (16, 29, 30, 32) (pooled OR = 0.90, 95% CI = 0.69–1.18, I^2 = 62%), asthma (31, 32), allergic rhinitis (32), or STR to allergens (29) in childhood.

Fruits

Six prospective cohort studies (16, 27, 28, 30, 32, 33) and one retrospective cohort study (34) evaluated the relation between maternal intake of fruits during pregnancy and the outcomes of interest. We found no significant association between maternal fruit intake during pregnancy and asthma (32), wheeze (16, 30, 32) (pooled OR = 1.03, 95% CI = 0.81–1.31, I^2 = 56%), eczema (16, 33), or allergic rhinitis (32) in childhood.

Fish

Eleven prospective cohort studies (27–33, 35–38) and one retrospective cohort study (34) examined maternal fish consumption during pregnancy and asthma or allergic diseases. We found no significant association between maternal fish intake during pregnancy and wheeze (30, 32, 35, 36, 38) (pooled OR = 1.00, 95% CI = 0.89–1.13, I^2 = 26%), asthma (31, 32), eczema (27, 28, 31, 35, 36, 38) (pooled OR = 0.84, 95% CI = 0.68–1.05, I^2 = 56%), allergic rhinitis (28, 32), or sensitization to allergens [assessed by specific IgEs (27, 35) or allergy skin testing (35)] in childhood.

Meat

Six cohort studies evaluated the association between maternal meat intake during pregnancy and atopic conditions (28, 32, 33, 36–38) and so did one retrospective study (34). There was no relation between maternal meat intake and wheezing (32, 36, 38) (pooled OR 1.16, 95% CI 0.97–1.40, I^2 35%), asthma (32), eczema (36, 38), or allergic rhinitis (32).

Dairy

Six prospective cohort studies (25–28, 30, 32, 33) and one retrospective cohort study (34) examined maternal consumption of dairy products during pregnancy and atopic diseases in childhood. Maternal dairy intake during pregnancy was associated with a 17% reduction in the risk of wheeze in one cohort (33) (95% CI for RR = 0.72–0.96) but not in other four studies (25, 26, 30, 32) (pooled OR = 0.88, 95% CI = 0.69–1.13, I^2 = 62%). There were negative findings for asthma (26, 32), eczema (25–27, 32), allergic rhinitis (32), or an increased total IgE (27) during childhood.

Fats

Six cohort studies investigated the association between maternal intake of (any type of) fats during pregnancy and asthma or atopic outcomes in childhood (32, 33, 36–39). Maternal consumption of saturated fatty acids (SFAs) was associated with decreased odds of wheeze in three studies (36, 38, 39) (pooled OR = 0.80, 95% CI = 0.65–0.97, I^2 = 0%), but not in a fourth study (33) (RR = 1.08, 95% CI = 0.93–1.26). There were negative findings for childhood eczema (36, 38, 39) or allergic rhinitis (39).

Maternal dietary intake of monounsaturated fatty acids (MUFAs) during pregnancy was not associated with wheeze (33, 36, 38, 39), eczema (33, 36, 38, 39), or allergic rhinitis (39) in childhood. Similarly, there was no significant association between maternal consumption of n3 or n6 polyunsaturated fatty acids (PUFAs) during pregnancy and wheeze (36, 38, 39), eczema (36, 38, 39), or allergic rhinitis (39) in childhood. We also found no significant association between maternal intake of total fats during pregnancy and asthma (32), eczema (36, 38, 39), or allergic rhinitis (32, 39) in childhood.

In summary, we found limited and inconsistent evidence of an inverse association between maternal intake of SFAs during pregnancy and wheeze. Maternal consumption of any other type of fats (MUFAs, n3 PUFAs, n6 PUFAs) or total fat during pregnancy was not significantly associated with asthma or any other atopic conditions.

Mediterranean diet and other dietary patterns

Two prospective cohort studies (29, 33) and two retrospective cohort studies (40, 41) examined the relation between a maternal 'Mediterranean diet' during pregnancy and asthma or other atopic conditions. Whereas two studies (29, 40) found a significant inverse association between a maternal 'Mediterranean diet' and atopic conditions [including persistent wheeze (29), atopic wheeze (29), STR to allergens (29), asthma ever (40), and rhinitis ever (40)] at ages 6–7 years, the other two studies yielded negative findings for wheeze or eczema (33,41).

Two cohort studies analyzed the association between specific maternal dietary patterns during pregnancy and the outcomes of interest (42, 43). In the first study (42), none of five maternal dietary patterns (health conscious, traditional, processed, vegetarian, and confectionery) was significantly associated with asthma, wheeze, allergic rhinitis, or eczema in childhood. The second study (43) examined three maternal dietary patterns during pregnancy (healthy, western, and Japanese). In that study, a maternal western diet during pregnancy was inversely associated with wheeze (OR = 0.59, 95% CI = 0.35–0.98) but not with eczema in childhood. Neither a healthy diet nor a Japanese diet during pregnancy was associated with wheeze or eczema in childhood.

In summary, there is inconsistent or nonsignificant evidence for an association between maternal dietary patterns during pregnancy and asthma or other atopic conditions in childhood.

Sweetened beverages

A single cohort study assessed maternal consumption of artificially sweetened soft drinks during pregnancy and asthma or other atopic conditions (44). In that study, maternal intake of ≥1 soft drink per day was associated with increased odds of asthma (OR = 1.23, 95% CI = 1.13–1.33) but not with allergic rhinitis.

Discussion

Because *in utero* exposures likely affect the development of asthma and other common allergic illnesses (food allergy, allergic rhinitis, and eczema), identifying and modifying such exposures could have a substantial impact on public health. After conducting a meta-analysis of recently published studies on maternal dietary intake (as specific nutrients or dietary patterns) and asthma or atopic conditions in childhood, we found suggestive evidence of a protective effect of maternal dietary intake of each of three vitamins or nutrients (vitamin D, vitamin E, and zinc) against wheeze during childhood. However, none of these nutrients was consistently associated with asthma *per se* or other atopic conditions, and thus, there is inconclusive evidence for either a true cause–effect relationship or the mechanisms underlying our findings.

In a pooled analysis of four studies (including ~4570 mother–child pairs), we found that higher maternal intake of vitamin D during pregnancy was significantly associated with reduced odds of wheeze. Our findings for vitamin D are consistent with those of previous reviews (45, 46) which concluded that maternal dietary intake of vitamin D may protect against childhood wheeze. On the other hand, we and others have found inconsistent or nonsignificant evidence for an association between maternal vitamin D intake during pregnancy and atopy or asthma. As wheeze in early childhood may be 'transient' or 'viral-induced' and not due to 'true asthma', these findings suggest that the maternal vitamin D intake during pregnancy may not be immune modulatory but either affect lung development or protect against viral infections [a theory supported by both experimental and human studies showing potential effects of vitamin D against severe asthma exacerbations in children, which are often induced by viral illnesses (46, 47)]. Given that childhood wheeze causes significant suffering and is a major public health problem (regardless of its etiology), there is ample justification for ongoing clinical trials of prenatal vitamin D supplementation to prevent asthma or wheeze (48). Long-term follow-up of children participating in these trials should help determine not only whether vitamin D supplementation during pregnancy helps prevent wheeze, but also whether such supplementation reduces the risk of asthma or other atopic conditions.

We also found that higher maternal intake of vitamin E or zinc during pregnancy is associated with reduced risk of childhood wheeze. Although the total sample size of the studies pooled in our meta-analysis was smaller for zinc than for vitamin E, all studies included in the meta-analysis of each nutrient had results in the same direction and there was very low heterogeneity ($I^2 = 0\%$).

Oxidative stress, an imbalance between pro-oxidant and antioxidant, can cause dysfunction in cell signaling and arachidonic acid metabolism and increase airway and systemic inflammation (49). Because vitamin E is an antioxidant and may inhibit secretion of IL-4 by T cells (50), there has been interest in the role of vitamin E supplementation to prevent or treat asthma in children and adults, particularly in children with asthma exposed to outdoor pollution (51). However, a recent Cochrane review of five randomized controlled trials concluded that additional research is needed to establish whether vitamin E supplementation (in pre- or postnatal life) protects against inception or morbidity from asthma (including that induced by air pollution) or particular asthma endotypes (e.g., exercise-induced bronchoconstriction) (52).

Zinc deficiency has been associated with impaired fetal lung growth in rats (53), and *ADAM33* (a gene implicated in asthma susceptibility) is a zinc-dependent metalloproteinase (54). At least one randomized controlled trial has reported that zinc supplementation, together with usual therapy, leads to improvement in lung function and respiratory symptoms in subjects with asthma (55).

Even though we found an inverse relation between maternal SFA and a western diet pattern intake with wheeze, these data come from a limited number of studies, so it should be cautiously interpreted.

We recognize limitations of our findings. Firstly, our results for maternal dietary patterns or certain nutrients during pregnancy must be cautiously interpreted due to the paucity of studies available for meta-analysis. In contrast to our results, a Mediterranean-style postnatal diet was significantly associated with lower risk of asthma in a recent meta-analysis that included almost 40 000 children in eight studies (56). Moreover, a recent large meta-analysis found that postnatal dietary intake of vegetables and/or fruits was associated with a reduced risk of wheeze or asthma in children and adults (57). Secondly, we may have failed to identify some studies in spite of using a systematic approach, and thus, the studies included may not represent the entire body of knowledge on this topic. Also, the pooled estimates are only adjusted for the covariates included in the original studies, and thus, we cannot exclude residual confounding by unmeasured factors. Finally, all studies recorded food consumption using a food frequency questionnaire, not a daily register which would be more accurate. Some included cohorts previously performed validation of their questionnaires, comparing this instrument with a 3-day diet record and serum biomarkers (58, 59), finding a good correlation between all these methods.

In summary, there is insufficient evidence to recommend any dietary pattern or nutrient supplementation to prevent or treat asthma or allergies. Our findings fully support ongoing clinical trials of vitamin D supplementation during pregnancy to prevent wheeze or asthma.

On the other hand, additional research studies (either observational longitudinal studies or clinical trials of postnatal supplementation) are needed to determine whether a randomized clinical trial of prenatal supplementation of certain nutrients (e.g., vitamin E or its isoforms, zinc) is warranted, particularly given potential and long-lasting adverse effects (e.g., in cancer in adults supplemented with vitamin E). A more fundamental question in this field is whether a 'whole-diet' approach is preferable to supplementation with individual nutrients or vitamins, particularly when such nutrients or vitamins are largely derived from dietary intake.

Intake of single nutrients from food is generally correlated with the type of diet; for example, individuals with high intake of vegetables generally have high intake of, for example, both vitamin C and beta-carotene. We did not adjust each particular vitamin by other nutrients or dietary pattern. Ongoing and future studies (both observational and interventional) should help answer this important question over the next few years.

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Conflict of interest

The authors declare that they have no conflict of interests.

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