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As You Eat It: Effects of Prenatal Nutrition on Asthma

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Abstract

Asthma most frequently develops early in life, and increased recognition of the role of lifestyle and environmental factors in asthma susceptibility raises the possibility that dietary exposures during pregnancy may influence the risk of asthma in offspring. This review discusses the latest evidence with regard to the effect of diet during pregnancy on childhood asthma risk, including potential mechanisms, outcomes of randomized clinical trials, and results from observational studies. Vitamin D and polyunsaturated fatty acid intake during pregnancy are highlighted as areas with large and growing bodies of literature to support a potential role in prenatal modulation of subsequent asthma risk. Several other nutritional interventions are under active investigation, and recommendations regarding dietary modifications during pregnancy will likely need to be personalized based on factors such as maternal smoking and genetic variants. Although nutrition during pregnancy is uniquely challenging to investigate, and definitive recommendations cannot be made without additional high-quality evidence and knowledge regarding long-term effects of interventions, the modifiable nature of the diet and sizeable potential reduction of morbidity supports ongoing research to determine how to optimize nutrition during pregnancy to prevent asthma in offspring.

Keywords

Asthma; Wheezing; Nutrition; Prenatal; Pregnancy; Vitamin D; Omega-3

The increasing prevalence of asthma¹ over the past several decades has been attributed to lifestyle and environmental changes; however, the key risk factors and mechanisms behind this change have yet to be elucidated. Asthma-associated inflammation and deficits in lung function may begin before birth, and a range of prenatal exposures contribute to the risk of asthma, including maternal smoking and obesity.² Maternal nutrition during pregnancy could influence the risk of asthma and other allergic diseases in offspring through several plausible mechanisms, including direct immunologic effects of dietary components,

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modulation or enhancement of environmental exposures, epigenetic changes and other influences on gene transcription, or modification of the composition of the microbiome.³

Our objective is to review the recent evidence with regard to the effect of diet during pregnancy on childhood asthma risk, including nutritional intervention trials, meta-analyses, and observational studies. Vitamin D and polyunsaturated fatty acids will be highlighted as nutrients with large and growing bodies of evidence assessing the association between prenatal intake and risk of asthma or wheeze in offspring.

VITAMIN D

Vitamin D deficiency is defined by a 25-hydroxyvitamin D (25OHD) concentration less than 20 ng/mL by the Institute of Medicine, primarily for bone health.⁴ However, other experts suggest that a level of at least 30 ng/mL is desirable based on nonskeletal effects⁵ and on observations that serum parathyroid hormone suppression appears to plateau at about this level of 25OHD.^{6,7} Although the threshold for adequate circulating vitamin D concentration with regard to effects beyond calcium homeostasis and skeletal health remains controversial,⁸ vitamin D deficiency is common both in the general population⁹ and among pregnant women.¹⁰ The risk of deficiency during pregnancy varies by factors including those related to amount of sun exposure, including season, latitude, clothing, and sunscreen use,^{11–13} and deficiency may be particularly detrimental via effects on maternal and fetal health and susceptibility to chronic disease in offspring.^{10,14} Vitamin D supplementation is a particularly appealing intervention given the exceedingly rare occurrence of adverse events observed in several randomized clinical trials of vitamin D supplementation during pregnancy, including doses up to 4400 IU/day.^{15–18}

Vitamin D has effects on *in utero* immunologic development that are relevant to asthma pathophysiology.¹⁴ *In vitro* studies demonstrate that in addition to promoting the innate antimicrobial response,^{19,20} vitamin D influences T-cell differentiation and cytokine production, including promotion of regulatory T-cell differentiation and IL-10 production.^{21,22} Human studies corroborate these findings.^{23,24} For example, in an ancillary analysis of a randomized clinical trial of vitamin D supplementation (4400 IU/day vs 400 IU/day) during pregnancy,²⁵ high-dose vitamin D supplementation resulted in increased cord blood mononuclear cell production of proinflammatory cytokines in response to toll-like receptor agonist and mitogenic stimuli, and increased IL-10 production after dexamethasone treatment in culture.²⁶

Pulmonary development may also be influenced by prenatal vitamin D status. In a mouse model, *in utero* vitamin D deficiency is associated with increased airway smooth muscle mass and hyperresponsiveness.²⁷ Human data on prenatal vitamin D status and subsequent lung function are sparse. In one community-based prospective birth cohort, maternal serum vitamin D concentration at 16 to 20 weeks of gestation was positively associated with forced vital capacity Z-scores in both sexes and forced expiratory volume in 1 second Z-scores in females at age 6 years; however, differences in lung function by maternal vitamin D concentration were minimal at age 14 years.²⁸

Observational studies have yielded conflicting results regarding the association between prenatal maternal vitamin D status and childhood asthma, as demonstrated by the findings of multiple recent systematic reviews.^{29–31} A meta-analysis of birth cohort studies investigating maternal venous or cord blood vitamin D concentration found a trend toward an inverse association with both asthma (pooled odds ratio [OR] from 10 studies = 0.84, 95% confidence interval [CI] 0.70–1.01) and wheeze (pooled OR from 10 studies = 0.77, 95% CI 0.58–1.03) in offspring.²⁹ A subgroup analysis of studies that measured cord blood levels showed a statistically significant inverse association with childhood wheeze (pooled OR 0.43, 95% CI 0.29–0.62).²⁹ In contrast, a dose-response analysis of 15 prospective studies found evidence of a U-shaped relationship between maternal vitamin D concentration and risk of childhood asthma, with lowest risk at approximately 70 nmol/L (28 ng/mL).³⁰ Of note, stratification by time of vitamin D concentration measurement revealed that significant associations were found only where vitamin D was measured in early-to-mid gestation, suggesting that early pregnancy is a critical time period with regard to the effect of vitamin D on asthma risk.³⁰

These studies of single measures of vitamin D status may be problematic as they do not account for fluctuations in 25OHD levels. Studies evaluating peripheral or cord blood vitamin D concentrations are limited in that these concentrations may be less important than tissue or intracellular levels, and food-based approaches may better reflect long-term vitamin D exposure. A meta-analysis of 5 cohort studies assessing maternal vitamin D intake during pregnancy based on food frequency questionnaire responses found an inverse association with childhood wheeze (pooled OR 0.58, 95% CI 0.38–0.88)³¹; however, the authors found no association with asthma in offspring.³¹

There have been 3 randomized clinical trials of vitamin D supplementation in pregnancy for prevention of asthma or recurrent wheeze in offspring.^{17,18,32} A 2013 study conducted in the United Kingdom randomized 180 pregnant women of various ethnicities at 27 weeks of gestation to either no vitamin D, 800 IU ergocalciferol daily for the remainder of pregnancy, or a single bolus of 200,000 IU cholecalciferol.³² The authors found no association between treatment assignment and wheeze in offspring at age 3 years.³² Two larger double-blind randomized clinical trials reported results in 2016: a trial conducted within the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC 2010) cohort randomized 623 pregnant women at 24 weeks of gestation to either 2800 IU or 400 IU cholecalciferol daily until 1 week after delivery,¹⁸ and the Vitamin D Antenatal Asthma Reduction Trial (VDAART) randomized 876 pregnant women at 10 to 18 weeks of gestation to 4400 IU or 400 IU cholecalciferol daily until delivery.¹⁷ VDAART offspring were at high risk for allergic outcomes, as study inclusion required that at least one biological parent have a history of atopy.²⁵ In primary outcome analyses, neither trial found a significant association between treatment assignment and persistent wheeze¹⁸ or the composite outcome of recurrent wheeze or physician-diagnosed asthma in the first 3 years of life.¹⁷ However, a recent meta-analysis of all 3 trials found that prenatal vitamin D supplementation is significantly associated with reduced risk of recurrent wheeze (risk ratio 0.81, 95% CI 0.67–0.98).³³

The randomized trials conducted to date have had limitations that may have reduced their ability to detect an effect of prenatal vitamin D on asthma and wheezing outcomes in offspring. Individual trials were underpowered, and supplementation may need to begin earlier in pregnancy to influence fetal pulmonary development. Highlighting the importance of vitamin D status in early pregnancy, a secondary analysis of VDAART data found that high-dose vitamin D supplementation in combination with baseline maternal vitamin D concentration >30 ng/mL was significantly inversely associated with asthma or recurrent wheeze in offspring, in comparison with low-dose vitamin D supplementation in combination with baseline maternal vitamin D concentration <20 ng/mL (OR 0.42, 95% CI 0.19-0.91).³⁴ Finally, causes and prognoses of wheezing before age 3 years are heterogeneous.³⁵ Both VDAART and COPSAC 2010 cohort follow-up studies are ongoing, and evaluation of outcomes later in childhood may provide greater insight regarding the relationship between vitamin D supplementation during pregnancy and childhood asthma. An individual participant data meta-analysis of vitamin D in pregnancy is being planned and may shed further light on these effects. These randomized trials so far have only tested the effect of prenatal exposure to vitamin D, as postnatal vitamin D was not administered in the trials. However, a recent study by Hollams et al³⁶ suggests that postnatal vitamin D status throughout childhood may also be important in protecting against asthma development.

OMEGA-3 POLYUNSATURATED FATTY ACIDS

Omega-3 and omega-6 fatty acids are major families of polyunsaturated fatty acids. The essential fatty acids alpha-linoleic acid and linoleic acid are the simplest members of the omega-3 and omega-6 fatty acid families, respectively. Ingested polyunsaturated fatty acids are critical sources of bioactive metabolites and cell membrane phospholipid components: alpha-linoleic metabolites include eicosapentaenoic acid and docosahexaenoic acid, and linoleic acid metabolites include arachidonic acid. Dietary intake is a major determinant of the proportions of bioactive omega-3 and omega-6 metabolites in tissue phospholipids.³⁷ Major food sources of omega-3 fatty acids (and vitamin D) include oily fish such as salmon, mackerel and herring, and cod liver oil.

Because of changes over the 20th century, such as increased consumption of linoleic acid-rich soybean oil,³⁸ the ratio of omega-6 to omega-3 fatty acids in the Western diet has increased.³⁹ This shift has been proposed as a potential cause of the increased occurrence of allergic disease over the past few decades, via perturbations in the proportion of downstream bioactive metabolites.³⁹ Arachidonic acid is a precursor for inflammatory and anti-inflammatory lipid mediators that contribute to asthma pathophysiology.⁴⁰ Increased dietary omega-3 fatty acids could displace arachidonic acid or result in production of less potent inflammatory eicosanoid metabolites from eicosapentaenoic acid.⁴¹ Omega-3 fatty acids are also sources of specialized proresolving mediators such as resolvins and protectins that have been shown to reduce airway inflammation in mouse models.⁴²⁻⁴⁴

Limited evidence from human studies supports an influence of prenatal omega-3 fatty acid supplementation on immune function in offspring. Neutrophil production of leukotriene B₄, an arachidonic acid metabolite, and plasma IL-13 are significantly reduced in neonates whose mothers received fish oil supplementation during pregnancy, and both are inversely

correlated with cell membrane levels of omega-3 fatty acids.^{45,46} Expression of genes encoding type 2 T helper cytokines is also reduced in cord blood from offspring of mothers who received fish oil supplementation during pregnancy.⁴⁷

Although several cross-sectional studies suggest an association between diets high in omega-6 or low in omega-3 fatty acids and development of atopic disease,³⁹ prospective cohort studies have yielded inconsistent findings. Of 3 recent meta-analyses of cohort studies evaluating omega-3 fatty acid dietary intake during pregnancy, 1 suggested a trend toward an inverse association with childhood asthma and wheeze⁴⁸ and the others found no association.^{31,49} Studies evaluating blood concentrations of polyunsaturated fatty acids during pregnancy, rather than dietary intake, have similarly failed to detect an association with childhood asthma or wheezing.^{50,51}

Until recently, clinical trials have also provided little evidence that increased omega-3 fatty acid intake in pregnancy reduces asthma or wheezing in offspring. Two systematic reviews of randomized clinical trials of omega-3 fatty acid supplementation during pregnancy found no association with asthma or wheeze in offspring: one included 3 randomized clinical trials,⁴⁸ the other, a Cochrane review, included 5 trials of supplementation during pregnancy, 2 during lactation, and 1 during pregnancy and lactation.⁵² One registry-based ancillary study of a randomized trial reported a significant reduction in “any asthma” and “allergic asthma” at age 16 years and in having had asthma medication prescribed by age 24 years in offspring of mothers who were randomized to fish oil supplementation during pregnancy compared with the “olive oil” control group; however, the occurrence of these outcomes was similar between the fish oil group and a second “no oil” control group.^{53,54}

These negative findings contrast with the recent results of a clinical trial conducted within the COPSAC 2010 cohort in which 695 women were randomized to omega-3 fatty acid (n = 346) or olive oil (n = 349) supplementation daily starting at 24 = weeks of gestation.⁵⁵ There was a statistically significant 30.7% relative reduction in risk of persistent wheeze or asthma at age 3 years in the treatment group (16.9% risk) compared with the control group (23.7% risk).⁵⁵ These findings may differ from the results of prior trials in part because of the relatively high dose (2.4 g daily) of omega-3 fatty acid used, and because this study evaluated the outcome of overall wheeze rather than wheeze with sensitization.³⁹

The COPSAC 2010 study provided some insight regarding who may benefit most from omega-3 fatty acid supplementation: risk reduction was greatest in offspring of mothers with the lowest blood concentrations of eicosapentaenoic acid and docosahexaenoic acid at study entry.⁵⁵ Interestingly, a subset of participating mothers also participated in the trial described above of prenatal high-versus low-dose vitamin D supplementation as part of a nested factorial study design, and exploratory stratified analysis suggested that omega-3 fatty acid supplementation had greater benefit in offspring of mothers who were *not* randomized to the high-dose vitamin D supplementation group.⁵⁵ These findings suggest that there may be overlap between or redundancy in the mechanisms by which polyunsaturated fatty acid and vitamin D intake influence asthma risk.

Whether to supplement with omega-3 fatty acids during pregnancy remains controversial and the long-term safety of such an intervention requires further study.⁵⁶ Despite the overall conflicting body of clinical evidence, the promising results of the COPSAC 2010 trial support the need for further randomized controlled trials investigating the efficacy and safety of omega-3 fatty acid supplementation during pregnancy, and perhaps even combined supplementation with vitamin D.

OTHER VITAMINS AND MINERALS

Vitamins E and C

A meta-analysis of 7 prospective observational studies found that maternal dietary vitamin E intake during pregnancy was associated with a 46% reduction in the odds of wheeze, though was not associated with asthma in offspring.³¹ The evidence regarding the effect of vitamin E on pulmonary inflammation, including variable effects of different vitamin E isoforms, has been discussed in detail elsewhere^{57,58} and is beyond the scope of the present review. Although a food-based intervention to increase vitamin E intake in pregnant woman for intended use in a randomized clinical trial has been recently developed, to the authors' knowledge, there have been no randomized trials investigating prenatal vitamin E status alone and childhood asthma to date.⁵⁹ An ancillary analysis of a trial of 643 women at risk of preeclampsia in the United Kingdom that randomized participants to daily vitamin C (1000 mg) and E (400 IU RRR α -tocopherol) supplementation or placebo during pregnancy found no difference between treatment groups in asthma diagnosis by age 2 years.⁶⁰

Based on evidence that vitamin C decreases the effects of nicotine *in utero* on primate pulmonary function, a pilot trial was conducted that randomized 179 smoking pregnant women to 500 mg of vitamin C daily or placebo.⁶¹ Offspring of those assigned to vitamin C supplementation had improved pulmonary function, and, in a secondary outcome analysis, decreased wheezing through age 1 year (15/70 or 21% vs 31/77 or 40%) compared with offspring of those assigned to placebo.⁶¹ A follow-up trial is ongoing to more definitively investigate this association.⁶²

Selenium

In an analysis of data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, cord tissue selenium concentration was negatively associated with wheeze in early childhood.⁶³ In an intriguing follow-up analysis of data from the same cohort, maternal blood selenium was inversely associated with asthma or wheeze in offspring at age 7 years only in genetically susceptible children who were homozygous for the minor allele of gene encoding glutathione peroxidase 4 (*GPX4*), which encodes glutathione peroxidase, a selenium-dependent antioxidant enzyme.⁶⁴ Maternal and cord plasma selenium concentrations were inversely associated with wheeze at age 2 years, but not at age 5 years, in a separate cohort; though this analysis did not stratify by *GPX4* genotype.⁶⁵ We are not aware of any randomized clinical trial evidence regarding selenium intake during pregnancy to prevent childhood allergy.

Evidence has been negative or inconclusive with regard to intake during pregnancy of other nutrients and minerals, including vitamin A, vitamin B complex, vitamin C, zinc, copper, calcium, magnesium, manganese, and folic acid, and risk of asthma in offspring.^{31,33,66}

DIETARY PATTERNS

Evidence regarding an influence of dietary patterns during pregnancy on asthma risk in offspring comes from observational studies, with, to our knowledge, no large randomized clinical trial data available.

Mediterranean diet

The Mediterranean diet, characterized by high intake of olive oil, nuts, fruits, and vegetables and low intake of dairy, red meat, and processed meat, has received increasing attention in recent years because of the growing literature supporting its role in reduction of cardiovascular and other diseases.^{67,68} Findings have been mixed regarding the association of the Mediterranean diet during pregnancy and risk of asthma in offspring. Two observational studies, one retrospective⁶⁹ and one prospective,⁷⁰ found an inverse association between Mediterranean diet during pregnancy and asthma or wheeze in offspring at age 6 to 7 years. In contrast, 2 other observational studies investigating an earlier outcome—wheeze in the first year of life—found no association with Mediterranean diet during pregnancy.^{71,72}

Sugar and sweetened beverages

Three large observational studies investigated maternal intake of sugar and sweetened beverages and risk of childhood asthma. In an analysis of nearly 9000 subjects from the ALSPAC birth cohort, maternal intake of free sugar—sugar added to foods or drinks or naturally present in honey, syrups, and juices—during pregnancy was associated with atopy and atopic asthma in offspring at age 7 to 9 years.⁷³ The authors speculate that inflammatory and other effects of fructose consumption, which has increased markedly over recent decades,⁷⁴ may be responsible for the observed association.⁷³ Similarly, the Project Viva birth cohort found that high (highest quartile vs lowest quartile) maternal intakes of sugar sweetened beverages and total fructose were associated with a 58% to 70% increased risk of current asthma in mid-childhood.⁷⁵ In addition, these authors found that higher early childhood intake of fructose also increased the risk of asthma by mid-childhood. Artificially sweetened beverage consumption during pregnancy has also been investigated as a risk factor for childhood asthma: a Danish National Birth Cohort study of more than 60,000 pregnant women found that maternal intake of at least 1 artificially sweetened beverage per day during pregnancy was associated with increased risk of asthma diagnosis in offspring (OR 1.23, 95% CI 1.13-1.33).⁷⁶ These findings require replication before their clinical relevance can be ascertained.

Other dietary patterns

Although some observational studies support an inverse relationship between fruit and/or vegetable intake during pregnancy and asthma or wheezing in offspring, results have been found to be inconsistent in multiple systematic reviews.^{31,77,78} Similarly, the evidence is

inconclusive with regard to associations between meat or dairy intake during pregnancy and childhood asthma.³¹ One retrospective population-based study found a dose-dependent association between fast food consumption during pregnancy and asthma risk at age 3.5 years.⁷⁹ However, these results are subject to recall bias and confounding as diet exposure was ascertained 3 to 6 months after birth.⁷⁹

Unsupervised analysis has been applied to food frequency data to identify, independent of asthma or allergy outcomes, dietary patterns during pregnancy and then to seek associations between these patterns and allergic outcomes in offspring. An analysis of 1376 mother-infant pair participants in the Project Viva birth cohort found that dietary patterns, including “Western” and “Prudent” diets based on principal component analysis, and scores on a Mediterranean diet score and Alternate Healthy Eating Index modified for pregnancy were not associated with recurrent wheeze at age 3 years.⁸⁰ Factor analysis of dietary questionnaires in a Japanese birth cohort identified 3 dietary patterns: healthy, Western, and Japanese; surprisingly, only the Western diet, characterized by high intake of vegetable oil, salt-containing seasonings, meat, eggs, and white vegetables, was inversely associated with risk of childhood wheeze.⁸¹

CONCLUSIONS

Nutrition during pregnancy is modifiable and may impact lifelong trajectories of health in offspring. Investigating the impact of maternal nutrition on health outcomes has challenges,⁸² including uncertainty with regard to the critical developmental time periods, unique physiologic changes during pregnancy, and difficulty recruiting women early in pregnancy or, ideally, before conception for randomization to nutritional interventions. In addition, drastic changes in food production and distribution over the past 50 years make it difficult to compare findings from recent studies with past studies. Depending on the population or subpopulations being studied, there may be differences in availability of fresh food, particularly fresh fruits and vegetables. Finally, current studies of diet have not accounted for the fact that in recent years, pharmaceuticals, including antibiotics and hormones, have leached into our food and water systems.^{83–85} Although these pharmaceuticals are in miniscule concentrations, the effects of these chronic exposures during critical developmental periods remain unknown and may lead to subtle changes in risk for later disorders.⁸⁶ Newer studies may need to assess the effects of these low-level exposures.

We summarize the designs and results of randomized clinical trials conducted to evaluate antenatal nutritional interventions to reduce asthma in offspring in Table I.
17,18,32,46,53–55,60,61,87–90 With regard to prevention of childhood asthma, a growing body of evidence supports a protective role of vitamin D supplementation, though the dose of vitamin D needed for prevention remains undefined. Omega-3 fatty acid and vitamin E supplementation are also promising interventions that warrant further investigation. Recommendations will likely need to be personalized, and there is already evidence of differential benefit of nutritional interventions in some subgroups of mother-child pairs, such as vitamin C supplementation for smoking women and selenium supplementation for offspring with specific genetic variants. Overall, although there is a need for further research into the possible associations of the Mediterranean diet and intake of sugar and artificial

sweeteners during pregnancy and risk of asthma or wheeze in offspring, the available evidence suggests that individual nutrients may play a larger role than overall dietary patterns.

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Abbreviations

25OHD	25-Hydroxyvitamin D
ALSPAC	Avon Longitudinal Study of Parents and Children
CI	Confidence interval
COPSAC 2010	Copenhagen Prospective Studies on Asthma in Childhood 2010
GPX4	Gene encoding glutathione peroxidase 4
OR	Odds ratio
VDAART	Vitamin D Antenatal Asthma Reduction Trial

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TABLE I

Randomized clinical trials of nutritional interventions during pregnancy to prevent asthma in offspring

First author, publication year	Participants	Intervention	Asthma outcome and results
PUFA			
Dunstan, 2003 ⁴⁶	98 atopic nonsmoking pregnant women in Australia	3.7 g n-3 PUFA (56.0% DHA, 27.7% EPA) daily in fish oil capsules compared with olive oil capsules from 20 wk of gestation to delivery	Nonsignificant decreases in recurrent wheeze, persistent cough, and asthma diagnosis at age 1 y in intervention vs placebo group
Olsen, 2008 ⁵³ Hansen, 2017 ⁵⁴	533 pregnant women in Denmark	2:1:1 randomization to 2.7 g n-3 PUFA (23% DHA, 32% EPA) daily in fish oil capsules, olive oil capsules, or no oil capsules, respectively, from 30 wk of gestation to delivery	Significant reduction in hazard rate of asthma or allergic asthma by age 16 y and prescribed asthma medication by age 24 y in those randomized to fish oil vs olive oil; however, outcomes similar between those randomized to fish oil and no oil
Furuhjelm, 2011 ⁸⁷	145 pregnant woman whose offspring had at least one first degree relative with atopy in Sweden	1.6 g EPA and 1.1 g DHA daily in fish oil capsules compared with soy oil capsules from 25 wk of gestation to at least delivery	No difference between groups in total asthma or IgE-associated asthma at age 2 y
Noakes, 2012 ⁸⁸	123 women with low habitual oily fish intake whose offspring had at least one first degree relative with atopy in the United Kingdom	150 g salmon portion twice weekly (1160 mg DHA and 570 mg EPA) compared with continued habitual diet low in oily fish from 20 wk of gestation to delivery	No significant difference between groups in incidence of wheeze in first 6 mo of life
Palmer, 2012 ⁸⁹ Palmer, 2013 ⁹⁰	706 women whose offspring had at least one first degree relative with atopy in Australia	800 mg DHA and 100 mg EPA in fish oil capsules compared with vegetable oil capsules from 21 wk of gestation to delivery	No significant difference between groups in asthma with or without sensitization in the first 3 y of life
Bisgaard, 2016 ⁵⁵	695 women including 623 who participated in nested factorial design antenatal vitamin D trial ¹⁸ in Denmark	2.4 g n-3 PUFA (55% EPA, 37% DHA) in fish oil capsules compared with olive oil capsules from 24 wk of gestation to delivery	Statistically significant 30.7% relative reduction in risk of persistent wheeze or asthma at age 3 y in the treatment group compared with control; most of the effect was seen in the children born to mothers in the lowest tertile of EPA and DHA levels
Vitamin D			
Goldring, 2013 ³²	180 women of various ethnicities in the United Kingdom	Single dose of 200,000 IU cholecalciferol or daily 800 IU ergocalciferol from 27 wk of gestation to delivery	No association between group assignment and wheeze at age 3 y
Litonjua, 2016 ¹⁷	880 women with atopy or partner with atopy in the United States	4400 IU compared with 400 IU daily oral cholecalciferol from 10 to 18 wk of gestation to delivery	Nonsignificant 6.1% decrease in incidence of asthma and recurrent wheeze in high-dose vitamin D compared with low-dose vitamin D group; largest effect in children born to mothers with higher baseline vitamin D in secondary analyses ³⁴
Chawes, 2016 ¹⁸	623 women who also participated in a trial of antenatal n-3 PUFA ⁵⁵ in Denmark	2800 IU compared with 400 IU daily oral cholecalciferol from 24 wk of gestation to delivery	No significant association between study group assignment and persistent wheeze in the first 3 y of life. Treatment was associated with a reduction in "troublesome lung symptoms" in a secondary analysis
Vitamin C and/or E			
Greenough, 2010 ⁶⁰	643 women at risk of pre-eclampsia in the United Kingdom	1000 mg vitamin C and 400 IU RRR α -tocopherol daily compared with placebo from second trimester to delivery	In an ancillary analysis of a trial to reduce maternal pre-eclampsia, there was no difference between groups in offspring asthma diagnosis by age 2 y
McEvoy, 2014 ⁶¹	179 smoking pregnant women in the United States	500 mg crushed vitamin C daily compared with ground cornstarch from 22 wk of gestation to delivery	Randomization to vitamin C associated with improved neonatal pulmonary function and

First author, publication year	Participants	Intervention	Asthma outcome and results
			decreased wheezing through age 1 y compared with placebo

DHA, Docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *IU*, international units; *PUFA*, polyunsaturated fatty acid.

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