



Prenatal Diet and the Development of Childhood Allergic Diseases: Food for Thought

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Abstract

Purpose of Review The development of allergic disease is shaped by genetics and the environment, including diet. Many studies suggest a role for maternal diet during pregnancy. In this article, we discuss potential mechanisms by which specific nutrients, particular foods, and dietary patterns may influence allergic disease development and review studies examining the relationship between prenatal diet and the risk of childhood allergy.

Recent Findings The combination of *in utero* exposures and genetic predisposition may contribute to the development of allergic disease by altering immune and organ development. Inflammation predominates in the first and third trimesters whereas the second trimester is characterized by anti-inflammatory and Th2 immune responses. Maternal dietary exposures during pregnancy may interact with inherited genetic risk factors influence immune system development.

Summary There are varied results regarding the impact of maternal prenatal diet on the development of childhood allergies. Well-designed randomized controlled studies are needed to clarify this area.

Keywords Maternal diet · Prenatal · Childhood allergy · Atopic disease · Vitamins · Nutrients

Abbreviations

CRP	C-reactive protein
DC	Dendritic cells
FFQ	Food frequency questionnaire
IgE	Immunoglobulin E
IL	Interleukin
IU	International units
MHC	Major histocompatibility complex
OVA	Ovalbumin
RCT	Randomized controlled trial
SPT	Skin prick test
Th1	T helper 1
Th2	T helper 2
Treg	T regulatory

Introduction

The prevalence of allergic diseases worldwide has risen over the past few decades [1–3]. In the USA, skin and food allergies increased from 7.4 and 3.4% in 1997 to 12.5 and 5.1% in 2011, respectively [3]. Changes in environment and lifestyle such as diet, antibiotic use, and hygiene may have influenced this rise, and such exposures may exert effects as early as the *in utero* period [4•].

The prenatal period is a critical period for immune system development. Maternal diet during pregnancy has been proposed as a risk factor for childhood allergic disease such as asthma, food allergy, eczema, and allergic rhinitis. Because the aggregate of current available evidence is inconsistent and inconclusive, current guidelines do not recommend maternal allergen avoidance or supplementation of nutrients during pregnancy for the primary prevention of allergic disease in children [5].

In this article, we first discuss the rationale for considering maternal diet during pregnancy as a risk factor for childhood allergic diseases. From the perspective that diet can be considered as specific nutrients, particular foods, as well as dietary patterns [6], we then review studies that have been conducted to investigate the effects of prenatal diet on childhood allergic

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diseases. We close by offering our perspectives on research needed to advance this intriguing area of inquiry.

Rationale for Considering Prenatal Diet as a Risk Factor for Childhood Allergic Diseases

Pregnancy encompasses different immunological stages with mechanisms specific to each trimester. Inflammation at the implantation site aids with adhesion and development in the first trimester whereas the second trimester is characterized by anti-inflammatory and Th2 type immune responses [7•]. In the third trimester, conditions switch back to an inflammatory and Th1 type immune state necessary for labor and delivery [7•]. The phenotypes and functions of innate and adaptive immune cells in pregnancy are determined by signals from the placenta, and this *in utero* environment may be influenced by external factors in the maternal circulation [7•, 8]. Environmental exposures such as diet and toxin exposures can alter the epigenome and interact with inherited genetic risk to influence organ development and immune programming [8, 9].

Maternal nutrients and microbiota can influence the expansion of innate immune cells, development of intestinal epithelial cells, and formation of lymphoid organs [10–12]. For example, murine studies have shown that nutrients such as retinoic acid *in utero* are associated with fetal innate lymphoid cell maturation [10]. In addition, maternal levels of dietary retinoids can influence the size of secondary lymphoid organs and immune system responses in adult offspring [10]. Because the developing fetus relies on the mother to provide nutrients necessary for immune system and overall development, maternal diet is important. Malnutrition directly affects placental function and fetal immune development and has been associated with increased risk of obstructive airway disease [8]. Maternal intake of specific nutrients, particular foods, and dietary patterns has been studied as a risk factor for the development of atopic disease with many proposed mechanisms for its effects (Fig. 1 and Table 1).

General dietary guidelines recommend consuming foods that meet nutritional needs without exceeding limits of constituents such as sugars, saturated fats, and total calories. Nutritional needs should be met primarily from foods that are nutrient-dense with high levels of essential vitamins, minerals, and fiber [37]. Components of a diet are also commonly broken down into food groups such as vegetables, fruits, grains, dairy, protein foods, and oils [37]. Eating an appropriate mixture of particular foods from food groups and subgroups is important since each of these groups provide key nutrients to the diet. For instance, vegetables are an important source of vitamin A, vitamin C, vitamin E, iron, and folate [37]. Another common way to think about diet is through dietary patterns which describe a customary mode of eating

from which an individual obtains his or her nutrients and calories [37]. Well-known dietary patterns include the Mediterranean diet, a “healthy” diet, and the Western diet. Many of the studies reviewed in this article focus on specific nutrients, though some target particular foods. Evaluating specific nutrients provides nutrient-specific information with relevance to biologic mechanisms, but the effects and logistics of implementing nutrient-specific interventions is difficult to discern since multiple nutrients contribute to and interact in an individual’s diet. Focusing on specific nutrients, though, simplifies the question at hand and specific supplementation can be considered. Studies of particular foods offer the advantage that food composition data are not needed and results can easily translate into dietary advice, but analysis at this level also does not account for nutrient synergy between foods. Studies on dietary patterns reflect a more encompassing approach that may be more applicable to real-life intake practices [6].

Intake of Specific Nutrients During Pregnancy and Childhood Allergic Disease

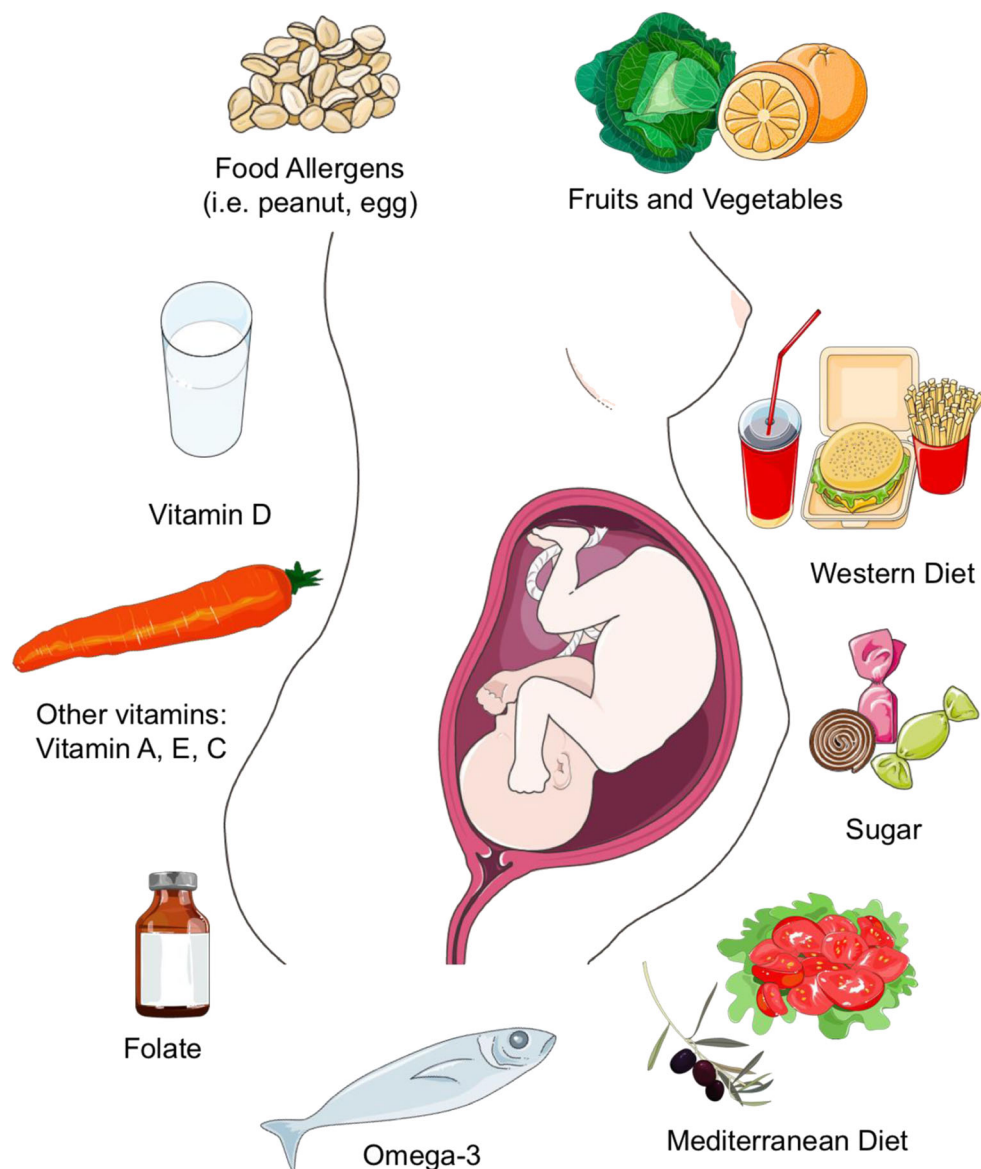
Vitamin D

Several studies support that vitamin D modulates immune system development (Table 1). Vitamin D supplementation is associated with decreased T cell proliferative responses and major histocompatibility complex class II expression on dendritic cells (DCs) as well as increased Treg cell proliferation and interleukin (IL)-10, IL-4, and interferon-gamma production [13•, 14•, 15–17]. Deficiency, thus, may lead to increased risk for sensitization, compromise immune tolerance, and contribute to food allergy development. Additionally, vitamin D deficiency has been associated with abnormal microbial flora, abnormal epithelial barrier, and impaired repair that may cause increased exposure to excess luminal antigens and microbial products [11, 13•, 14•].

Epidemiological studies have reported that high maternal dietary vitamin D intake during pregnancy is associated with reduced risk of asthma and recurrent wheeze in children [38, 39]. Protective effects have also been reported for upper airway allergy. In a US study of 1248 mother-child pairs unselected for any disease, each 100 IU/day increment of prenatal food-based vitamin D intake during the first and second trimesters of pregnancy was associated with 21 and 20% reduced odds of allergic rhinitis at school age (OR 0.79, 95% CI 0.67–0.92, and OR 0.80, 95% CI 0.68–0.93, respectively) [40]. Prenatal vitamin D intake has also been implicated in childhood food allergy risk. Within the Finnish Type 1 Diabetes Prediction and Prevention study, maternal vitamin D supplementation during the eighth month of pregnancy and third month of lactation in 4921 mothers were evaluated

Fig. 1 Dietary exposures during pregnancy encompass specific nutrients, particular foods, and dietary patterns.

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as risk factors for cows' milk allergy in children at age 3 years [22]. Vitamin D intake from foods during pregnancy was associated with decreased risk of cow's milk allergy (adjusted OR 0.86, 95% CI 0.74–1.01), while vitamin D intake via supplementation was associated with increased risk of cow's milk allergy (adjusted OR 1.37, 95% CI 1.034–1.81) [22]. However, the findings from this Finnish study were not statistically significant after controlling for the false discovery rate.

Randomized controlled trials (RCTs) have also examined the effect of prenatal vitamin D on childhood allergic disease (Table 2). Many did not find significant differences for wheeze/asthma or eczema in children whose mothers had been supplemented with vitamin D, although in a few studies there were notable trends toward reduction in pulmonary symptoms [41, 42•, 43•, 44•]. A meta-analysis of two

interventional trials—the US-based Vitamin D Antenatal Asthma Reduction Trial (VDAART) and the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) trials—where pregnant women were randomized to daily high-dose vitamin D3 (4000 IU/day and 2400 IU/day, respectively) or placebo, showed a significant combined effect [64•]. High-dose vitamin D during pregnancy was associated with a 25% reduced risk of asthma or recurrent wheeze in children at age 0–3 years (OR 0.75, 95% CI 0.57–0.96) [64•].

Vitamins A, E, and C

Prenatal exposure to vitamin A and its metabolites has also been implicated in immune system development relevant to allergy. Murine studies have demonstrated effects on both lymphoid and myeloid cell development. Retinoic acid

Table 1 Proposed mechanisms for the immunological effects of dietary exposures on allergy outcomes

Dietary exposure	Proposed mechanism
Vitamin D	• Promotes innate and adaptive antimicrobial response [13•, 14•] • Decreases T cell proliferation responses, MHCII expression on DCs, and levels of IL4 and IFN-gamma [14•, 15, 16] • Increases tolerogenic DCs, Treg cell proliferation, and IL10 [11, 17] • Deficiency decreases tolerance possibly leading to food allergy [13•, 14•, 15]
Vitamin A	• Important for growth, homeostasis, and development, especially for T and B lymphocytes [18] • Required for thymic development, myeloid cell differentiation, and size of secondary lymphoid organs [8, 10] • Increases type 1 immune responses [18]
Vitamin E	• Antioxidant effects [19] • Lower proliferative responses of mononuclear cells to antigen stimulation [19] • Suppresses IL4 gene expression [20]
Vitamin C	• Antioxidant effects [19]
Folate	• Essential for cell division and nucleic acid synthesis [21•] • Functions as a dietary methyl donor, altering gene expression through DNA methylation to induce asthma and immune effects on the offspring [22, 23•, 24]
Fish oil	• Decrease Th2 cell responses and increase Th1 cell and Treg cell responses [25]. • Anti-inflammatory—leads to production of less potent inflammatory eicosanoid metabolites [26] • Reduces neutrophil production of LTB4 and IL13 [27] • Epigenetically modifies histone acetylation, associated with protective effects for allergy [9] • Sources of specialized lipid mediators that reduce airway inflammation in mouse models [28]
Particular foods	• Nutrients and proteins from the maternal diet pass through the placenta [29••] • The fetus is able to produce total and specific IgE to food antigen exposure [29••] • Possibility of fetal sensitization to food allergens through <i>in utero</i> exposure [29••]
Mediterranean diet	• Multiple factors including increased intake of antioxidants and beneficial fats as well as decreased intake of sugars [30–32]
High-sugar diet	• Increases intestinal formation and absorption of advanced glycation end-products which may affect lung development [12] • High fetal exposure to fructose may cause persistence of Th2 immune responses postnatally and allergic inflammation in the developing lung [33•] • Conditions the gut microbiome [11] • Increases CRP and uric acid level which amplifies Th2 immunity and allergic inflammation [34, 35]
Other diets	Healthy diet—high in fruits and vegetables • Increased antioxidants Western diet • Linked to obesity, which reduces Bacteroidetes that have been documented to promote Treg responses [11] • Increases inflammatory lipid mediators based on increased ratio of omega-6 to omega-3 fatty acids [36]

signaling *in utero* has been shown to influence mouse fetal innate lymphoid cell differentiation [10]. Retinoic acid is also required for myeloid cell differentiation and thymic and secondary lymphoid tissue development [10].

Several human cohort and prospective studies examining maternal intake of vitamin A and atopic outcomes have yielded diverse results [18, 19, 65–67]. Two studies found no significant association between maternal vitamin A intake during pregnancy and childhood asthma [18, 66]. Studies evaluating pro-vitamin A carotenoids showed that alpha-carotene consumption was not associated with wheezing [19] or eczema [66], and beta-carotene was not associated with wheezing [19, 65, 67], eczema [66, 67], rhinitis [66], or food allergy [67]. One survey-based study of 763 Japanese mother-child pairs found that higher maternal intake of beta-carotene during pregnancy was significantly associated with reduced risk of eczema but not wheeze. For eczema, the adjusted OR for the fourth vs first quartiles of beta-carotene exposure was 0.52 (95% CI 0.30–0.89) [68].

Two major randomized controlled trials have examined maternal intake of vitamin A and the development of childhood atopic disease (Table 2). A study of 1371 children of women in a vitamin A-deficient population in rural Nepal found that maternal supplementation of vitamin A (compared to beta-carotene or placebo) was associated with improved lung function in offspring at age 9–13 years [45]. A trial in 229 pregnant Indonesian women who were randomized to take 4.5 mg daily of beta-carotene, 30 mg daily of zinc, or beta-carotene plus zinc found that children of mothers who supplemented with beta-carotene had lower levels of interferon-gamma in the supernatant of lipopolysaccharide-stimulated blood [46].

Vitamin E exerts antioxidant effects, suppresses IL-4 gene expression, lowers proliferative responses to mononuclear cells to antigen stimulation, and plays a role in airway development [18–20]. Observational studies of maternal vitamin E intake during pregnancy have demonstrated protective effects against childhood wheeze and asthma and no association with

Table 2 Randomized clinical trials of dietary interventions during pregnancy and their impact on childhood allergic disease

Study	Sample	Timing of intervention	Study groups	Major findings
Vitamin D				
Golding 2013 [41]	180 pregnant women UK	From 27 weeks of gestation to delivery	1. Single dose of 200,000 IU cholecalciferol 2. Daily 800 IU ergocalciferol	No statistically significant difference between group assignment and risk of wheeze, atopy, or eczema at age 3 years
Chawes 2016 [42••]	623 pregnant women Denmark	From 24 weeks of gestation to delivery	1. 2800 IU daily oral cholecalciferol 2. 400 IU daily oral cholecalciferol	No statistically significant difference in wheeze, allergic sensitization, or eczema at age 3 years
Grant 2016 [43•]	260 pregnant women and their infants New Zealand	From 27 weeks of gestation to delivery	1. Maternal/infant dose of 1000 IU/400 IU or 2000 IU/800 IU vitamin D daily 2. Placebo	At age 18 months, serum IgE were obtained and showed that children of mothers who received vitamin D supplementation had a decrease in primary care visits for asthma (placebo 11%, lower dose 0%, higher dose 4%, $p = 0.002$). There was also a greater reduction in dust mite sensitization in children at age 18 month (all $p < 0.05$): Der-f1 (18%, 10%, 2%), Der-f2 (14%, 3%, 2%), Der-p1 (19%, 14%, 3%), and Der-p2 (12%, 2%, 3%) Nonsignificant 6.1% decrease in asthma and recurrent wheezing in children at age 3 years in the higher dose group [44••] Cord blood samples of mothers who were on the higher dose of vitamin D had enhanced proinflammatory cytokine responses to innate and mitogenic stimuli as well as enhanced IL-10 response to dexamethasone treatment in culture compared to those on the lower dose [14•]
Litonjua 2016 [44••]	881 women with atopy or partner with atopy USA	From 10 to 18 weeks of gestation to delivery	1. 4400 IU cholecalciferol daily 2. 400 IU cholecalciferol daily	
Hornsby 2018 [14•]				
Other vitamins				
Checkley 2010 [45]	Follow-up study of 1371 children of married women of childbearing age in a vitamin A-deficient population Rural Nepal 229 pregnant women Indonesia	Before, during, and after pregnancy in a 3-year time period	1. Vitamin A 23300 IU weekly (7000 µg retinol equivalents) 2. Beta carotene 42 mg weekly (7000 µg retinol equivalents) 3. Placebo All received iron (30 mg) and folic acid (0.4 mg) Plus: 1. Beta carotene 4.5 mg daily 2. Zinc (sulfate) 30 mg daily 3. Beta carotene plus zinc (4.5 and 30 mg) daily.	Maternal supplementation of vitamin A (compared to beta carotene or placebo) improved lung function (FEV1, 46 ml higher with vitamin A; 95% CI 6–86; FVC 46 ml higher with vitamin A; 95% CI 8–84) in children at age 9–13 years Children of mothers supplemented with zinc had a nonsignificant increase in episodes of cough in the first 6 months of life compared to those without zinc supplementation (1.3 and 0.9 episodes, respectively). Newborns of mothers who supplemented with beta carotene had lower levels of interferon-gamma in LPS-stimulated blood whereas those who received zinc had higher IL-6 levels
Wieringa 2010 [46]		From less than 20 weeks of pregnancy until delivery		No difference between groups in children with asthma diagnosis by age 2 years
Greenough 2010 [47]	643 pregnant women at risk of pre-eclampsia UK	From second trimester to delivery	1. 1000 mg vitamin C and 400 IU RRR alpha-tocopherol (vitamin E) daily 2. Placebo	Vitamin C supplementation was associated with improved neonatal pulmonary function and decreased wheezing through age 1 year compared to placebo (21% vs 40%; RR 0.56, 95% CI 0.33–0.95; $p = 0.03$)
McEvoy 2014 [48]	179 smoking pregnant women USA	From 22 weeks gestation to delivery	1. 500 mg crushed vitamin C daily 2. Ground cornstarch	

Table 2 (continued)

Study	Sample	Timing of intervention	Study groups	Major findings
Fish oil/omega-3				
Dunstan 2003 [27]	98 atopic pregnant women Australia	From 20 weeks gestation to delivery	1. Fish oil capsules (3.7 g n-3 PUFA – 56.0% DHA, 27.7% EPA) daily 2. Olive oil capsules	Infants in the fish oil group were 3 times less likely to have a positive SPT to egg at age 1 year but not statistically significant (OR 0.34, 95% CI 0.11–1.02; $p=0.055$). There was no difference in frequency of atopic dermatitis but infants in the fish oil supplementation group had significantly less severe disease (OR 0.09, 95% CI 0.01–0.94, $p=0.045$)
Olsen 2008 [55] Hansen 2017 [56••]	533 pregnant women Denmark	From 30 weeks of gestation to delivery	2:1:1 randomization to daily: 1. Fish oil capsules (2.7 g; n-3 PUFA-23% DHA, 32% EPA) 2. Olive oil capsules 3. No oil capsules	In children of mothers randomized to fish oil compared to olive oil, there was a significant hazards rate ratio for asthma diagnosis (hazard rate ratio 0.37, 95% CI 0.15–0.92, $p=0.03$) and allergic asthma (hazard rate ratio 0.13, 95% CI 0.03–0.60, $p=0.01$) at age 16 years. At age 18–19 years, asthma medication prescription was significantly reduced in the fish oil group compared to the olive oil group (hazard ratio 0.54, 95% CI 0.32–0.90, $p=0.02$). This trend was similar, but not significant, for allergic rhinitis medication use. At age 18–19 years there was no difference found between the groups to diagnosis of asthma, asthma medication use, lung function, and IgE sensitization Lower prevalence of food allergy and incidence of IgE-associated eczema in the omega-3 group compared to placebo
Furuhjelm 2009 [49]	145 pregnant women with allergies or husband or previous child with allergies Sweden	From 25 weeks gestation to 3–4 months of breastfeeding	1. 1.6 g eicosapentaenoic acid and 1.1 g docosahexaenoic acid daily 2. Placebo	No difference in total asthma or IgE-associated asthma at age 2 years
Furuhjelm 2011 [50]	145 pregnant women with children who had ≥ 1 first degree relative with atopy Sweden	From 25 weeks gestation to at least delivery	1. Fish oil capsules (1.6 g EPA and 1.1 g DHA) daily 2. Soy oil capsules	No significant difference between groups in incidence of wheeze in first 6 months of life
Noakes 2012 [51]	123 women with low oily fish intake with children who had ≥ 1 first degree relative with atopy UK	From 20 weeks gestation to delivery	1. 150 g of salmon twice a week (1160 mg DHA and 570 mg EPA) 2. Continued diet low in oily fish	No significant difference between groups in asthma with or without sensitization in the first 3 years of life. No significant difference in IgE-associated disease such as food allergy. No significant difference in IgE-associated disease (eczema, allergic rhinoconjunctivitis, wheeze) at age 6 years
Palmer 2012 [52] Palmer 2013 [53] Best 2016 [54••]	706 women with children who had ≥ 1 first degree relative with atopy Australia	From 21 weeks gestation to delivery	1. Fish oil capsule (800 mg DHA and 100 mg EPA) daily 2. Vegetable oil capsules	In children of mothers who received DHA compared to placebo, there was a reduction in nasal symptoms, i.e., congestion, discharge (IRR 0.743, 95% CI 0.633–0.871) $p<0.001$, fever with phlegm with congestion and/or nasal discharge (IRR 0.517, 95% CI 0.377–0.702, $p<0.001$), wheezing with fever (IRR 0.432, 95% CI 0.214–0.830, $p=0.007$), and coughing with wheezing and/or breathing difficulty (IRR 1.263, 95% CI 1.002–1.594, $p=0.042$) Statistically significant 30.7% relative reduction in risk of persistent wheeze or asthma at age 3 years in the treatment group compared to the control group (hazard ratio 0.69, 95% CI 0.49–0.97, $p=0.035$)
Escamilla-nunez 2014 [57]	1094 pregnant women Mexico	From 18 to 22 weeks gestation through delivery	1. 400 mg/day of algal docosahexaenoic acid (DHA) 2. Placebo	
Bisgaard 2016 [58••]	736 pregnant women Denmark	From 24 weeks of gestation to 1 week after delivery	1. Fish oil capsules (2.4 g n-3 PUFA – 55% EPA, 37% DHA) daily 2. Olive oil capsules	

Table 2 (continued)

Study	Sample	Timing of intervention	Study groups	Major findings
Particular foods				
Lilja 1988 [59]	165 pregnant women with atopic respiratory disease with allergy to pollen and/or animal dander Sweden	From third trimester	1. Diet free from hens' egg and cows' milk 2. Normal diet with 0.5 L of milk daily and 3 hens' eggs weekly 3. Reduced intake of hens' eggs and cows' milk 4. High diet with intake of 1 egg and 1 L of milk daily	No difference in cord blood IgE levels, and there was no specific IgE antibodies to ovalbumin, ovomucoid, and beta-lactoglobulin in cord blood
Faith-Magnusson 1992 [60]	209 women with a personal history or family history in ≥ 1 other family member of allergy Sweden	From 28 weeks of gestation to delivery	1. No cow's milk or egg in diet 2. Standard diet	At age 5, no difference in the incidence of eczema, allergic rhinitis, and asthma between the two groups. Children of mothers who had avoided milk and egg had a significantly higher rate of egg intolerance compared to those in the control group (7.1% vs to 0%, $p < 0.05$)
Zeiger 1989 [61] Zeiger 1995 [62]	288 mothers of families with an atopic parent USA	From third trimester through lactation	1. Mothers avoided cow's milk, egg, and peanut (third trimester and lactation) and children avoided cow's milk, egg, peanut, and fish 2. Standard diet	There was a significant reduction in food-associated atopic dermatitis, urticaria and/or gastrointestinal disease by 12 months (5.1 vs 16.4%; $p = 0.007$), as well as any positive food SPTs by 24 months (16.5 vs 29.4%; $p = 0.019$). The change in food SPTs was caused primarily by fewer positive milk SPTs (1% vs 12.4%; $p = 0.001$). At age 7 years, though, there was no difference in food allergy, atopic dermatitis, allergic rhinitis, asthma, any atopic disease, lung function, food or aeroallergen sensitization, or serum IgE level between the two groups
Mediterranean diet				
Sewell 2017 [63]	30 pregnant women at high-risk of having a child with allergic disease UK	From 12 weeks gestation through 36 weeks gestation	1. Mediterranean diet 2. Standard diet	No difference between urinary nitrite or urinary ferric reducing antioxidant potential between the two groups. Mainly focused on assessing feasibility of conducting such a trial and did not address conclusions regarding atopy development in children

There were no published randomized controlled studies on folic acid or diets high in sugar at the time of publication

eczema [19, 65, 66, 68]. Similarly, a meta-analysis showed that higher maternal vitamin E intake was associated with reduced childhood wheeze (OR 0.60, 95% CI 0.46–0.78), but there was no association between maternal vitamin E intake and asthma, eczema, allergic rhinoconjunctivitis, or allergic sensitization [4]. Results from a RCT where mothers in the UK received daily high dose vitamins E (400 IU RRR α -tocopherol) and C (1000 mg vitamin C) versus placebo were less convincing, finding no difference in rates of asthma diagnosis by age 2 years among the children [47].

The antioxidant properties of vitamin C are thought to underline its main effects. An Australian cohort study found that higher maternal vitamin C intake was associated with reduced risk of infant wheeze (adjusted OR for the fourth quartile vs first quartile 0.40, 95% CI 0.16–0.98) [67]. These findings are consistent with a more recent RCT study of 179 pregnant US women reporting improved neonatal pulmonary function and decreased wheezing through age 1 year in children of women who were randomized to receive vitamin C compared to cornstarch placebo (21 vs 40%; RR 0.56, 95% CI 0.33–0.95) [48].

Folate (Vitamin B9)

Because supplemental folic acid during pregnancy reduces the risk of fetal neural tube defects, the US Department of Health recommends that pregnant women consume 400 μ g of folic acid daily [21]. Folate is essential for cell division and nucleic acid synthesis (Table 1). Animal models of folate as a dietary methyl donor show that this function may induce experimental asthma [22, 23•]. Rich natural dietary sources of folate include liver and green leafy vegetables, and certain foods like cereals that are fortified with folic acid.

Several case-control and cohort studies have examined maternal intake of folic acid during pregnancy and atopic outcomes [19, 22, 23•, 24, 66, 69–71, 72•]. Many found no significant association between maternal intake of folic acid and childhood wheeze [19, 69, 70], allergic rhinitis [66], and eczema [24, 66, 69]. In one prospective study of 2640 pregnant mothers, maternal folic acid supplementation was not associated with increased risk of wheeze, lung function, asthma, or related atopic outcomes in children, but there was a dose-dependent trend toward decreased asthma risk at age 6 to 7 years with higher intracellular folic acid levels in pregnancy (P for trend = 0.05) [70].

More recent studies suggest that increased prenatal intake of folic acid is associated with increased risk of wheezing or asthma in childhood [23•, 24, 71, 72•] and food allergy [22], but the timing of supplementation initiation in these studies has been varied. A study evaluating the association between maternal folic acid supplementation intake via third trimester food frequency questionnaire (FFQ) and infant outcomes at age 1 year showed that infants exposed to > 500 μ g/day folate supplementation were more likely to develop eczema than

those taking < 2000 μ g/day (OR 1.85, 95% CI 1.14–3.02) [24]. An observational case-control Norwegian study reported that maternal intake of folic acid during the first trimester was associated with increased risk of wheezing in children age 6 to 18 months [71]. More recently, the effect of maternal folic acid supplementation on childhood lung function was reported to be dependent on MTHFR-C677T carrier status [23•]. These findings highlight that the etiology of atopic disease is complex and multifactorial.

There have been no blinded, placebo-controlled trials evaluating folic acid supplementation and the development of atopic disease in childhood, likely due to the proven positive effects of prenatal folic acid supplementation in the prevention of fetal neural tube defects. Further studies, though, are needed to determine the impact of dosage and timing of initiation of folate supplementation on childhood allergic disease.

Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) are thought to exert anti-inflammatory effects, with several studies reporting that they decrease Th2 cell responses and increase Th1 cell and Treg cell responses [9, 25]. Fish oil has also been found to epigenetically modify histone acetylation of key genetic patterns, including protein kinase C (PKC) ζ , which plays an important role in the development of Th1 phenotypes [9]. In mouse models, exposure to omega-3 PUFAs results in production of less potent inflammatory eicosanoid metabolites and yields lipoxins that reduce airway inflammation [26, 28]. Major food sources of omega-3 fatty acids include oily fish such as salmon, mackerel, and herring, and cod liver oil.

Multiple interventional trials investigating the effect of omega-3 supplementation during pregnancy on the development of childhood allergic disease have been performed with inconsistent results [27, 49–53, 55•, 56, 57]. A majority found no significant association between supplementation and childhood wheezing or immunoglobulin E (IgE)-associated disease [27, 50–53, 56•]. More recent randomized controlled trials, though, support that omega-3 supplementation during the second and/or third trimester may decrease child risk of atopic disease and allergic disease/respiratory symptoms [49, 54, 55•, 57, 58•]. In a relatively recent study in Denmark, 736 pregnant women at 24 weeks gestation were randomized to receive fish oil or placebo (olive oil) daily until 1 week after delivery [55•]. This double-blinded study with follow-up at age 3–5 years found that the risk of wheeze in the treatment group was reduced by a third compared to the control group [55•]. The study populations and environments of the omega-3 trials have varied, with some studies targeting high risk mothers [27, 50, 52, 53] and others targeting lower risk mothers; this may account for the variability of findings.

Intake of Particular Foods During Pregnancy and Childhood Allergic Disease

The most common food allergens in the USA are peanut, tree nuts, milk, egg, wheat, soy, fish/shellfish, and seeds [5]. Given rising prevalence rates of food allergies, the consideration of food allergen elimination from maternal diet during pregnancy has been a topic of interest [3]. The possibility of fetal sensitization to food allergens through *in utero* exposure remains controversial, however [29••]. Prior studies have shown that the fetus is able to produce total and specific serum IgE, and antigen-specific immune reactivity may start from the second trimester [29••].

Specific food allergens can be detected in cord blood. A study evaluating exposure of the fetus and infant to egg ovalbumin through the placenta and breast milk in relation to maternal intake of dietary egg discovered that ovalbumin protein was also detectable in umbilical cord blood [29••]. Interestingly, rigorous dietary egg exclusion did not eliminate transplacental and breast milk egg allergen passage, as egg ovalbumin was still found in blood and breast milk in mothers on an exclusion diet [29••]. These levels were of unclear significance since they were not related to maternal dietary intake or atopic predisposition [29••]. However, a later study suggested that allergen-specific IgE in cord blood may reflect maternal sIgE [73].

Although some studies have reported no association between inclusion of allergenic food in prenatal maternal diets and the development of atopic disease [74], other studies provide contrasting results. In some studies, maternal intake of specific foods was found to be associated with increased risk of allergic sensitization and food allergy in children [60, 75–77]. A birth cohort study of 4146 Dutch pregnant women (1327 atopic and 2819 nonatopic) found that daily consumption of nut products compared to rare consumption was associated with increased odds of childhood wheeze and asthma symptoms [77]. A Consortium for Food Allergy Research study of 503 high risk infants reported that recalled peanut intake during pregnancy was associated with a peanut sensitization in children (OR 2.9, 95% CI 1.7–4.9) [75]. Prenatal diet was assessed based on recall after the children were born and their atopic status was known, thus raising recall bias as a limitation of this study.

In contrast, multiple other studies have shown that maternal intake of specific foods is associated with decreased childhood atopic disease. In a pre-birth cohort study of mothers and children unselected for any disease, higher maternal intake of peanut during the first trimester was associated with a 47% reduced odds of peanut allergy at school age [78••]. A strength of this study was that dietary intake was assessed during pregnancy, before any outcomes in the children were known, thus mitigating recall bias. Independently, a cohort study of 8205 children showed that the incidence of peanut

or tree nut allergy was significantly lower among children of nut-nonallergic mothers who consumed peanuts or tree nuts greater than five times monthly in their prenatal diet compared with children of mothers who consumed peanuts or tree nuts less than once monthly (≥ 5 times vs < 1 time per month: OR 0.31 95% CI 0.13–0.75, P for trend = 0.004) [79]. Protective effects for prenatal egg and milk exposure have been observed.

RCTs examining intake of particular foods during pregnancy and childhood allergy dated from over 20 years ago have also demonstrated similarly disparate effects [59, 61, 62]. In an early prospective study, 209 Swedish mothers at high risk of food allergy were randomized to a diet without milk and egg versus unrestricted diet found that egg intolerance was significantly more common at age 5 years in the children of the mothers who had avoided egg and milk (7.1% vs 0%, $p < 0.05$) [60]. The results from this study would support inclusion of egg and milk in prenatal diets. On the other hand, an RCT evaluating maternal avoidance of cow's milk, egg, and peanut during the third trimester and lactation, found that reduced exposure was associated with reduced food-associated atopic dermatitis, urticarial and/or gastrointestinal disease by 12 months (5.1% vs 16.4%; $p = 0.007$), as well as any positive food SPTs by 24 months (16.5% vs 29.4%; $p = 0.019$) [61]. However, there was no difference between the two populations at age 7 years [62], and there was also no difference in the incidences of allergic rhinitis, asthma, and inhalant SPT positivity [61]. Another trial of 165 atopic pregnant women reported no appreciable effects of maternal intake of milk and egg during pregnancy [59]. No significant differences in cord blood IgE levels or IgE/IgG antibodies to milk or egg antigens were noted in spite of differences in maternal diet [59].

Prenatal Dietary Patterns and Childhood Allergic Disease

Though studies focused on specific nutrients or particular foods are valuable, typical diets contain multiple combinations of food groups that may have combinatorial and interacting effects. Thus, studies evaluating dietary patterns can better capture nutrient synergy and uncover important information.

Healthy Diets

Multiple studies have evaluated “healthy eating patterns”—defined as a high intake of fruits, vegetables, and fiber, moderate meat intake, and low trans-fat consumption—during pregnancy [30, 68, 77, 80–82]. These studies reported no associations between healthy eating patterns and allergy outcomes in childhood.

High maternal intake of fruits and vegetables during pregnancy has been variably associated with risk of atopic disease in children [68, 80, 83]. Intake of green and yellow vegetables and citrus fruits during pregnancy was associated with reduced early childhood eczema [68], whereas green leafy vegetables and fruits like apples was associated with reduced risk of early childhood wheeze and asthma [80, 83]. A Finnish birth cohort study of 2441 children reported that high maternal intake of fruit and berry juices were associated with increased allergic rhinitis at age 5 years [83]. These disparate findings are likely due to the varied antioxidant content of fruits and vegetables as well as the broad definition of a diet high in these items [80].

Western Diet

The Western diet, defined as a high intake of red and processed meats, sugar, butter/vegetable oil, and refined grains, has been implicated in the rise of allergies and other health problems in industrialized countries [80]. This may have to do with the Western diet's effect on the gut and the increased ratio of omega-6 to omega-3 fatty acids, which may lead to increases in inflammatory lipid mediators [11, 36].

In a survey-based study of 763 Japanese mother-child pairs, Western diet during pregnancy was inversely associated with the development of wheeze in infants (adjusted OR 0.59, 95% CI 0.35–0.98) [84]. Conversely, a diet high in processed foods was shown in a longitudinal UK cohort study to be positively associated with early wheezing, but negatively associated with atopy in childhood [30]. However, after controlling for confounders, these effects lost significance [30]. A Boston prebirth cohort of 1376 mother-infant pairs similarly reported no association between Western diet and recurrent wheeze [81].

Mediterranean Diet

The Mediterranean diet—with high intake of plant, grains, legumes and nuts, low to moderate amounts of dairy products and eggs, and limited amounts of red meat—has been linked to many health benefits [31, 32]. The potential positive effects of this diet on prevention of atopic disease could arise from multiple factors including increased intake of antioxidants and beneficial fats and low sugar intake [30–32]. Cross sectional studies in Greece and Spain have indicated that a high level of adherence to a Mediterranean diet during childhood may have advantageous effects on preventing atopic disease [32, 85, 86].

A few studies have examined maternal prenatal adherence to a Mediterranean diet and child development of atopic disease. In a prospective Spanish study of 460 children, FFQs were administered to mothers and children. A high Mediterranean diet score during pregnancy was associated

with reduced persistent wheeze (adjusted OR 0.22, 95% CI 0.08–0.58), atopic wheeze (adjusted OR 0.30, 95% CI 0.10–0.90), and atopy (adjusted OR 0.55, 95% CI 0.31–0.97) at age 6.5 years [32]. A later meta-analysis by that same group, however, showed that a Mediterranean diet had no effect on risk [86]. Similarly, other studies found no association between maternal Mediterranean diet in pregnancy and wheeze [81, 87–89], rhinitis [87, 89], and dermatitis [87].

There has been one randomized controlled study evaluating adherence to a Mediterranean diet during pregnancy in 30 high-risk mothers [63] (Table 2). This study was small, however, and its report focused more on feasibility of study implementation than on development of atopic disease [63].

High-Sugar Diet

Fructose consumption, in the form of high fructose corn syrup, has increased from near 0% to almost 30% of refined sugars consumption per capita in the USA between 1970 and 2000 [33•]. This consumption has led to increased obesity and many other complications [33•].

Studies have demonstrated a link between obesity and asthma, but independent of high body mass index, increased intake of sugar is associated with higher asthma rates in children [12, 90•]. Sugars are hypothesized to increase intestinal formation and absorption of advanced glycation end-products that can affect lung development [12]. Additionally, high fetal exposure to fructose is associated with persistence of Th2 immune responses postnatally and allergic inflammation in the developing lung [33•]. Fructose may also influence atopic immune responses by conditioning the gut microbiome [11]. RCTs in adults have shown that dietary sugar, particularly fructose, is associated with c-reactive protein (CRP) levels and uric acid that can amplify Th2 immunity and allergic inflammation [34, 35].

RCT studies on the relationship between total maternal consumption of sugar during pregnancy and respiratory and atopic outcomes in children are lacking. In observational studies, a maternal diet high in sugar has demonstrated inconsistent associations with atopy and asthma in children [33•, 90•, 91]. In a study of more than 60,000 Danish mothers and infants, maternal sugar-sweetened beverage ingestion was not associated with childhood asthma at age 7 years [91]. Two other studies reported an increased association between maternal prenatal sugar intake and childhood atopy [33•, 90•]. One study examined current doctor-diagnosed asthma, wheezing, hay fever, eczema, atopy, serum total IgE, and lung function in 8956 children aged 7–9 years [33•]. In this longitudinal birth cohort study, maternal intake of free sugar was positively associated with atopy (OR for highest vs lowest quintile of sugar intake 1.38, 95% CI 1.06–1.78) and atopic asthma (OR 2.01, 95% CI 1.23–3.29) [33•]. Another recent prospective pre-birth cohort

study found that higher sugar-sweetened beverage and fructose intake during the first- and second- trimesters were associated with childhood asthma development (OR 1.70, 95% CI 1.08–2.67 and OR 1.58, 95% CI 0.98–2.53, respectively) [90•].

Other Diets

Several studies have also examined other common diets. No associations with childhood allergies were observed for a maternal Japanese diet (high intake of rice, miso soup, and seafood) [69], prudent diet (high intake of vegetables, fruit, legumes, fish, poultry, eggs, and whole grains) [81], traditional British diet (vegetables, red meat, and poultry) [30], vegetarian diet [30], or confectionary-based diet [30].

Emerging Research and Future Directions

Characterizing the effects of prenatal diet on childhood atopic disease is a challenging endeavor given the myriad of dietary and other variables that interact with genetic predisposition in the development of allergic diseases over time. Pinpointing the individual effects of a specific nutrient or particular food is challenging since most human diets are varied and encompass numerous nutrients and foods. Nutrients, foods, and dietary patterns also overlap (e.g., a Mediterranean diet is enriched in produce, fish, omega-3, and antioxidants). Thus, it is difficult to quantify diet as an exposure in and of itself.

One of the main limitations to the available data on prenatal diet and the development of allergic disease lies in the design of studies that have been conducted. Much of the data available is observational, with a limited number of RCTs conducted to date. This is understandable given the challenges of conducting interventional trials in pregnant women as well as the duration of follow-up needed to detect meaningful and robust allergic outcomes in children. Many of the observational studies to date have relied on subject report of diet and/or outcomes, including diet based on distant recall, which introduces recall bias. In addition to prospectively obtained dietary assessments, the incorporation of nutrition-related biomarkers could help improve the accuracy of dietary exposure assessments [80]. Additionally, the duration of follow-up for studies in this area is a key consideration given the varying natural histories of individual allergic diseases. Although challenging to conduct, well-designed randomized controlled trials with rigorously defined dietary exposures and outcomes and appropriate periods of follow-up should be pursued to generate robust evidence in this area.

A number of additional limitations constrain the interpretation of studies on this topic toward coherent and generalizable conclusions. Many studies in this field are heterogeneously

designed with different time points and periods of intervention and observation. Dietary exposures and clinical outcomes have also been differentially defined. Additionally, the populations studied have varied widely in background and size. Whereas some studies have been of unselected populations, many have been of targeted samples selected for high risk of allergic disease. Also, the aggregate literature in this area now spans decades when the underlying prevalence of allergy and management practices have changed. This all leads to difficulty in synthesis of findings and potential translation to clinical applicability.

Clinical Implications

Given the heterogeneous results from studies of prenatal diet and childhood allergic disease thus far, current guidelines and practice parameters do not advise avoidance diets or the additional supplementation of specific nutrients during the prenatal period for the prevention of atopic disease [5]. This is due to the lack of conclusive and consistent evidence on whether such interventions are effective. Thus, an important role of clinical allergists is to help expectant parents be informed about the available evidence and their limitations.

It is essential for the clinician to discuss the available data and the potential risks and benefits of prenatal dietary changes with parents. In general, women who are eating unrestricted diets before pregnancy need not to change their diets during pregnancy for the sole purpose of preventing allergic disease in their children. For women with a restricted diet due to food allergy or personal preferences, a dietary evaluation is recommended to determine the nutritional adequacy of their diets. A balanced and healthy diet should be the main emphasis in dietary recommendations for all expectant mothers.

Common nutrient supplementation widely practiced and recommended during the prenatal period, such as folic acid for the prevention of neural tube defects, should still be implemented. Though not routinely recommended for preventing allergic disease in children, the initiation of other nutrient supplementation during pregnancy may have other benefits, such as vitamin D for maintaining bone health [44•]. The cardiovascular and other benefits of specific dietary patterns such as the Mediterranean diet and sugar-restricted diets has made these dietary patterns generally welcomed as healthy interventions to be considered by all populations [37]. The ultimate decision to initiate nutrient supplementation and/or dietary changes falls on the patient, though, and the main role of the allergist is to provide the patient with a robust repertoire of knowledge for them to make an individualized, informed decision.

Recommendations for maternal dietary changes during pregnancy should be personalized and made by the patient

after weighing any possible risks and benefits. Certain diets, like an elimination diet, may have potential emotional and nutritional risks that should be considered. Changes to the maternal diet may cause harm if such changes limit diet to a point where fetal development is compromised, or if supplementation levels are too high and potentially toxic for the mother and/or fetus.

Many studies and clinical experience show that regardless of adherence to specific dietary interventions during pregnancy, mothers may still have children with atopic disease. This highlights that prenatal dietary influences on the development of these diseases are multifactorial and complex, and it is important to reassure parents to not feel guilty about their past dietary decisions. Counseling should stress that in mothers at risk for having atopic children, a healthy balanced diet and good early childhood care are most important [5].

Conclusions

The role of maternal diet during pregnancy and the development of childhood allergy is a complicated topic due to many interacting variables spanning genetics, environment, and lifestyle. Studies thus far have been performed in varied populations with disparate exposures and outcomes measured. Varying evidence has been provided for the possible roles of specific nutrients, particular foods, and dietary patterns in the development of childhood atopic disease. Rigorous, well-powered, randomized placebo-controlled trials have the capacity to provide robust evidence for this topic of ongoing interest, but are admittedly challenging to perform well.

The allergist plays an integral role in educating and informing patients about the available data in this area. The lack of consistent results and conclusive guidelines on prenatal diet for the prevention of atopic disease makes this counseling to expectant parents challenging. Before recommending a specific diet and supplementation to a pregnant woman, the clinician should recognize the potential lack of effect and even harmful effects for the mother if specific nutrients, particular foods, or dietary patterns are restricted or added in excess. Thus, until more robust and consistent evidence becomes available, a varied, balanced diet during pregnancy encompassing a range of healthy nutrients is most beneficial to recommend.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- There was no difference between the control and fish oil group in the percentage of children at age 6 years with IgE-associated disease.**
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