Dietary strategies for the prevention of asthma in children

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Purpose of review
This review summarizes information relating to dietary intake during pregnancy, lactation and early life that may prevent childhood asthma. This review also summarizes how future studies may be improved.

Recent findings
Recent findings from observational studies suggest that eating according to certain dietary patterns during pregnancy, such as the dietary inflammatory index, Mediterranean diet and Maternal diet index, may reduce asthma and or wheeze in the child. Vitamin D supplementation with higher doses than recommended during pregnancy may be associated with reduced early transient childhood wheezing in the offspring. Higher levels of omega-3 fatty acids in breast milk may be protective against childhood asthma. Breastfeeding infants has been shown to offer many benefits to mother and child but a direct relationship between breastfeeding and the development of asthma has not been established. During childhood, infants and children may need to reduce their intake of advanced glycation end products, increase their food intake according to the traditional Mediterranean diet and increase the diversity of foods eaten.

Summary
Current evidence provides limited suggestions regarding dietary changes for preventing early transient childhood wheezing. In order to harmonize methods for future data collection and reporting, it is important to harmonize relevant definitions and other important factors. The aim of the considerations described here is to enable a better comparison of future studies and provide better guidance to patients and families.

Keywords
asthma, infant diet, maternal diet, prevention

INTRODUCTION

Allergic diseases are an increasing public health concern [1,2]. Asthma, eczema, allergic rhinitis and food allergies form the four major presentations of allergic diseases. Allergic diseases affect more than 50 million Americans [1]. Asthma is reported to affect 300 million people world-wide [3] and 10.4% of children in the US have a diagnosis of asthma [4]. Early life factors, including dietary intake during pregnancy, lactation and early life, have been considered as possible risk factors for the development of childhood asthma. However, despite data from a pool of studies focusing on dietary intake and asthma outcomes, the results do not give clear guidance on which dietary factors to address [5,6]. It is also unclear when the intervention should be commenced and discontinued. Results and conclusions for systematic reviews are clearly different when data from pregnancy, breastfeeding and early life feeding practices are treated as distinct entities vs. pooling data from interventions covering more than one time period [5,7▪]. Globally, recommendations on dietary intake during pregnancy, lactation and early life for the prevention of asthma are sparse and most guidelines focus on interventions for the prevention of eczema and/or food allergies [8,9,10▪,11▪▪]. The

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KEY POINTS

- During pregnancy, eating a less inflammatory diet, and eating according to the Mediterranean diet and according to the Maternal diet index may reduce asthma and/or wheeze in the child.
- No conclusion can be drawn regarding the effect of maternal diet during lactation, but higher levels of omega-3 fatty acids in breast milk may be protective.
- Reducing intake of AGEs, increasing food intake aligning with the traditional Mediterranean diet and methods (mainly plant based, slow cooked meats with herbs), and increasing the diversity of foods eaten during infancy and early childhood may prevent the development of asthma in later childhood.

limited information on dietary interventions to prevent asthma/wheeze is further confirmed by the Global Initiative for Asthma (GINA) guidelines [12▪]. These guidelines suggest that correcting vitamin D deficiency in pregnant women or women who plan to get pregnant may reduce offspring wheeze. Breastfeeding is advised for reasons other than preventing asthma [12▪]. After a review of available guidelines, Linneman *et al.* [13] concluded that there is no need to exclude allergens from the maternal diet for asthma prevention. Further, observational studies in early life suggest that a Mediterranean style diet in younger children is associated with a lower prevalence of asthma [6].

Two nutrients have in particular been hypothesized to play a role in the prevention of wheeze and/or asthma and will be highlighted in this review. The active metabolite of vitamin D, 1,25-(OH)2D3, has immunomodulatory activity, and deficiency of this metabolite has been proposed as a factor in the increase of asthma and allergic diseases in the recent decades. Although studies relating to wheeze and asthma outcomes focus on vitamin D intake/supplement, correcting vitamin D levels may also have to correct lifestyle changes. Safe-sensible UVB exposure, however, may be the most effective method of ensuring sufficient vitamin D exposure and has been associated with reduced eczema outcomes [14]. Current reference ranges for 'normal' vitamin D levels, similar to dietary recommendations, mainly reflects ranges for reducing rickets and are not focused on 'immunological and nutritional health benefits (Fig. 1).

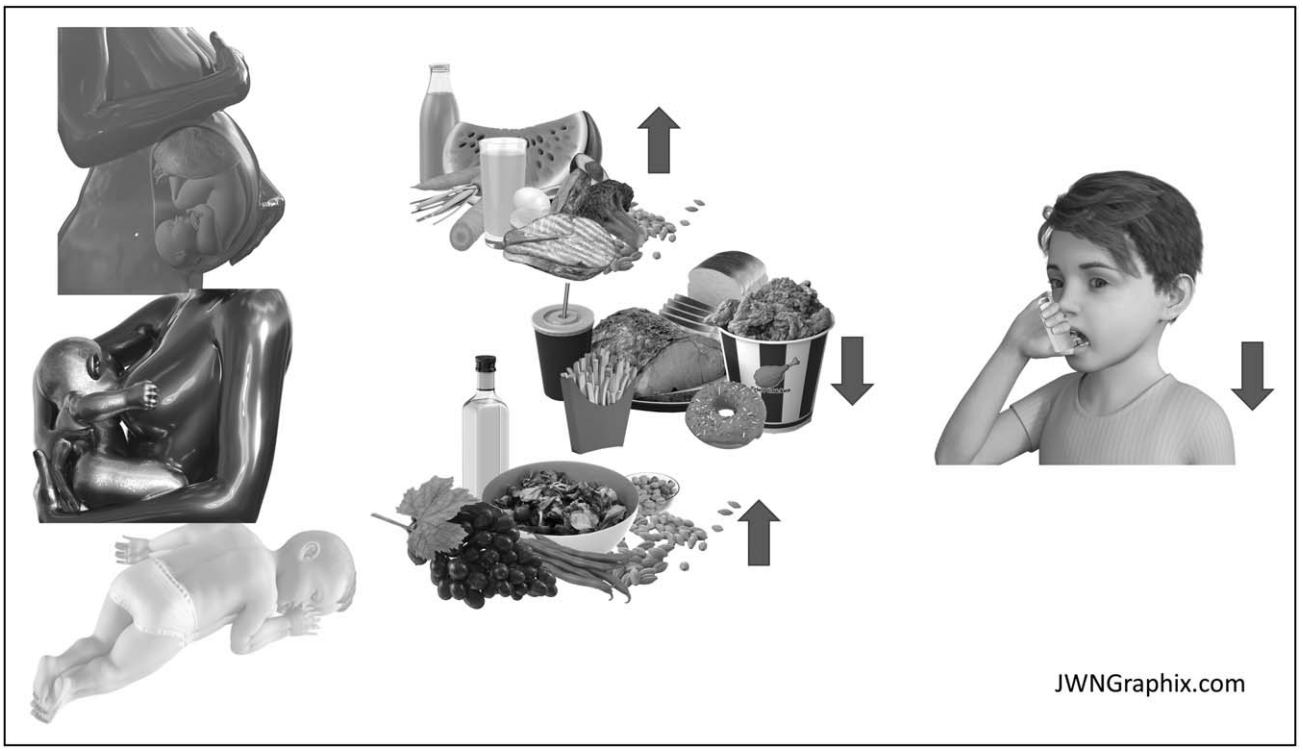

FIGURE 1. Summary of current data regarding Dietary Strategies for the Prevention of Asthma in Children. Dietary factors associated with reduced asthma/wheeze in childhood: Pregnancy: Reduced scores on the Diet inflammatory index, Increased scores on the Mediterranean diet index and Vitamin D supplementation. Breastfeeding: Increased Omega-3 fatty acid levels in breast milk. Infancy: Reduced intake of advanced glycation end products, Omega-3 fatty acid supplementation.

The immunomodulatory effects of omega-3 fatty acids have also been highlighted and described in many studies [15▪▪]. Nutrients, however, do not exist in isolation and to fully understand the role of dietary intake on disease outcomes, it is important to study food and nutrient intake using a whole diet approach. Three terms that are used to describe and summarize overall diet intake are diet patterns, diet indices and diet diversity [6]. Diet patterns is a term used to describe food intake, usually in relation to cultural eating practices. Diet indices summarize food intake to describe the quality of the diet. Diet diversity is defined as the number of different foods or food groups consumed over a given reference period. Diet variety, a term often used in the literature, is considered synonymous with diet diversity [6,16]. The mechanistic basis for how overall dietary intake potentially affects allergy outcomes needs further clarification, but may ultimately be mediated through an effect on the microbiome and subsequent immune modulation or a direct effect of increased intake of immunomodulatory nutrients [6,17].

Studying asthma as an outcome is also not without its pitfalls. Early childhood wheeze may not lead to allergic asthma outcomes in later childhood, as not all infants/young children who wheeze will develop asthma [18]. Therefore, we will focus on reported asthma/wheeze in children 3 years and older whenever this data is available.

The overall aim of this review is to summarize the role of dietary intake during pregnancy, lactation and early life on the development of childhood asthma whereas highlighting concerns with research findings and possible solutions (Table 1).

PREGNANCY

Observational data

Foods and nutrients

An EAACI systematic review [7▪] reported that intake of vitamin D, Vitamin E, zinc, fruits and vegetables, nuts, fish/fatty fish and meat during pregnancy were associated with reduced offspring asthma or wheeze across all ages. Factors associated with an increased risk of offspring asthma or wheeze were the consumption of pasta, fish sticks and arachidonic acid (ARA) during pregnancy. However, the authors mention that the doses of foods or nutrients studied were heterogeneous and were not consistent with current nutrition guidelines, which make practical implementation of the findings troublesome.

Food components

Advanced glycation end products

Observational data indicate that increased intake during the childhood of foods typical of the Western diet, such as burgers, sugar and high fructose corn syrup [19], and food preparations, such as frying, may be associated with the increase in allergic diseases, particularly asthma [20]. These foods are sources of advanced glycation end products (AGEs), compounds that form when sugar binds to protein or it is formed via lipoxidation [19]. AGEs may contribute to the development of asthma via their effect on both Th2 and inflammatory cytokines. This is referred to as the false alarm hypothesis [20]. Asthma and wheeze are characterized by

Table 1. Difficulties with determining study outcomes and future recommendations

Current problems with research findings	Suggestions/recommendations
Amounts of foods and nutrients studied does not relate to nutrition guidance for healthy eating.	Compare study findings with nutritional recommendations from the particular country. Doses summarized should be clearly identified in review and guideline papers.
Lack of validated dietary intake questionnaires for establishing dietary intake	Study timelines should allow for validation of research tools.
Different criteria and definitions used for health outcomes in studies make it difficult to compare studies head-to-head.	Standardized criteria for health outcomes should be used.
Studies look at health outcomes at different ages which makes the data difficult to interpret.	Set ages of determining health outcomes should be used when possible.
Conclusions reached by review papers combining interventions during pregnancy and/or lactation and/or infancy differ from systematic reviews focusing on single outcome.	The timelines summarized should be clearly identified in review and guideline papers.

Current problems with presented research finding and suggestions or recommendations on improving future studies.

underlying inflammatory processes. The Receptor for AGE (RAGE) is activated by dietary intake of AGEs which leads to up-regulation of TNF-α, IL-1, IL-6 and IL-8 [21]. RAGE and its activation ligands are central to the development of allergic responses and sensitization seen in asthma [20,22,23]. In addition, higher levels of soluble RAGE (a decoy ligand) are protective against asthma [24]. Despite this compelling information, Venter *et al.* did not find any association between maternal AGEs intake during pregnancy and offspring asthma outcomes before or after adjusting for potential confounders [25▪▪].

Food patterns and indices

Four diet indices in pregnancy have been studied in relation to asthma outcomes; (i) dietary inflammatory index (DII) [26,27,28▪▪], (ii) the healthy eating index (HEI) [26,29,30], (iii) the Mediterranean diet index [29,31–34]. and (iv) the Maternal diet index [35▪]. A number of other food patterns have also been studied, primarily identified from studies using principal component analysis [36,37].

Dietary inflammatory index

The DII is a complex index that provides an estimate of the inflammatory potential of the diet based on the combination of foods and nutrients with high and low inflammatory potential in single index [38]. Positive weights are assigned to inflammatory foods and nutrients, such as trans fats, and negative weights to less or anti-inflammatory nutrients, such as omega-3 fatty acids. One recent study showed an association between maternal energy-adjusted DII [26] scores during pregnancy and offspring asthma outcomes over 10 years. Another study found an association between maternal DII scores [27] and offspring wheeze trajectories, but not asthma, up to 7.5 years of age. Venter *et al.* [28▪▪] concluded that their results suggested that a maternal diet that scored higher on the DII was associated with increased odds of offspring asthma and/or wheeze by age 4 years.

Healthy eating index

Three studies have used the HEI as a measure of healthy eating to study the role of dietary intake in pregnancy on childhood allergy outcomes [26,29,30]. The Food Allergy and Intolerance Research Study (FAIR), UK, showed that the Alternate HEI in pregnancy (AHEI-P) was not associated with any allergic outcomes (including asthma) in the offspring at 3 or 10 years [30]. Lange *et al.* [29] reported data from Project Viva cohort (US) and found no association between the HEI and recurrent wheeze and children at the age of 3 years. In contrast, Chen *et al.* [26] used data from an Irish cohort and reported that higher HEI-2015 scores were associated with lower risk of asthma in the offspring up to 10 years.

Mediterranean diet index

Associations between the Mediterranean diet index and asthma/wheeze outcomes have been reported by five studies [29,31–34] (two from Spain, one from Greece, one from the USA and one from the UK). Reduced outcomes of childhood persistent wheeze, atopic wheeze and atopy were associated with the Mediterranean diet index in only one of the studies [33]. Another study [34] found a protective association between the Mediterranean diet score and childhood maximal mid-expiratory flow, as well as $FEF_{25-75\%}$ *z*-scores.

Maternal diet index

Venter *et al.* [35▪] developed an index of maternal diet during pregnancy, using data from the Healthy Start study, Colorado (US). The index was associated with reduced odds of any allergy in a birth cohort of >1200 mother-offspring dyads up to 4 years of age. The index was associated with 16% reduced odds of asthma and 20% reduced odds of wheeze in offspring by four years [35▪].

Other diet patterns or indices

Using principal component analysis, two studies showed that a maternal Western diet pattern was associated with a reduced risk of wheeze [36,37], which highlights the complexities of studying diet intake during pregnancy and offspring allergy outcomes. The generation R study found no significant association between maternal diet quality in pregnancy and asthma at 10 years [39].

Randomized controlled trials

Vitamin D

A systematic review with meta-analysis [7▪] reported that prenatal supplementation with vitamin D in doses higher than recommended by most countries, may have beneficial effects for the prevention of asthma/wheeze in the offspring. RCT doses included 800 IU, 2400 IU, and 4000 IU (https://www.aafp.org/news/health-of-the-public/20101201iomrpt-vitdcal.html). The Institute of Medicine recommendations for intake of vitamin D are summarized in Table 2.

Omega-3 fatty acids

The same meta-analysis that summarized vitamin D interventions [7▪] also indicated that there was a

Table 2. Institute of Medicine recommendations for vitamin D intake

Age	Male	Female	Pregnancy	Lactation
0–12 months	10 mcg (400 IU)	10 mcg (400 IU)		
1–13 years	15 mcg (600 IU)	15 mcg (600 IU)		
14–18 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
19–50 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
51–70 years	15 mcg (600 IU)	15 mcg (600 IU)		
>70 years	20 mcg (800 IU)	20 mcg (800 IU)		

https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/.
Institute of Medicine recommendations for the intake of vitamin D throughout the lifespan.

Table 3. Institute of Medicine recommendations for omega-3 fatty acids intake

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months[a]	0.5 g	0.5 g		
7–12 months[a]	0.5 g	0.5 g		
1–3 years[b]	0.7 g	0.7 g		
4–8 years[b]	0.9 g	0.9 g		
9–13 years[b]	1.2 g	1.0 g		
14–18 years[b]	1.6 g	1.1 g	1.4 g	1.3 g
19–50 years[b]	1.6 g	1.1 g	1.4 g	1.3 g
51+ years[b]	1.6 g	1.1 g		

https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/.
Institute of Medicine recommendations for the intake of omega-3 fatty acids throughout the lifespan.
[a]As total omega-3s.
[b]As ALA.

trend towards a protective effect for omega-3 supplementation during pregnancy, on offspring asthma/wheeze outcomes, but it did not reach statistical significance. The Institute of Medicine recommendations for intake of omega-3 fatty acids are summarized in Table 3.

BREASTFEEDING

Observational studies

Foods and nutrients

Omega-3 fatty acids

High levels of *n*-6 PUFAs in breast milk have been associated with an increased risk for asthma-like symptoms [40]. In addition, another study reported reduced offspring asthma in allergic mothers with higher omega-3 levels in breast milk and increased offspring asthma in nonallergic mothers who had higher omega-6 levels in breast milk [41]. Contrary to this, Lumia *et al.* [42] reported that maternal fatty acid intake during lactation did not influence offspring risk of asthma by 5 years of age. Huan and Yang [43] reported on two studies [44,45] showing that omega-3 fatty acid levels in expressed breast milk are inversely associated with offspring asthma when comparing highest to the lowest group of omega-3 fatty acid levels. Studying the role of omega-3 fatty acids in allergy outcomes may need to be extended beyond merely studying supplementation and include monitoring of serum or erythrocyte fatty acid levels. We don't only need to address omega-3 supplements but also address that ratio of omega 3:omega-6 fatty acids. On a basic immunological level, sufficient omega-3 levels are required for cardiolipin function in mitochondria. In mitochondria with suboptimal levels of cardiolipin, mitochondria in naïve T cells conserve energy by directing expression of Th2 cells rather than Th1 cells [46,47]. To alter 50% of omega-3 on a cardiolipin molecule can take several hundred days, indicating that long-term supplementation may be required to improve clinical outcomes.

Food patterns and indices

There is currently no published data on the association between overall maternal diet during breastfeeding and offspring asthma outcomes.

Randomized controlled trials

Vitamin D

In a UK based study, breastfeeding mothers ($n = 164$) of infants with facial eczema at their 1 month check-up were randomly assigned to receive either vitamin D3 supplements ($n = 82$; 800 IU/day) or placebo ($n = 82$) for a six week period. There was no difference in reported wheeze between the groups up to 2 years of age [48].

Breastfeeding duration

A recent systematic review by the United Kingdom Food Standards Agency concluded that they did not find any evidence for any duration of breastfeeding on asthma prevention in the offspring [5]. This is echoed by the GINA guidelines [12▪]. However, breastfeeding is always recommended for the many other benefits to both mother and infant [49].

EARLY LIFE

Observational studies

Nutrients and food

Fish intake/omega-3 fatty acids

Kull *et al.* reported that regular fish consumption during the first year of life was associated with a reduced risk for allergic disease by age 4 [50]. A systematic review focusing on fish intake in infancy concluded that fish intake, not specifically, omega-3 fatty acids, during infancy may prevent allergic outcomes, although no association was seen between infant fish intake and childhood asthma outcomes [51].

Vitamin D

A prospective birth cohort study of 123 infants recorded vitamin D3 intake during the first year of life and dichotomized intake as equal to or less than 13.00 μg per day, or higher than 13.00 μ g/day. By 6 years of age, allergic manifestations including asthma were more prevalent in the group with higher intake of vitamin D3 [52]. In support of this, Kull *et al.* reported that children supplemented with vitamins A and D in water-soluble form, as opposed to those children that received their supplements in a fat-soluble form, during the first year of life had an almost 2-fold increased risk of asthma by 4 years of age [53].

Food components

Advanced glycation end products

A study from the US indicated that increased AGEs intake in children 5–9 years of age was significantly associated with increased odds of wheezing, wheeze-disrupted sleep, and wheezing requiring prescription medication [54▪▪].

Food patterns, indices and diversity

Diet indices

In children, studies focusing on the Mediterranean diet report on *current* dietary intake for asthma outcomes, and therefore do not assess the preventive effect of early (infancy) dietary intake with later (childhood) asthma outcomes. Three systematic reviews focusing on dietary intake and asthma outcomes concluded that the Mediterranean diet (using the Mediterranean diet index) in childhood [55–57] shows an inverse relationship with reported wheeze and asthma. Papamichael *et al.* [56] reported an inverse association between Mediterranean diet pattern and asthma in children. Nurmatov *et al.* [55] and Lv *et al.* [57] reported a possible association between the Mediterranean diet and reduced prevalence of childhood wheeze.

Other dietary patterns

A number of studies showed an increased prevalence of wheeze/asthma in children consuming a Western diet [58–60]. In contrast to these studies, the Dutch Generation R cohort did not find an association between a healthy dietary pattern in early life and a lower risk of atopic diseases, including asthma, in childhood [39,61].

Diet diversity

Data relating to diet diversity in infancy and asthma/wheeze in childhood were reported by the PASTURE study [62] and the Finnish Type I Diabetes Prediction and Prevention Study Prospective Cohort Study [63]. In the PASTURE cohort, Roduit *et al.* [62] showed that increasing diet diversity in the first year of life was associated with reduced asthma by 6 years. In fact, a 26% reduction was reported for each additional food introduced. Nwaru *et al.* [63] noted that reduced diet diversity at 12 months of life was associated with a greater risk for the development of asthma at age 5, as well as an increased risk for any wheeze.

Randomized controlled trials

Omega-3 and omega-6

Four papers reported using omega-3 and omega-6 supplementation in newborns with a family history of allergy for the first 6 months of life [64–67]. The active arm contained 135 mg docosahexanoic acid (DHA) and 32 mg eicosapentanoic acid (EPA). No differences in the prevalence of asthma or wheeze were seen between the two arms when children were 5 years of age. The outcomes wheeze ever, doctor visits for wheeze, bronchodilator use and nocturnal coughing at 18 months were significantly reduced in children in the higher exposure quintiles to omega-3 fatty acids. Reduced prevalence of any wheeze and a reduction in prevalence of wheeze for more than one week by 18 months was reported for the group receiving omega-3 supplements. Birch *et al.* [68] supplemented healthy term infants with DHA (0.32–0.36% of total fatty acids) and ARA (0.64–0.72% of total fatty acids) vs. a placebo for the first year of life. Infants fed formula supplemented with DHA and ARA had a reduced incidence and delayed onset of upper respiratory infection and wheezing/asthma by 3 years of age. D'Vaz *et al.* [69] supplemented infants at high risk of allergy for the first 6 months with EPA and DHA (280 mg DHA and 110 mg EPA) vs. placebo for the first 6 months of life. Elevated plasma levels of DHA and total omega-3 fatty acid levels at 6 months of age were associated with a reduced risk of recurrent wheeze in the first 12 months of life. Foiles *et al.* [70] supplemented healthy term infants with DHA and ARA (0.64% of total fatty acids as ARA and either 0.32, 0.64, or 0.96% of total fatty acids as DHA) vs. a placebo throughout infancy. The risk of skin and respiratory allergic diseases in childhood was influenced by a maternal history of allergies. Incidence of wheezing/asthma were significantly lower in the subgroup who received the fatty acid supplement and whose mothers reported a positive history of allergy compared to those with no supplementation and a maternal history of allergy. Fatty acid supplementation did not show any effect on allergy outcomes compared to no supplementation in children with no maternal history of allergy.

Vitamin D

Children of mothers with 25-hydroxyvitamin D levels $\geq$50 nmol/L were randomized to receive oral vitamin D supplementation of 400 IU/day ($n = 97$) or a placebo ($n = 98$) for the first six months of life. There was no significant difference for reported wheeze by 1 year of age or for wheeze/asthma at 2.5 years between the two groups [71▪]. This may once again highlight the importance of sun exposure rather than supplementation. Studies focusing on vitamin D intake may also show improved outcomes by adding a vitamin K_2 supplement to increase vitamin D receptors [72].

CONCLUSION

Overall, the data suggest that eating according to certain dietary patterns during pregnancy such as the DII, Mediterranean diet and Maternal diet index may reduce asthma and/or wheeze in the child. Vitamin D supplementation in pregnancy may be associated with reduced asthma outcomes in the offspring. No conclusion can be drawn regarding the effect of maternal diet during lactation but higher levels of omega-3 fatty acids in breast milk may be protective. Infants should ideally be breastfed for the many benefits to mother and child. Limited data suggest that infants and children may want to reduce their intake of AGEs, increase food intake according to the Mediterranean diet and to increase the diversity of foods eaten. In order to harmonize methods for future data collection and reporting, it is important to harmonize relevant definitions and other important factors such as timing of supplementation, nutrient interactions and environmental exposures, e.g., sunlight. It is hoped that the considerations described here will enable better comparison of future studies to provide improved guidance to patients and families.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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This is the systematic review underpinning the EAACI prevention guidelines. The paper concludes: 1) Prenatal supplementation with vitamin D may prevent offspring. 2) No consistent patterns for other nutrients and foods were found for asthma and allergy prevention. 3) Studies using similar methodology and outcome measures are required.

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10. ■ Halken S, Muraro A, de Silva D, *et al.* EAACI guideline: preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol 2021; 32:843–858.

This is the latest summmary guidelines on food allergy prevention from EAACI. The paper concludes that: 1) There is uncertainty on how to prevent food allergy. 2) Introduction of well cooked egg and peanut in the first year of life may prevent egg and peanut allergy. 3) Supplementation with cow's milk formula in the first week of life should be avoided.

11. ■■ Fleischer DM, Chan ES, Venter C, *et al.* A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. J Allergy Clin Immunol Pract 2021; 9:22–43.

This is the latest consensus document from North America and Canada on food allergy prevention. The paper concludes that: 1) Peanut and egg should be introduced around 6 months of life, but not before 4 months for prevention of peanut and egg allergy. 2) Other allergens should be introduced once solid food introduction commences. 3) Maternal avoidance of food allergens during pregnancy and/or lactation to prevent food allergy is not recommended.

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This is the latest guidance from GINA. The guidelines conclude that: 1) There is limited information on dietary interventions to prevent asthma/wheeze. 2) The guidelines suggest that correcting vitamin D deficiency in pregnant women or women who plan to get pregnant may reduce offspring wheeze. 3) Breastfeeding is advised for reasons other than preventing asthma.

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This review summarizes the complexity of factors between diet and allergy or asthma prevention. The paper concludes that: 1) There is enthusiasm for the potential of diet to impact the immune system and prevent disease. 2) Nutrition scientists is challenged by defining and conducting nutrition research. 3) Further studies of dietary patterns, immune system and gut microbiome composition and function, and subsequent epigenetic modifications are needed to improve current knowledge of diet-immune system interactions.

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This is the first paper with extensive data on maternal intake of AGEs during pregnancy. 1) The data shows no effect on chilhood asthma and allergy outcomes. 2) Exposure to AGes during pregnancy may not have the same impact on child allergy and asthma outcomes as postnatal exposure.

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