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Food allergy prevention: Where are we in 2023?

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ABSTRACT

Food allergy prevention involves recommendations to the maternal diet during pregnancy and breast feeding, early life feeding and introduction of solid foods. Pregnant and breastfeeding women are not recommended to exclude any food allergens from their diet, but data are lacking to support active consumption of food allergens for prevention of food allergy. Breastfeeding is recommended for the many health benefits to the mother and child but has not shown any association with reduction in childhood food allergies. There is currently no recommendation regarding the use of any infant formula for allergy prevention, including the use of partially or extensively hydrolyzed formulas. Once the introduction of solid food commences, based on randomized controlled trials, it is advised to actively introduce peanuts and egg early into the infant diet and continue with consumption of these. Although there are limited data with respect to other major food allergens and whether early introduction may prevent allergy development, there is no need to delay the introduction of these allergens into the infant diet. Interpreting food allergen consumption in the context of cultural food practices has not been studied, but it makes sense to introduce the infant to family foods by 1 year of age. Consumption of foods typical of the Western diet and foods high in advanced glycation end products may be associated with an increase in food allergies. Similarly, intake of micronutrients, such as vitamin D and omega-3 fatty acids in both the maternal and infant diet, needs further clarification in the context of food allergy prevention.

Keywords: Food allergy; microbiome; nutrients; nutrition; prevention

1. Introduction

Food allergy prevention guidelines have changed to a great extent in the past 2 decades [1-7] (**Table 1**).

These changes include dietary advice given regarding the maternal diet during pregnancy and breastfeeding (BF) and age of introduction of potentially allergenic foods during infancy. Knowledge regarding the overall maternal and infant diet and the role of micronutrients in food allergy prevention has increased. Understanding about the interconnectivity of nutrition, microbiome, immune system, and epigenetics has also increased, highlighting the advances made in the knowledge base underpinning food allergy prevention.

This review article will provide an overview on the role of the maternal diet during pregnancy and lactation, the infant diet, the role of BF, and formula feeding in food allergy prevention. The characteristics and function of the microbiome in food allergy prevention will also be discussed. The article will summarize information from observational studies, randomized controlled trials (RCTs), systematic reviews, and guidelines/consensus documents.

2. Maternal diet in pregnancy and during BF

2.1. Food allergens

Earlier, allergy prevention guidelines recommended that pregnant and BF women from high-risk families should avoid peanut and other food allergens in the United States and elsewhere [9]. A meta-analysis conducted by the Food Standards Agency in the United Kingdom summarizing 5 RCTs [8, 10-13] concluded that there was no evidence that food allergen avoidance, either single or multiple foods, with or without other interventions, was associated with reduced offspring food allergy outcomes [14]. Food allergen avoidance during pregnancy and BF for prevention of food allergy in offspring is currently not recommended by national [2, 15-17]and international [3-6, 9, 18, 19] guidelines and consensus statements. Guideline documents (**Table 1**) also highlight that food allergen avoidance during pregnancy and lactation may also lead to nutritional deficiencies [20].

There is some conflicting evidence about consumption of food allergens during BF and infant food allergy outcomes [21, 22]. Regarding food allergen consumption during pregnancy and lactation, one study indicated that maternal peanut consumption during pregnancy, and followed by introduction of peanut into the infant diet while still being breastfed, may prevent peanut sensitization [23]. This finding was supported by another study, which indicated that maternal peanut intake during BF may prevent peanut sensitization [24]. Neither of these studies looked at clinical food allergy as an outcome, and more studies are needed to address the complexity of food allergen consumption by pregnant women, BF mothers, and infants

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Table 1.

Summary of the national and international guidance on the prevention of food allergies

	Consensus statement: American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; Canadian Society of Allergy and Clinical Immunology (2020) [2]	European Academy of Allergy and Clinical Immunology (2020) [3]	Japanese Pediatric Guidelines for Food Allergy (2020) [4]	Canadian Pediatric Society (2019) [5]	Asia Pacific Academy of Pediatric Allergy, Respirology, and Immunology (2018) [6]	Australasian Society of Clinical Immunology and Allergy (2016) [7]
Foods of relevance	All foods	All foods	All foods	All foods	All foods	All foods
BF	EBF recommended for all mothers; no association between EBF and prevention of FA	EBF for around the first 6 months of life and continued BF for the first year	No evidence that BF prevents food allergy	BF for up to 2 years and beyond	Continue BF up to 2 years	BF for at least 6 months and for as long as mother and infant wish to continue
Pregnant or BF mothers	Does not recommend maternal exclusion of common allergens Does not support the use of any food supplement	Recommends against avoiding food allergens	Recommends against avoiding allergens			Recommends a healthy diet Exclusion of any foods (including allergenic) not recommended Recommends up to 3 servings of oily fish per week No recommendation on probiotics
Introduction of solid foods		All infants: Some families choose to start CF at age 4–6 months	All infants: start at around age 5–6 months	Infants at no or low risk of FA: introduce CF at around age 6 months	Healthy infants: start CF at age 6 months.	All infants: start when infant is ready—around 6 months of age but not before age 4 months.
Introduction of food allergens	Introduce peanut and cooked hen's egg to all infants starting around age 6 months but not before age 4 months. Do not delay introduction of other allergenic CF (CM, soy, wheat, tree nuts, sesame, fish, shellfish) at around age 6 months but not before age 4 months.	All infants: introduce peanut and well-cooked hen's egg as part of CF starting at age 4–6 months.	All infants, including high-risk infants: delayed introduction of food allergens is not recommended.	High-risk infants: introduce allergenic solids at around age 6 months but not before age 4 months. Introduce allergenic foods one at a time, to gauge reaction, without unnecessary delay between each new food. Once tolerated, offer the allergenic food a few times a week to maintain tolerance.	High-risk infants with family history of FA: do not delay introduction of allergenic foods. High-risk infants with severe eczema: skin prick test or oral food challenge (or both) to peanut and egg may be required. Do not delay introduction of allergenic foods.	All infants, including high-risk infants: introduce allergenic solid foods, including peanut, cooked hen's egg, dairy, and wheat, within the first year of life. High-risk infants: there is good evidence that regular peanut intake before age 12 months can reduce peanut allergy; moderate evidence that cooked hen's egg before age 8 months (in infants with family history of allergy) reduces risk of developing hen's egg allergy.
Continued intake	No frequency, just add as regular part of diet					Unless there is an allergic reaction to the food, continue to give the food to your baby regularly (twice weekly), as part of a varied diet. Trying a food and then not giving it regularly may result in food allergy development.
Formula	Recommends against the use of any hydrolyzed formulas for prevention of FA or sensitization	No recommendation for or against the use of hydrolyzed infant formulas Recommends against soy protein formula in the first 6 months of life	Insufficient evidence on the usefulness of hydrolyzed milk in preventing the onset of food allergies			Does not recommend hydrolyzed (partially or extensively) infant formula for prevention of allergic disease Recommends use of standard CMF when BF is not possible
Other	Recommends feeding infants a diverse diet, as this may prevent FA No recommendation on prebiotics and probiotics	No recommendations for or against: -vitamin supplements, fish oil, prebiotics, probiotics, or synbiotics in pregnancy, when BF, or in infancy -altering the duration of EBF -hydrolyzed infant formulas	No recommendation on probiotics during pregnancy			

AD, atopic dermatitis; BF, breastfeeding; CF, complementary foods; CMF, cow's milk formula; EBF, exclusive breastfeeding; FA, food allergy; NIAID, National Institute of Allergy and Infectious Diseases.

Adapted with permission from Sampath et al. [1].

and the overlap between BF and infant food allergen introduction. Studies need to evaluate clinical outcomes.

2.2. Maternal food diversity patterns

The role of diet diversity (DD) in pregnancy and lactation in offspring allergy outcomes has only been reported in one study. Venter et al. [25]. computed DD scores [26] using dietary data obtained from food propensity questionnaires (FPQs) [27] that were completed by mothers at 2 time points during pregnancy. Total DD scores were computed using all 41 questions included in the FPQ. The healthy DD scores included FPQ items identified as healthy according to the US dietary guidelines [28]. The unhealthy DD scores included FPQ items identified as unhealthy per the US dietary guidelines [28]. The adjusted models showed that increases in maternal healthy DD scores were significantly associated with lower odds of children diagnosed with "any allergy excluding wheeze," atopic dermatitis, asthma, and wheeze up to age 4. The adjusted models showed that increases in maternal unhealthy DD scores were significantly associated with higher odds of children diagnosed with atopic dermatitis by age 4. The adjusted models showed no significant associations between the maternal total DD during pregnancy and any of the offspring allergy outcomes up to age 4. There were no significant associations between any of the 5 measures of maternal diet and child food allergy by age 4 due to lack of power. No study has investigated the association between DD during BF and offspring allergy outcomes.

2.3. Diet indices

Four diet indices have been studied to investigate the association between maternal diet during pregnancy and offspring allergy outcomes: the healthy eating index (HEI) [29-31], the diet inflammatory index (DII) [31, 32], the Mediterranean diet index (MDI) [29, 33-36] and the maternal diet index (MDI) [37]. One study found no association between the HEI and childhood atopy and reported allergy outcomes (including food allergy) at 3 and 10 years [30]. Studies using the DII [31, 32] and the MDI [29, 33-35] in pregnancy did not report on associations with offspring food allergies. Venter et al. [37]. recently developed and replicated a diet index showing that increased maternal intake of vegetables and yogurt, and reduced intake of fried potatoes, red meat, rice and grains, pure fruit juice, and cold cereals were significantly associated with a reduced risk of allergic rhinitis, atopic dermatitis, asthma, and wheeze in offspring up to 4 years of age. A 16% reduction in food allergy was seen but this was not significant. The role of different diet indices during lactation and in allergy prevention in infants has also not been studied. Therefore, no recommendations can be made about the role of dietary patterns or indices in pregnancy and lactation and offspring food allergy outcomes.

2.4. Food types and nutrients

2.4.1. Foods RCTs using single foods during lactation have not been performed. One observational study showed that citrus and kiwi fruit consumption during lactation may be associated with a reduced risk of cow's milk allergy in infants [38]. A European Academy of Allergy and Clinical Immunology (EAACI) systematic review noted there was no evidence to suggest that intake of any particular food during pregnancy or lactation reduces food allergy outcomes [26].

2.4.2. Nutrients The EAACI systematic review found weak evidence from observational studies that increased intake of copper and vitamin C during pregnancy may reduce offspring food allergy outcomes [39].

A systematic review and meta-analysis based on 2 RCTs from EAACI [39] indicated that omega-3 fatty acid intake during pregnancy was not associated with reduced offspring food allergy outcomes. Vadhaninia et al. [40]. reported in their systematic review that omega-3 supplementation in pregnancy significantly reduced sensitization to egg and peanut in offspring. There are no RCTs using omega-3 supplementation in lactation only. One RCT administered omega-3 fatty acids during pregnancy and BF in high-risk mothers and found a decrease in food allergy [41]. In their systematic review, Garcia-Larsen et al. [14] reported reduced sensitization to peanut and egg in the infant and/or child if omega-3 fatty acids were administered during pregnancy and/or lactation.

2.5. Vitamin D

Goldring et al. [42] reported no significant association between vitamin D supplementation in pregnancy, given either as a single, large bolus or as daily intake of vitamin D, and offspring allergy outcomes. Garcia-Larsen et al. [14] indicated in their systematic review that vitamin D supplementation in pregnancy and/or lactation and/or early life feeding was not associated with offspring food allergies [14]. There is currently no evidence to support vitamin D supplementation during pregnancy or lactation for food allergy prevention.

2.6. Prebiotics and probiotics

Several studies have investigated the association between probiotic intake during pregnancy and/or lactation and offspring allergy outcomes. None of them reported on food allergy as an outcome. In addition, there are no reported data from RCTs using prebiotics and synbiotics in pregnancy and/or lactation only and food allergy outcomes. Only 1 RCT used probiotic supplementation in high-risk women during pregnancy in addition to prebiotics and probiotics in early life and reported reduced food allergy outcomes in the supplemented group [43]. Garcia-Larsen et al. [14]. summarized studies throughout pregnancy, lactation, and early life and found a significant reduction in CM sensitization, but not offspring food allergy.

In summary, the only recommendation that can be made to pregnant and lactating women is that there is no need to exclude food allergens from their diets. There is, however, also no evidence to suggest that they must eat these foods during pregnancy if not part of their normal diet. Pregnant and lactating women should follow a healthy, nutritious diet, although evidence linking healthy eating or any other measure of overall food intake with food allergy prevention is lacking. Intake of nutrients, prebiotics, probiotics, and synbiotics during pregnancy and/or lactation and offspring allergy outcomes need further investigation.

3. Infant diet

3.1. BF and formula feeding

Breast milk is considered the optimal source of nutrition for infants. Although breast milk is known for its beneficial effects on the infant's gut microbiome and immune system, it's role in food allergy prevention remains unproven (**Table 1**).

EAACI [3, 14, 44] and the UK Food Standards Agency concluded from their systematic reviews that BF may not reduce the risk of food allergy. This conclusion is further supported by

recommendations from the American Academy of Pediatrics [16] and the American Academy of Asthma, Allergy and Immunology/ American College of Allergy and Asthma and Immunology/ Canadian Society of Allergy and Clinical Immunology (AAAAI/ ACAAI/CSACI) 2020 [15] consensus statements indicating that the role of BF in food allergy prevention is uncertain. BF should, however, always be supported due to its benefits for the mother and infant [45].

Current, international food allergy guidelines do not support the use of any infant formula for food allergy prevention (**Table 1**). This is a change from previous guidelines that recommended the use of partially and/or extensively hydrolyzed formulas in food allergy prevention. This particularly contradicts the US Food and Drug Administration decision that a partially hydrolyzed formula could reduce the risk of eczema and conclusions from a previous Cochrane review, which reported that hydrolyzed formulas could prevent the development of CM allergies [46].

In summary, BF should be supported when mothers choose to breastfeed. For those mothers who choose not to breast feed, a standard cow's milk formula (CMF) should be recommended due to the lack of alternative recommendations.

4. Early allergen introduction and prevention of food allergy

To date, many allergen-specific RCTs have investigated the effects between early introduction of major allergens and the prevention of the respective food allergy. These RCTs have been performed in both standard-risk and high-risk infants (**Table 2**).

4.1. Peanut

Two RCTs have investigated the timing of peanut introduction and the risk of developing peanut allergy. The intention to treat (ITT) analysis of the Learning Early About Peanut Allergy study demonstrated a statistically significant risk reduction (17% absolute risk reduction [ARR]) associated with early peanut introduction in 4- to 11-month-old high-risk infants (having severe eczema and/or egg allergy) [47]. The per protocol (PP) analysis (not the ITT analysis) of the EAT study [55] noted small, significant ARR differences for introduction of peanut at 3 months compared with introduction after 6 months (ARR, 2.5%) in infants not considered by investigators to be at high risk for the development of food allergy. A meta-analysis inclusive of 1,550 infants from these 2 studies performed by Ierodiakonou et al. noted "moderate certainty" of evidence that introducing peanut between 4 and 11 months reduced the risk of developing peanut allergy (relative risk [RR] 0.29; 95% confidence interval [CI], 0.11–0.74) [57].

4.2. Egg

Five RCTs have investigated the timing of egg introduction and risk of egg allergy. Two studies targeted high-risk infants with eczema: the Solids Timing for Allergy Reduction (STAR) trial [48], which found a trend toward reduced risk of developing egg allergy at 1 year (RR, 0.65, P = 0.11) associated with introduction of raw, pasteurized, powdered egg protein at 4 vs 8 months of life; and the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study [49], which noted a strong protective effect in the early introduction group (RR, 0.22; 95% CI, 0.08–0.61; P = 0.0012; numbers needed to treat [NNT], 3.4) who consumed 50 mg/day heated egg powder from 6 to 9 months of life, and then 250 mg/day from 9 to 12 months (vs placebo). In 2 studies that defined infants at higher risk because of having an atopic relative, the Starting Time for Egg Protection (STEP) study [50] noted a nonsignificant 3.3% ARR in the development of egg allergy at age 1 in infants who received raw, pasteurized egg protein at 4 to 6 vs 10 months, and in Beating Egg Allergy Trial (BEAT) study [51], there was no significant difference in egg allergy at age 1 in infants who were randomized to raw, pasteurized egg introduction at 4 to 6 vs 8 months, but there was a 9.7% ARR in egg sensitization associated with earlier introduction. In the standard-risk infant study, Hen's Egg Allergy Prevention (HEAP) [52], there was no significant difference in rates of egg sensitization or oral food challenge (OFC)-proven egg allergy at age 1 in infants introduced to raw, pasteurized egg vs placebo at 4 to 6 months (RR, 3.3; P = 0.35). Lastly, the PP analysis of the EAT study noted small, significant ARR differences for introduction of egg at 3 months compared with introduction after 6 months (ARR 4.1%) in infants not at risk for the development of food allergy [55].Based on a meta-analysis of 5 RCTs (STAR, STEP, BEAT, HEAP, and PETIT), inclusive of 1,915 children, Ierodiakonou et al. also determined there was a "moderate certainty" of evidence that introducing egg between 4 and 6 months reduced the risk of developing egg allergy (RR, 0.56; 95% CI, 0.36–0.87). In terms of safety, collectively, the studies showed that early introduction of well-cooked egg is safer and more effective than raw, pasteurized egg for prevention of egg allergy.

4.3. Milk

Two RCTs have examined the timing of CM introduction and the risk of CM allergy development. The Atopy Induced by Breastfeeding or Cow's Milk Formula (ABC) trial [53] was performed in infants at intermediate risk due to a first-degree relative with atopy who were randomized to BF with or without an amino-acid-based elemental formula (EF) for at least the first 3 days of life (BF/EF group) or supplemented with CMF from the first day of life (BF/CMF group). Although the study noted higher rates of CM sensitization and CM allergy in the BF/CMF group, it is difficult to interpret the study findings because the duration of CMF intake before discontinuation differed widely among infants, and some did not stop. In the normal-risk Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy (SPADE) study [54], infants randomized to CM at 1 to 2 months of age were found to have a significantly lower rate of CM allergy compared with those randomized to avoidance of CM (use of soy formula). Although the above 2 RCTs differ in their results, it should be noted that in the normal-risk EAT [55] and prevent atopic dermatitis and allergies (PreventADALL) [56] studies, there was no significant finding with respect to the timing of CM introduction in the EAT study [55], but the PreventADALL study [56] did show an overall reduced prevalence of food allergy in the food intervention group.

4.4. Other major food allergens

There are less data regarding early introduction of other potentially allergenic complementary foods. There have been no RCTs for the remaining other 6 major food allergens, but data from the EAT study on wheat, sesame, and codfish showed no significant association with reduced (or increased) rates of allergy

Table 2.

Summary of randomized controlled trials of early allergenic food introduction for food allergy prevention

Study	Full title	Study type	Population	Intervention	Primary outcome	Results
LEAP (UK) [47]	Learning Early About Peanut Allergy	Nonblinded RCT ($n = 640$)	High-risk infants • moderate-to-severe eczema and/or egg allergy	•Thrice weekly consumption of 2 g of peanut protein vs complete avoidance of peanut after randomization at 4–11 months, through 60 months of life	IgE-mediated peanut allergy based on OFC at month 60	• ITT analysis showed prevalence of peanut allergy 13.7% in the avoidance group vs 1.9% in the consumption group ($P < 0.001$)
STAR (Australia) [48]	Solid Timing for Allergy Reduction	Blinded RPCT ($n = 86$)	High-risk infants with moderate-to-severe eczema	• Daily consumption of egg vs placebo powder from 4 to 8 months • 0.9 g raw whole egg powder daily (0.4 g protein/day) • Cooked egg at 8 months	IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC	• Study terminated early: 1/3 of patients reacted to egg at entry OFC • At 12 months, 33% had egg allergy in the egg group vs 51% in control (not significant)
PETIT (Japan) [49]	Preventing Egg Allergy in Infants with AD	Blinded RCT ($n = 121$)	High-risk infants with atopic dermatitis	• Daily consumption of 50 mg heated egg from 6 to 9 months • Daily consumption of 250 mg heated egg from 9 to 12 months	IgE-mediated egg allergy at 12 months of age based on OFC	• Prevalence of egg allergy 37.7% in placebo vs 8.3% in the egg group ($P = 0.0013$) • No SAEs
STEP (Australia) [50]	Starting Time for Egg Protein	Blinded RPCT ($n = 820$)	Intermediate risk: • atopic moms (allergic disease + positive envir SPT) • Infants: no allergic dz	• Daily consumption of egg vs placebo powder from 4 to 6.5 months • 0.9 g raw whole egg powder daily (0.4 g protein/day)	IgE-mediated egg allergy at 12 months based on positive SPT and egg OFC	• No significant differences in egg allergy between groups • No anaphylactic reactions at initial egg introduction
BEAT (Australia) [51]	Beating Egg Allergy Trial	Blinded RPCT ($n = 319$)	Intermediate risk: • Infants with first-degree relative with atopy • Infants: negative egg SPT	• Daily consumption of egg vs placebo powder at 4 months • 350 mg protein daily raw whole egg powder • Cooked egg at 8 months	Sensitization to egg by SPT at 12 months of age	• Subjects in egg group vs placebo had significantly less egg sensitization (10.7% vs 20.5%, $P = 0.03$) • No harm with egg introduction
HEAP (Germany) [52]	Hen's Egg Allergy Prevention	Blinded RPCT ($n = 406$)	Normal-risk general population: • Infants with IgE < 0.35 kU/L at enrollment	• Thrice weekly 2.5 g egg protein from 4 to 6 months of age until 12 months	Sensitization to egg based on egg IgE ≥ 0.35 kU/L at 12 months of age	• No evidence of preventing egg sensitization or allergy • High rate of anaphylaxis at egg introduction at entry
ABC Trial (Japan) [53]	Atopy Induced by Breastfeeding or Cow's Milk Formula	Nonblinded RCT ($n = 312$)	Intermediate risk: • Infants with first-degree relative with atopy	• Randomized to 2 interventions: • (1) active: BF and/or CMF in first 3 days of life; (2) placebo: BF and/or amino-acid (EF)-based formula in first 3 days	Primary: Sensitization to CM Secondary: IgE-mediated milk allergy at 24 months based on OFC	• Primary outcome: 24 infants (16.8%) sensitized in the BF/EF group vs 46 infants (32.2%) in the BF plus CMF group (relative risk [RR], 0.52; 95% CI, 0.34–0.81). • Secondary outcome: IgE-mediated CM allergy in the BF/EF vs BF plus CMF groups (4 [2.6%] vs 20 [13.2%]; RR, 0.20; 95% CI, 0.07–0.57)
SPADE (Japan) [54]	Strategy for Prevention of Milk Allergy by Daily Ingestion of Infant Formula in Early Infancy	Nonblinded RCT ($n = 518$)	Normal-risk general population	• Randomized between 1 and 2 months of age to daily consumption of at least 10 mL of a CMF or avoidance of CM (soy formula) • Ongoing BF recommended until 6 months of age	IgE-mediated milk allergy at 6 months of age based on OFC	• ITT analysis showed 2 of 242 ingestion-group infants (0.8%) vs 17 of 249 avoidance group (6.8%) had milk allergy ($P < 0.001$) • Screening OFC at age 1 month to 20 mL of CMF; no SAEs
EAT (UK) [55]	Enquiring About Tolerance	Nonblinded RCT ($n = 1,303$)	Normal risk: Exclusively breastfed until allergenic foods introduced	• EIG introduced 2 g of protein twice weekly at 3 months of peanut, cooked egg, CM, sesame, whitefish, wheat • SIG at 6 months of above 6 foods	IgE-mediated food allergy to at least 1 of the 6 allergens at 1 or 3 years of age based on OFC	• ITT analysis showed no difference in food allergy between EIG vs SIG • PP analysis showed significantly less prevalence of peanut allergy ($P = 0.003$) and egg allergy ($P = 0.009$) in EIG vs SIG
PreventADALL (Norway, Sweden) [56]	Preventing Atopic Dermatitis and ALLergies	Nonblinded RCT ($n = 2,397$)	Normal-risk general population	• Randomized to 4 intervention groups: (1) no intervention; (2) skin; (3) food; (4) combined skin and food • Food: introduction of peanut, CM, egg, and wheat from 3 months of age vs no specific advice on food introduction	IgE-mediated peanut, CM, egg, or wheat allergy at 36 months of age based on OFC	• ITT analysis showed prevalence of food allergy reduced in food intervention group compared to no food intervention group: risk difference –1.6% (95% CI, –2.7 to –0.5); OR, 0.4 (95% CI, 0.2–0.8) • Reduced risk of food allergy seen with peanut but not with other 3 foods

BF, breastfeeding; CM, cow's milk; CMF, cow's milk formula; dz, disease; EF, elemental formula; EIG, early introduction group; envir, environment; IgE, immunoglobulin E; ITT, intention to treat; OFC, oral food challenge; PP, per protocol; RCT, randomized controlled trial; RPCT, randomized placebo controlled trial; SAEs, serious adverse events; SIG, standard introduction group; SPT, skin prick test.

development to these items (respectively) based on the early vs. standard time of introduction, and may serve as the highest quality evidence to evaluate the effect of potential early introduction that is available for these allergens [55]. Data are even more sparse for other major food allergens: no RCTs have investigated challenge-proven prevention outcomes associated with the timing of introduction of soy, tree nuts, or shellfish [57].

In summary, current data from RCTs strongly support the early introduction of peanut and egg in infant diets for the prevention of these food allergies. Although some RCT data on early CM introduction are conflicting, early and ongoing exposure to CMF supplementation may prevent CM allergy. While there are limited or no RCT data for other highly allergenic foods, there are no data showing harm in introducing these allergenic foods within the first year of life, and thus early introduction may be beneficial as well.

5. Infant DD

DD is defined as the number of foods or food groups consumed over a given reference period [58]. Diet variety is synonymous with DD [58]. DD can be defined as the number of foods [59-65], food groups [59, 66-80], foods within a food group [81-85] eaten, and data can be collected over a time period ranging from a day to 1 year [26]. An EAACI [26] task force report concluded that higher DD in infancy may reduce the odds of developing food allergy in later childhood. This article set standards for measuring DD, suggesting that the food items consumed, the time period, and the frequency of consumption should be reported.

5.1. Infant DD and food allergen sensitization

Three studies reported on the association between infant DD and food allergen sensitization (**Table 3**). All 3 studies reported that increased DD in infancy was associated with reduced sensitization in childhood [86, 87, 90].

5.2. Infant DD and food allergy

Four observational studies in infancy studied the association between infant DD and childhood food allergy. Roduit et al. [86] reported that infants with a more diverse diet had a lower prevalence of reported doctor's diagnosed food allergy by 6 years. In this study [91], there was no association between DD in the second year of life and food allergy at 6 years. Consumption of yogurt and CM were, however, inversely associated with food allergy development. Venter et al. [85]. reported that increased DD at 6 and 9 months was significantly associated with reduced food allergy over the first 10 years of life. For each additional food consumed by 6 months, the odds of developing food allergy by 10 years were reduced by 11%. Based on the World Health Organization (WHO) definition of DD and fruits and vegetables diversity by 6 months, a significant reduction in the odds of developing food allergy by 10 years was seen. Food allergen diversity by 12 months was significantly associated with reduced odds of food allergy by 10 years. For each further food allergen introduced, the odds of food allergy were reduced by 33%.

Comparing intake of 1 to 5 food groups vs 8 to 11 food groups, Zhong et al. [88]. reported that reduction in food diversity at 12 months of age was significantly associated with an increased risk of parent-reported food allergy by 2 years of age.

Table 3.

Common definitions of diet diversity used

Study	Definition
Protection Against Allergy Study in Rural Environments (PASTURE) [86]	1. Diet diversity: the 15 foods commonly eaten by 80% of the children in the study in the first year of life, which also included all food allergens: any cow's milk, yogurt, other milk products; eggs; nuts; vegetables or fruits; cereals; bread; meat; fish; soy; margarine or butter; cake; and chocolate
Multicenter EU study	2. A second definition: included the 6 major foods introduced in the first 6 months or first 12 months of life, which did not include all food allergens: vegetables or fruits; cereals; bread; meat; cake; and yogurt
Finnish study [87]	The number of foods introduced at 3, 4, and 6 months of age
Food Allergy Research and Intolerance study (FAIR) [85]	1. Count of 21 common foods eaten in infancy: overall diet diversity
UK	2. WHO definition of diet diversity (7 food groups: grains/roots/tubers, legumes/nuts, dairy, flesh foods, eggs, vitamin A-rich fruits and vegetables, other fruits and vegetables)
	3. Number of fruits and vegetables consumed: fruit and vegetable diversity
	4. Count of 8 common food allergens: milk, egg, wheat, fish, soy, peanut, tree nuts, sesame
China [88]	The number of food groups consumed (0–11 food groups)
Korea [89]	1. Food group diversity
	2. Food allergen diversity
	3. WHO definition of diet diversity

WHO, World Health Organization.

A research group from Korea [89] reported higher DD based on food group consumption, number of food allergens consumed, and the WHO definition of diversity at 3 and 4 months were associated with a lower prevalence of hen's egg allergy in the high-risk group. No associations were seen in the control group. Diversity scores at 6 months of age were not associated with food allergy outcomes.

5.3. Food allergen diversity based on RCTs

Quake et al. [92] performed an RCT, feeding 180 infants between 4 and 6 months of age single foods (milk, egg, or peanut as 300 mg protein/day: 2,100 mg protein/food allergen/week) vs 2 foods (milk/egg, egg/peanut, milk/peanut as 300 mg/mix/day: 1,050 mg protein/food allergen/week) vs a multiple food mix of 10 food allergens (milk/egg/peanut/cashew/almond/shrimp/walnut/wheat/salmon/hazelnut at low [300 mg/day: 21 [3 mg × 7] mg/food allergen/week], medium [63 [9 mg × 7] mg/food allergen/week], or high doses [210 [30 mg × 7] mg/food allergen/week]) vs no early introduction. All infants were breastfed until at least 6 months of age and assessed for food allergy at 2 to 4 years after the end of the study. The study outcomes indicated that the percent of participants able to consume 8 g of total protein from the 10-allergen mixture (800 mg allergen/food) was significantly higher in all mixed protein groups compared with controls ($q < 0.01$). The EAT study could also be considered a study using food allergen diversity, but data comparing food allergen diversity in the control vs active group were not reported [55]. A recent study indicates that early and regular consumption of food allergens on a population level shows a reduction in food allergies similar to RCTs. See **Table 4** for a DD and allergen diversity meal plan. This meal plan contains 7 food allergens and over 30 plant-based foods per week.

In summary, once infants are ready to eat, a diverse diet based on cultural food habits, which includes both plant-based

Table 4.

Diet diversity meal plan

	Infant: 7–9 months plus						
	Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Allergens	Peanut butter and yogurt	Cashew butter and walnut butter	Egg and sesame	Peanut butter Soy	Egg and walnut butter	Yogurt Soy	Cashew butter and sesame
Breakfast	2 TB white rice 1 TB homemade apple purée/ mash/baked apple slices with 1 teaspoon peanut butter	2 TB boiled brown rice with 1–2 teaspoons cashew butter 1 TB pitted cherry purée	2 TB oat baby cereal 1 TB pineapple purée	2 TB multigrain baby cereal with 1 teaspoon peanut butter 1 TB apricot purée	2 TB brown rice baby cereal 1 TB mango purée	2 TB quinoa baby cereal 1 TB prune purée	2 TB brown rice baby cereal teaspoon cashew butter 1 TB peach purée
Lunch	2 TB roasted sweet potato purée/ mashed/softly cooked slices 1 TB banana purée/strips 1 TB puréed meat/softly cooked meat	1 TB spinach purée/ mashed 1 TB puréed/boiled/ shredded chicken	1 TB Napa cabbage 1–2 TB tomato egg	2 TB purée/ softly cooked cauliflower mashed/chunky salmon	2 TB watercress purée 1–2 TB water-steamed egg	1 TB soybean sprouts 1 TB carrots 2.5 teaspoon yogurt	1 TB broccoli purée/softly cooked broccoli 1 TB pork purée/ pulled pork
Dinner	1 TB mung bean sprout purée 1 TB mango purée/slices 1–2 TB yogurt	1 TB kabocha squash ¾ to 1½ teaspoons walnut butter	1 TB mashed zucchini/ softly cooked slices ½ to 1 teaspoon sesame in sesame noodles	1 TB soybean sprouts 1 TB raspberry puréed/mashed/ soft fruit	1 TB mashed or sliced pear ¾ to 1½ teaspoons walnut butter	Softly cooked noodles (rice or wheat) 1 TB cooked puréed/ mashed or chunky tomato sauce	1 TB green peas ½ to 1 teaspoon sesame paste stir into vegetable purée

TB, tablespoon.

foods and food allergens, should be recommended. Once food allergens are introduced, frequent intake is recommended.

6. The bigger picture of prevention

6.1. Microbiome

The gut microbiome is found to be associated with food allergy outcomes in several studies [93-96]. The gut microbiome composition and diversity of children who develop milk and egg allergies differ from that of non-food-allergic children [94, 95]. Gut microbiome differences have also been reported in children who develop tolerance to milk and those who remain allergic [93]. Differences in the gut microbiome profile in children sensitized to food allergens and non-sensitized children have also been reported [97]. Hua et al. [98]. showed that microbial taxa and microbiota richness differed between food-allergic and non-food-allergic adults. However, it is still unclear which particular species or genus may prevent the development of food allergies [96, 99, 100], and the immunomodulatory effect of the gut microbiome may depend on its potential to produce butyrate [101].

Short-chain fatty acids (butyrate, acetate, and propionate) may protect against the development of food allergy [101]. Butyrate, in particular, may play a role in tolerance development through downregulating interleukin (IL)-5 and IL-13 (Th2 cytokine) production [102, 103], and modulating immune regulation in the gut and peripheral tissues [104-108].

Diet, particularly DD, plays an important role in the gut microbiome composition and function [27,110] Claesson et al. [109]. showed in an elderly population that increased diet was associated with increased gut microbial diversity. Similarly, increased DD in the infant diet during the first year of life is also associated with increased microbial diversity [110].

Recently, the EAT study showed that the introduction of 6 major allergenic foods leads to a significant increase in microbial diversity, measured by the Shannon index and increase of Prevotellaceae and Proteobacteria, compared with exclusively breastfed infants [111]. A Korean research group reported data on DD in infancy, gut microbial composition and development of hen's egg allergy [89]. DD was defined according to the WHO definition of minimum DD, food group diversity, and food allergen diversity. In high-risk infants, increased DD was associated with increased microbial diversity and reduced expression of IL-13. Lower DD was associated with increased expression of IL-4, IL-5, IL-6, and IL-8. Roduit et al. [101]. reported that a diverse diet rich in fruit, vegetables, fish, and yogurt in infancy was associated with increased butyrate production. A diet rich in dietary fibers [112] such as arabinoxylan [113], can also affect microbiome function, and is associated with increased butyrate production. A recent EAACI systematic review concluded that there is significant potential for using fiber intake to manipulate the gut microbiome composition and metabolic functions, thereby promoting immune health [114].

Consumption of plant-based foods and its role in gut microbiome composition have been highlighted by the American Gut Project [115]. This study showed that in adults, consumption of 30 plant-based foods per week leads to optimal gut microbial diversity (**Table 4**).

Targeted manipulation of the gut microbiome may support food allergy prevention and tolerance induction, but manipulation strategies are currently unclear. There has been a lack of data for the use of overall diet, nutrients, prebiotics, synbiotics, and probiotics during pregnancy, lactation, and early infancy for food allergy prevention. Further research is much needed.

6.2. Ultraprocessed foods and advanced glycation end products

The modern Western pattern diet is associated with increased consumption of ultraprocessed foods. This pattern of eating is linked to increasing rates of food allergy. Ultraprocessed diet is inadequate in terms of nutritional value; it is low in fiber and high in salt and sugars, particularly fructose [116]. Diets high in sugar combined with food processing such as dehydration, microwaving and frying lead to the formation of advanced

glycation end products (AGEs) that are epidemiologically and immunologically linked to trends in food allergy [117]. AGEs bind to receptors that are part of the innate threat reception network called the receptor for advanced glycation end products (RAGE). RAGE agonists include alarmins such as amyloid and danger-associated molecular patterns, including high-mobility molecular group box 1 and S100 proteins [118]. The foods being consumed in the Western dietary pattern, which is largely taken up globally, contain the ingredients to form compounds that signal tissue injury. High-fructose corn syrup is an ever-increasing component as sweeteners and as a component of animal feed and in soft drinks. The Western pattern diet contains approximately 2,000% more fructose than a traditional diet [119]. Fructose has a greater capacity than glucose to form AGEs.

RAGE ligands have the capacity to injure the gut epithelium [120], which may facilitate aberrant antigen presentation and food allergy. HMBG1–RAGE interactions are important in antigen uptake and presentation, T-cell, IgE responses [121]and Th2 polarization [122]. HMBG1 has been demonstrated to increase mast cell accumulation, and AGEs are capable of activating mast cells and promoting the release of proallergic mediators [123].

Epidemiological correlates of food allergy and high-sugar consumption in pregnancy are related to higher rates of inhalant and food allergies in offspring [18]. Urban eating patterns involve increased consumption of sugar and processed foods, and there is a corresponding higher rate of food allergies [124]. Although this observational data does not prove causation, it is worthy of consideration when assessing food allergy prevention and management.

Another possible axis for considerations of the effect of dietary AGEs is the microbiome, and high AGE consumption is shown to result in deleterious effects to the microbiome [125].

The Western pattern diet is estimated to result in consumption of 7 to 8 kg of synthetic chemical additives, including preservatives, acidity regulators, colorants, and emulsifiers [126],which have been proposed to contribute to food allergy via modification of the gut microbiome [127].

6.3. Micronutrients: vitamin D and omega-3 fatty acids

Low vitamin D levels are linked to increased risk of food allergy and anaphylaxis, evident from epidemiological data that indicate living in regions farther away from the equator can increase the risk of peanut allergy by up to 6-fold [128]. Birth in winter and spring (associated with lower levels of vitamin D in mother and offspring) is associated with increased risk of food allergy [129].

Long-chain omega-3 fatty acids (LCn3s) are mainly sourced either directly or via supplements from fish oils and include eicosapentaenoic acid and docosahexaenoic acid. Another source of LCn3s is from plants such as walnut, chia seeds, Brussels sprouts, and algae in the form of alpha-linolenic acid. Fatty acids are a source material for eicosanoids such as prostaglandins and leukotrienes, and LCn3s are reported to result in the production of less inflammatory products than omega-3 fatty acids (LCn6s), which appear as a frequently consumed fat in the Western diet. Antenatal consumption of fish oil during pregnancy and lactation is linked to lower levels of prostaglandin E2, and this has been suggested to alter the Th2 balance and risk for atopy in infants [130].

Another mechanism of response is due to dietary lipids and their interaction on gut microbiota [131]. Bacterial endotoxins cause systemic inflammation via endotoxemia (which is highest after meals), and this can be modified by dietary lipids [132, 133]. High-fat diet influences microbial composition, endotoxemia, and impairment of barrier function [134-136], and this can be modified by omega-3 polyunsaturated fatty acids (PUFAs) [133]. Inflammatory responses are reduced via LCn3s becoming incorporated into membrane signaling platforms called lipid rafts, which influences intracellular and intercellular signaling of immune cells [137-139]. G-protein coupled receptors can bind fatty acids such as GPR120, which influences nuclear factor B signaling and downstream genes [140].

Data on consumption of LCn3s in the antenatal period and early infancy have been reproduced in many studies worldwide for prevention of inhalant allergies, as summarized in recent reviews [141, 142]. The data on food allergy are not as reproducible or as strong. A murine study has shown that a diet comprising 13% salmon oil could partially prevent hen's egg allergy [143]. Another murine study with tuna oil showed a reduction in experimental CM and peanut allergy associated with in an increase in T regulatory cells with a reduction of both Th1 and Th2 activation [144, 145]. Several human studies have reported supplementation of LCn3s in pregnancy and in infancy can be associated with a reduction in atopic disease and food sensitization, particularly to hens egg [41, 146-149]. A meta-analysis [148] of 3 studies [41, 146, 149] examining hen's egg sensitization reported an effect with the RR of hen's egg sensitization in infancy (RR, 0.54; 95% CI, 0.39–0.75; $P < 0.0003$ and sensitization to any food RR 0.58; 0.45–0.75; <0.0001. This contrasts with other studies that did not find any effect of LCn3 supplementation [150, 151]. It is worth noting that 2 of these studies, which showed benefits came from Australia, where an early life rate of raw egg white sensitization was reported to be 16.5% (95% CI, 15.1–17.9) and challenge-proven raw egg allergy to be 8.9% (95% CI, 7.8–10.0), such that disease incidence may influence the results of an intervention [152]. There is variability across studies in the amount of LCn3 consumed and when considering lipids and their possible benefits, as well as consideration of omega 6 fatty acid intake [26]. Mothers cannot expect to supplement themselves and their offspring from a poor diet. Another possible benefit of LCn3s is that they are estimated to contain 70.6 IU vitamin D_3/mL [153], which is found, as outlined in this review, to have a strong association with reduced risk of food allergy, particularly in lipid form. It has been recommended that infants and children who have fish allergy can consume LCn3s in plant forms [154].

7. Summary and conclusion

Food allergy guidelines have changed over the past 2 decades. As clear risk factors for the development of food allergy are lacking, food allergy prevention guidelines are relevant to all families in that all families may be at some inherent risk today. Pregnant and BF women are not recommended to avoid food allergens. BF is not associated with reduced prevalence of food allergies, but it is recommended for all mother–infant dyads due to a range of other health outcomes. Peanut and cooked egg should be introduced as soon as solid food introduction commences, but there is no need to delay the introduction of other allergenic foods, and infants should be fed family foods. Once an allergen is introduced, frequent and continued intake is required to maintain tolerance. Mechanistic studies link maternal and infant diet with the microbiome, epigenetic, and immunological indices, but studies are required to establish clear pathways of interaction.

Conflicts of interest

Dr. Fleischer's institution has received research support from Aimmune Therapeutics and DBV Technologies; serves as a nonpaid member of the Medical Advisory Board for Food Allergy and Anaphylaxis Connection Team and the Medical Advisory Council National Peanut Board; receives royalties from UpToDate; and serves as a consultant for Aquestive, DBV Technologies, Genentech, and Nasus, all of which are outside of this submitted work. Dr. Smith reports personal fees from the Nestle Nutrition Institute and speaker fee from Danone and Bayer outside of the submitted work. Dr. Venter reports grants from Reckitt Benckiser Food Allergy Research and Education, National Peanut Board; personal fees from Reckitt Benckiser, Nestle Nutrition Institute, Danone, Abbott Nutrition, Else Nutrition, Before Brands and Owen outside the submitted work.

Author contributions

Each author drafted different sections of the article. The article was then circulated, and the authors approved the final version of the article.

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