Consensus Document

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

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The statement below is not to be construed as dictating an exclusive course of action nor is it intended to replace the medical judgment of healthcare professionals. The unique circumstances of individual patients and environments are to be taken into account in any diagnosis and treatment plan. The statement reflects clinical and scientific advances as of the date of publication and is subject to change.

For reference only.

Recently published data from high-impact randomized controlled trials indicate the strong potential of strategies to prevent the development of food allergy in high-risk individuals, but guidance in the United States at present is limited to a policy for only the prevention of peanut allergy, despite other data being available and several other countries advocating early egg and peanut introduction. Eczema is considered the highest risk factor for developing IgE-mediated food allergy, but children

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Abbreviations used

AAAAI- American Academy of Allergy, Asthma, and Immunology
AAP- American Academy of Pediatrics
ACAAI- American College of Allergy, Asthma, and Immunology
ARR- Absolute risk reduction
CM- Cow's milk
CMA- Cow's milk allergy
CSACI- Canadian Society of Allergy and Clinical Immunology
EAACI- European Academy of Allergy and Clinical Immunology
EAT- Enquiring About Tolerance
eHF- Extensively hydrolyzed formula
GINI- German Infant Nutritional Intervention study
HEAP- Hen's Egg Allergy Prevention
HF- Hydrolyzed formula
LEAP- Learning Early About Peanut Allergy
NIAID- National Institutes of Allergy and Infectious Diseases
NIAID-AG- NIAID Addendum Guidelines for the Prevention of Peanut Allergy
OFC- Oral food challenge
PETIT- Prevention of Egg Allergy with Tiny Amount Intake
pHF- Partially hydrolyzed formula
QALY- Quality-adjusted life-year
RCT- Randomized controlled trial
sIgE- Specific IgE
RR- Relative risk
STAR- Solids Timing for Allergy Reduction
SPT- Skin prick test

without risk factors still develop food allergy. To prevent peanut and/or egg allergy, both peanut and egg should be introduced around 6 months of life, but not before 4 months. Screening before introduction is not required, but may be preferred by some families. Other allergens should be introduced around this time as well. Upon introducing complementary foods, infants should be fed a diverse diet, because this may help foster prevention of food allergy. There is no protective benefit from the use of hydrolyzed formula in the first year of life against food allergy or food sensitization. Maternal exclusion of common allergens during pregnancy and/or lactation as a means to prevent food allergy is not recommended. Although exclusive breast-feeding is universally recommended for all mothers, there is no specific association between exclusive breast-feeding and the primary prevention of any specific food allergy. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: *Primary prevention; Food allergy; Peanut allergy; Egg allergy; Hydrolyzed formula; Risk; Cost-effectiveness; Diet diversity; Early introduction; Screening; Eczema; Breast-feeding*

INTRODUCTION

Food allergy is estimated to affect as many as 8% of children in the United States and 7% in Canada.[1,2] This is a disease that has no known cure and has seemingly risen in prevalence. Moreover, for some, food allergy can be quite severe, even potentially life-threatening.[3] Recently published data from high-impact randomized controlled trials (RCTs) indicate the strong potential of strategies to prevent the development of food allergy in high-risk individuals,[4-11] but guidance in the United States at present is limited to a policy for only the prevention of peanut allergy, despite other data being available.[12] Therefore, there is an opportunity to expand upon current recommendations, which are limited to peanut allergy prevention (in the 2017 National Institutes of Allergy and Infectious Diseases [NIAID] Addendum Guidelines for the Prevention of Peanut Allergy [NIAID-AG]), as well as those previously established in 2013 by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the Canadian Society of Allergy and Clinical Immunology (CSACI) regarding the prevention of food allergy.[12-14] Although recommendations for early peanut introduction as a preventative measure against peanut allergy exist, there are gaps in our understanding of how best to implement such early introduction and a need for additional knowledge translation for how such policy can be optimally incorporated into primary care and medical subspecialties.[11,12]

This document will address a number of other emerging issues related to food allergy prevention. This process will examine how to optimally define the "at-risk" or "high-risk" child (which we will use synonymously in this document). This is of concern given conflicting and recently changed definitions used in pivotal trials that now exist, and can help elucidate if being at risk for peanut allergy is distinct from being at risk for other food allergies. As well, this will help to provide an understanding of

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what the long-term risk of peanut allergy may infer for other atopic outcomes, including other food allergy. We will also clarify the necessity and value of screening at-risk patients before early, potentially allergenic complementary food introduction, informed by specific analyses of the health outcomes and cost-effectiveness of such assessment. Recently updated guidelines from the UK Department of Health, the British Society of Allergy and Clinical Immunology, the Australasian Society of Clinical Immunology and Allergy, as well as from the European Academy of Allergy and Clinical Immunology (EAACI) and the US Department of Agriculture recommend early introduction of selected high-risk foods without any preintroduction screening. This approach has also been adopted by Israel. Therefore, a systematic and comprehensive evaluation of such policies and implementation barriers is needed to update US and Canadian approaches.[15-20]

This document is strengthened by the inclusion of the 3 primary national allergy organizations in North America—the AAAAI, the American College of Allergy, Asthma, and Immunology (ACAAI), and the CSACI. Therefore, this represents a unique consensus on this topic for the first time by the US and Canadian professional allergy organizations, which can help to inform practical, policy-based recommendations for the primary prevention of food allergy through nutritional interventions. This clinical guidance is intended as a reference for specialists who care for and manage children with food allergies; primary care providers who care for the potentially at-risk child; dieticians; governments, and policymakers; as well as patients and patient-advocacy groups.

METHODS

The Adverse Reactions to Foods Committee of the AAAAI passed a motion at the 2017 Annual AAAAI Meeting to form a workgroup to update the 2013 statement on the primary prevention of food allergy through nutrition.[13] A workgroup chair (D.F.) and cochair (M.G.) developed a proposal for content development, which was submitted to the Practice, Diagnostics, and Therapeutics Committee of the AAAAI for approval. Several members of the working group were also committee chairs and/or members with leadership positions within the ACAAI and the CSACI, and included representation from the International Network for Diet and Nutrition in Allergy.

The content outline for the primary prevention of food allergy was reviewed and approved by the AAAAI and included the following themes with respect to the prevention of IgE-mediated food allergy: (1) the definition of the at-risk child; (2) recommendations for the timing of specific, potentially allergenic, complementary food introduction; (3) recommendations regarding the role of dietary diversity; (4) recommendations regarding the use of hydrolyzed formula; (5) recommendations regarding the role of prenatal/postnatal exposures and breast-feeding; and finally, (6) a cost-effectiveness analysis of the recommendations. From these themes, 5 key questions were postulated. Workgroup members were proposed by the project chairs and approved by the AAAAI Practice, Diagnostics, and Therapeutics Committee. The draft report underwent iterative review by the Practice, Diagnostics, and Therapeutics Committee and the worgroup, and then an interim draft underwent additional iterative review by the AAAAI Board of Directors before a final draft was approved for journal submission. The proposal was separately reviewed by the ACAAI, and the CSACI, who agreed to endorse the AAAAI workgroup report, and approved the interim and finalized report.

Literature searches and article selections used by Ierodiakonou et al,[11] the recent National Academies of Science report on the global burden of food allergy,[3] and the NIAID-AG[12] were used after a precursory review identified no new RCTs were published since the publication of these systematic reviews. We used additional, slightly older searches from the EAACI prevention guidelines to help supplement the systematic review.[21,22] Figure 1 details the literature search and manuscript selection process. Inclusion criteria comprised known meta-analyses/systematic reviews, randomized and/or controlled clinical trials, and cohort-based observational studies specifically investigating IgE-mediated food allergy or a specific IgE-mediated food allergy as an outcome, and studies that fit these designations, but investigated outcomes involving other allergic or atopic manifestations (eg, atopic dermatitis, allergic rhinitis, and asthma) that were not specific to food allergy or food sensitization were excluded.

A narrative approach to evidence synthesis was taken, given heterogeneity in the types of studies and the nature of the literature search, though 2 recent meta-analyses were included.[11,24] An approach to the guidance was used on the basis of previous procedures and evidence rating system used by the Joint Taskforce on Practice Parameters for non−Grading of Recommendations, Assessment, Development and Evaluation documents (strength of recommendation; evidence grade; strength of recommendation; with the addition of a risk of bias in the evidence statement; Table I), and a prespecified level of agreement with each recommendation and rating of 70% voting approval of the workgroup members. To further explore the recommendations, cost-effectiveness analyses were conducted using Markov modeling over a 20-year horizon, with outcomes of total costs, quality-adjusted life-years, cases of allergy prevented, reaction rates, and fatality rates, as recently described, using the Consolidated Health Economic Evaluation Reporting Guidelines.[25]

Individual sections were assigned by the project chair and written by subcommittees of 2 to 3 workgroup members, with each section reviewed for final agreement and inclusion in the main document by all workgroup members, and conflict on content or direction was resolved by consensus vote. The recommendations carefully considered the quality of existing literature surrounding these topics, the value/impact and resource utilization that the recommendations may have, and supplemented expert consensus where indicated. Inevitably, new research in forthcoming years will provide additional insight into these areas, and this document will continue to be updated as the current literature findings necessitate.

RESULTS

Question 1: What criteria define an infant at high risk for the development of food allergy?

Clinical context and background. There is no international consensus on the definition of what qualifies an infant as being at high risk of developing food allergy, and in the past 3 years the definition has evolved from that used in earlier prevention trials. Very recent criteria have emerged to define the risk for developing peanut allergy, used in the 2017 NIAID-AG, which defined an infant at high risk of developing peanut allergy on the basis of presence of severe eczema and/or egg allergy.[12] This definition was based on that used in the Learning Early About Peanut Allergy (LEAP) study, which was published

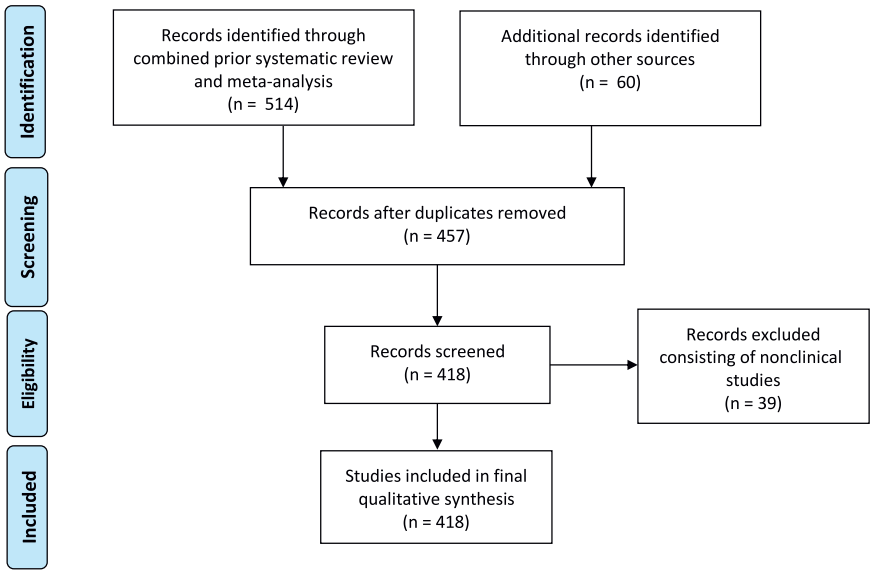

FIGURE 1. PRISMA diagram for the literature search. From Moher et al.[23]

in 2015, which also considered these 2 factors as high-risk criteria for peanut sensitization and allergy.[5] This definition was demonstrated to have potential validity when applied to the HealthNuts population-based cohort study from Australia, though nearly 25% of known peanut-allergic cases were missed when applying this definition retrospectively (Table II).[26,27]

The definition of severe eczema used in the NIAID-AG differs from the definition used in the LEAP study by emphasizing chronicity of the eczema and recalcitrance in response to escalating strengths of topical treatments.[5,12] However, variability exists in interpreting what is considered "severe," given no widely used objective measures in this definition. This may have unknown effects on the risk of and likelihood of preventing peanut allergy (Table II).[28] The definition of egg allergy also differs from that used in the LEAP study and defines this as a documented history of reactivity upon egg ingestion (Table II), and not just egg sensitization (without ingestion history) above a level that may be highly probable for egg allergy. The practical limitation using egg allergy as a risk criteria is that egg is rarely incorporated into the early North American infant diet (<2% of infants ingest egg before age 6 months) at a time when peanut may be introduced, and egg sensitization above a certain cutoff point (as used in the LEAP study; see Table III) is not specific enough to serve as a surrogate for egg allergy in the absence of a history of symptomatic egg ingestion.[42,43] Of note, the high-risk criteria for the LEAP study were not validated before their use in the trial.

Severe eczema is widely considered to be a significant risk factor for food allergy. Eczema is mediated by skin barrier dysfunction and may be associated with mutations in the filaggrin gene, which promotes dyshydrosis and loss of surface water.[44] Filaggrin mutations have been linked with both increased eczema severity and food allergy, supporting the concept of transcutaneous sensitization to food allergens, but not in individuals of all races.[29,45,46] In contrast, very little pathophysiologic linkage exists between challenge-proven egg allergy and the development of other food allergy, though there are studies that have noted an association between egg sensitization and some potential increase in the risk of developing other allergic manifestations, including food sensitization and food allergy.[40,47] An observational study (n = 512) has associated both cow's milk (CM) and egg-sensitized individuals (viewed as highly "probable" to be allergic to these foods) with an increased risk of developing peanut sensitization (and what investigators in the study considered was "probable" peanut allergy), but oral food challenges (OFCs) were not performed in all subjects to confirm these food allergies.[30] An additional study from the Isle of Wight cohort also noted an association between egg, peanut, and sesame sensitization, but it did not correlate this to an OFC-based outcome.[34] Little data exist about whether sensitization to other food allergies (such as wheat, fish, or tree nuts) place an infant at a higher risk of further food allergy development.

Although the NIAID-AG categorized infants with mild to moderate eczema as a separate, higher risk category (addendum 2) than the general population (addendum 3) for the development of peanut allergy, less severe forms of eczema were not defined, and the recommended handling of both groups of infants before peanut introduction is identical (no need for in-office assessment, in contrast to addendum 1).[12] Although the recommendation to create a separate addendum for the mild/moderate eczematous infant was largely based on expert opinion and extrapolation of a subset of data from 2 RCTs,[5,6] it may be supported with analyses from 2 large cohort studies.[26,31,48] A systematic review of 66 studies also noted a dose-dependent association between eczema, food sensitization, as well as OFC-confirmed food allergy.[41]

Previous multiple international guidelines (including the preceding 2006 ACAAI, 2013 AAAAI, and 2013 CSACI prevention guidelines) have defined an infant at high risk of developing allergic disease (including food allergy) as having 1 or more immediate family member (parent or sibling) with an allergic condition (such as eczema, food allergy, asthma, or allergic rhinitis).[13,14,49] In some studies, this definition has been condensed to a binary variable encompassing any "atopic manifestation," and has largely evolved from the definition used in the German Infant Nutritional

TABLE I. Classification and recommendations and evidence

Recommendation Rating scale		
Statement	**Definition**	**Implication**
Strong recommendation (Strong)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B). In some clearly identified circumstances, strong recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A moderate recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak (Weak)	A weak recommendation means that either the quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role.
Category of evidence	Ia Evidence from meta-analysis of RCTs Ib Evidence from at least 1 RCT IIa Evidence from at least 1 controlled study without randomization IIb Evidence from at least 1 other type of quasiexperimental study III Evidence from nonexperimental descriptive studies, such as comparative studies IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both	
Strength of recommendation	A Directly based on category I evidence B Directly based on category II evidence or extrapolated recommendation from category I evidence C Directly based on category III evidence or extrapolated recommendation from category I or II evidence D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence LB Laboratory based NR Not rated	

Intervention (GINI) study.[50-52] A major problem with this definition of high risk is that it is very widely inclusive, so that an infant may be considered at high risk if 1 or both parents or a sibling has an allergic disease such as allergic rhinitis, whereas another infant may be considered high risk if multiple siblings have severe asthma and/or multiple food allergies. Although the 2 infants used in this example are not at equivalent risk per se, the overinclusive definition helps ensure that the findings of studies can be applied to significant portions of the general population, and it also may combine higher and lower risk infants in whom the effect of these interventions may differ. This definition was used nearly universally as a high-risk criterion for recruitment in most food allergy prevention studies before the LEAP study.[50,53] However, the LEAP study intended to specifically target peanut allergy only, and not a general allergic disease risk, which may account for the differing criteria. Genetic susceptibility to food allergy has been supported to some degree by both genome-wide association studies[32,33] and population studies.[54,55] However, not all data have supported family history as significantly increasing the risk of allergic disease,[34] and parental report of allergy, which is often used for study inclusion, can be inaccurate.[56]

Of particular interest within the family history is the risk a younger sibling of a peanut-allergic child may also have of developing peanut allergy. Previous literature has been uncertain as to the degree of risk or increased prevalence (if any) in the younger sibling of a peanut-allergic individual, and guidance has been unclear whether these children benefit from routine preemptive testing.[57,58] The former recommendation was based on 3 observational studies that noted an increased prevalence of peanut allergy reported in these siblings, though the methods of assessing allergy in these studies are at high risk of bias, and for which confounding from delayed introduction was not

TABLE II. NIAID and LEAP definitions of severe eczema and egg allergy

Disease	LEAP study[5]	NIAID guideline[12]
Severe eczema	"A rash that required the application of a topical creams and ointments containing corticosteroids or calcineurin inhibitors and if the participant is: • <6 months of age, lasted for at least 12 out of 30 days on two occasions; or • >6 months of age, lasted for at least 12 out of 30 days on two occasions in the last 6 months; or • Has been described by the participant's parent or guardian in a pre-enrollment questionnaire as 'a very bad rash in joints and creases' or 'a very bad itchy, dry, oozing, or crusted rash'; or • Is currently or was previously graded ≥ 40 using the modified SCORAD evaluation."	"Persistent or frequently recurring eczema with typical morphology and distribution assessed as severe by a health care provider and requiring frequent need for prescription-strength topical corticosteroids, calcineurin inhibitors, or other anti-inflammatory agents despite appropriate use of emollients."
Egg allergy	"Children with either: 1. A SPT wheal diameter >6 mm from exposure to raw hen's egg white and no history of previous egg tolerance or 2. A SPT wheal diameter >3 mm from exposure to pasteurized hen's egg white and allergic symptoms related to exposure to hen's egg."	"A history of an allergic reaction to egg and a SPT wheal diameter of 3 mm or greater with egg white extract, or a positive oral egg food challenge result."

SCORAD, SCORing Atopic Dermatitis.

accounted.[35-37] A potential genetic risk of peanut allergy has been suggested by genome-wide association studies as well.[32,33] Most recently, a large US cohort study of food-allergic children and their siblings noted no statistically significant association between peanut allergy in the index child and their siblings, though they did note a high rate of clinically irrelevant sensitization in these siblings.[38] Part of the difficulty in assessing risk on the basis of older peanut-allergic siblings is multiple confounding factors and possible reverse causality from potential delayed ingestion/introduction, which may result in incorrect diagnosis based only on consideration of sensitization as a marker assumed to be pathognomonic for allergy.[59-61]

It should be noted that food allergy commonly develops even among children with no inherent risk factors, a point often overlooked. A population-based cohort study noted high rates of OFC-proven food allergy in the general population (11% at age 1 year),[39] and in the Enquiring About Tolerance (EAT) study of general population infants not considered by the study investigators in the recruitment strategy to be at high risk for food allergy, 24.3% had eczema and 62.6% had a maternal history of atopy.[6] Interestingly, on the basis of other definitions, this population could have been considered high risk, which speaks to the problem of inconsistency in the definition of high risk that has evolved over time. Both observational studies and RCTs have supported early egg, peanut, and milk introduction as potentially beneficial for prevention of egg, peanut, and milk allergy in the general population.[62-66] To date, no evidence exists to suggest that the pathophysiologic mechanisms of sensitization would differ in general population infants, suggesting that any recommendations made for at-risk populations would likely be applicable to the general population as well.[12]

Recommendation 1. Consider infants with severe eczema at the highest risk of developing food allergy. Consider infants with mild to moderate eczema, a family history of atopy in either or both parents, or infants with one known food allergy potentially at some increased risk of developing food allergy (or an additional food allergy). Be aware that food allergy often develops in infants who have no identifiable risk factors. There is no evidence to clearly support the younger sibling of a peanut-allergic child is at increased risk of developing peanut allergy, though such infants may be at risk of developing peanut allergy secondary to delayed introduction of peanut.

Recommendation: moderate; Strength of Recommendation: B; Evidence Category: IIa-IV; Risk of Bias: moderate

Agreement of workgroup. All 9 members agreed on this recommendation, and 7 of 9 agreed on the initial wording. Two members requested change to the wording regarding sibling risk from "are not felt to be at increased risk" to "there is no evidence to clearly support the younger sibling of a peanut-allergic individual is at increased risk," which is reflected in the final recommendation.

Comments. Table III provides a list of studies to date identifying risk factors for the development of food allergy. Lack of data exist comparing the relative risk of these factors within the same study, an approach that should be explored in future research.[3,11] Criteria between studies have been highly variable, making it difficult to identify which have the highest precision. Population-level data suggest that all infants in developed countries may be at increased risk of food allergy relative to children in lesser developed countries, and therefore prevention recommendations should be taken in context of the ambient prevalence of food allergy in that area of the world.[22] We propose a risk gradient for the development of food allergy, as detailed in Figure 2. Food allergy prevention recommendations appear to be most salient for those at highest risk, although again they likely apply to the general population in westernized countries as well, with little evidence of harm among those at lower risk. It should be noted that simply being at risk for developing a food allergy does not necessarily mean that the child will absolutely develop a food allergy.[3,27] This risk ladder should have applications beyond potential assessment for early allergenic solid introduction.

TABLE III. Studies of risk factors for the development of food allergy

Author	Study design	Results
Du Toit et al[5]	RCT of 640 infants with severe eczema and/or egg allergy randomized to peanut consumption (4-11 mo) or avoidance (5 y)	Significantly increased rate of PA with avoidance until age 5 y (17.2% vs 3.2%; $P < .001$)
Koplin et al[27]	Prospective population-based cohort of 5300 infants in Australia	13.9% (95% CI, 11.5-16.5) of the population categorized as "high risk" (egg allergy and/or early-onset eczema) had PA
Martin et al[26]	Prospective population-based cohort of 4453 infants in Australia	Infants with eczema were 11.0 times more likely to develop PA (95% CI, 6.6-18.6) by age 12 mo than infants without eczema
Venkataraman et al[29]	Prospective population-based cohort of 1536 children born on the Isle of Wight	Significant effect of FLG loss-of- function mutations on risk of food allergy at age 10 y (OR, 31.46; 95% CI, 2.86->100) and age 18 y (OR, 4.25; 95% CI, 1.55-11.61)
Sicherer et al[30]	Prospective observational study of 512 infants with positive SPT result to milk or egg and either clinical history of allergy to milk or egg or moderate to severe eczema	69% of the cohort members were sensitized to peanut; 28% of those with IgE quantization had sIgE >5 kUA/L to peanut
Perkin et al[6]	RCT of early (3 mo) vs standard (6 mo) introduction of 6 allergenic foods in 1303 general population infants	NS difference in rates of food allergy in intention-to-treat analysis; decreased PA in intention-to-treat analysis with early introduction (0% vs 2.5%; $P = .003$); high rates of atopy (24.4% eczema, 91.9% parental atopy)
Spergel et al[31]	RCT examining the long-term safety of pimecrolimus cream in infants with mild to severe eczema; food allergy development followed throughout the 3-y randomized double-blind and up to 33-mo open-label phases of the trial in 1901 infants with mild to severe eczema	Food allergy developed in 15.9% of infants by the end of the open-label phase; PA was the most common (6.6%)
Asai et al[32]	Genome-wide association study and meta-analysis of 850 PA cases and 926 controls	Genome-wide significance ($P = 7.50 \times 10^{-11}$) for C11orf30/EMSY locus for development of PA
Madore et al[33]	Genotypic and allelic profiles of 311 Canadian children with PA and 226 controls	Association between HLA-DQB1*02 allele and PA (OR, 0.09; 95% CI, 0.03-0.23) and HLA-DQB1*06:03 allele and PA (OR, 2.82; 95% CI, 1.48-5.45)
Bergmann et al[34]	Prospective study of 1314 newborn infants in Germany	31% of infants sensitized to 1 or more food or inhalant allergen; significantly associated with cord blood-IgE level (OR, 2.43; 95% CI, 1.69-3.49) and maternal sensitization (OR, 1.64; 95% CI, 1.18-2.41)
Hourihane et al[35]	Nationwide questionnaire of 622 subjects with PA and their families	Self-reported PA prevalence in 6.9% of siblings; significantly higher rate than among parents, aunts, uncles, or general population ($P < .001$)
Liem et al[36]	Survey of 560 Canadian household members of a nationwide cohort	Increased risk of PA in siblings of peanut-allergic children (OR, 6.72; 95% CI, 2.04-22.12)
Sicherer et al[37]	Survey of 58 twin pairs, at least 1 of whom had PA	Pairwise concordance of 64.3% among monozygotic twins, with established PA heritability of 81.6% (95% CI, 41.6%-99.7%)
Gupta et al[38]	Cohort study of 2834 children; 1120 children with food allergy and at least 1 biological sibling	Although 22.8% of siblings of peanut-allergic children were sensitized to peanut, only 4.9% were clinically reactive to peanut. PA in the index child did not significantly increase the risk of PA in siblings, nor did PA in siblings significantly increase the risk of PA in the index child
Peters et al[39]	Prospective population-based cohort study of 5276 infants in Australia	Prevalence of challenge-proven PA in 1-y-old general population infants was 3.1% (95% CI, 2.7%-3.6%)
Venter et al[40]	Cohort study of children born in the same geographic location over different time periods assessed for peanut sensitization at age 3-4 y (N = 2181, 1273, 891)	Children sensitized to peanut significantly more likely to have eczema ($P = .002$) and significantly more likely to be sensitized to house dust mite ($P < .001$), cat ($P = .013$), egg ($P < .001$), and sesame ($P < .001$) than children not sensitized to peanut

(continued)

TABLE III. *(Continued)*

Author	Study design	Results
Tsakok et al[41]	Systematic review of 66 studies (18 population-based, 8 high-risk cohorts, rest comprised patients with either established eczema or food allergy) to assess the association between eczema and food allergy	Likelihood of food sensitization significantly higher in infants with eczema (OR, 6.18; 95% CI, 2.94-12.98) in population-based studies. In studies including only patients with established eczema, prevalence of food sensitization up to 66% and challenge-proven food allergy prevalence up to 81%

NS, Nonsignificant; *OR*, odds ratio; *PA*, peanut allergy.

Current data do not clearly support that siblings of peanut-allergic children are at increased risk of developing peanut allergy based on any genetic or heritable factor.[3] Methodologies used in previous studies of this group are limited, and observed prevalence may be confounded by timing of introduction, but most importantly, these studies never denoted a specific difference in risk (eg, risk of one group developing peanut allergy relative to another), as opposed to denoting a prevalence rate felt to be higher than the general population rate.[37,38,61,67] These children should have early peanut introduction just like other children without an allergic older sibling. However, these children may need to be handled cautiously for a more practical reason—many parents may be reluctant to introduce peanut into the diet of an infant who has an older peanut-allergic sibling. Therefore, though indirect, this possibility of delayed introduction potentially places such infants at a higher risk for developing peanut allergy.[12,15,16] Irrespective of any baseline risk, the potential benefit of introducing peanut early into an infant's diet greatly outweighs delayed peanut introduction, and it is important to note that having a peanut-allergic sibling is not considered a risk factor in the NIAID-AG.[12] It is highly crucial for medical providers to have such discussions with families where there is another sibling with a food allergy to devise strategies to prevent delayed introduction.

Question 2: What is the evidence supporting the timing of introduction of potentially allergenic complementary foods and the development of IgE-mediated food allergy?

Clinical context and background. To date, 7 allergen-specific RCTs have investigated the effects between early peanut and early egg introduction and peanut or egg allergy prevention, in both standard-risk and high-risk infants, with the definition of "high-risk" specific to each study (and elaborated below).[4-10] The individual trials are detailed in Table IV.[11]

Peanut. Two RCTs have investigated the timing of peanut introduction and the risk of developing peanut allergy. The intention-to-treat analysis of the LEAP 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).[5] The per-protocol analysis (but not the intention-to-treat analysis) of the EAT study 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 (though by older trial definitions some of these infants could arguably be considered at risk due to presence of parental atopy).[6] Ierodiakonou et al[11] performed a meta-analysis of these 2 trials, inclusive of 1550 children, and noted "moderate certainty" of evidence that introducing peanut between age 4 and 11 months reduced the risk of developing peanut allergy (relative risk [RR], 0.29; 95% CI, 0.11-0.74).

Egg. For egg, 5 RCTs have specifically investigated the timing of egg introduction and risk of egg allergy. The Solids Timing for Allergy Reduction (STAR) study noted a trend toward reduced risk of egg allergy at 1 year (RR, 0.65; $P = .11$) associated with introduction of raw, pasteurized powdered egg protein at 4 versus 8 months of life in infants defined as high risk with moderate to severe eczema.[4] The Starting Time for Egg Protection study similarly noted a nonsignificant 3.3% ARR in the development of egg allergy at age 1 year in noneczematous infants born to atopic mothers who received raw, pasteurized egg protein at 4 to 6 versus 10 months.[9] The Beating Egg Allergy Trial noted no significant difference in egg allergy at age 1 year in infants with a first-degree atopic relative who were randomized to raw, pasteurized egg introduction at 4 to 6 versus 8 months, but found a 9.7% ARR in egg sensitization associated with earlier introduction.[7] The Hen's Egg Allergy Prevention (HEAP) study noted no significant difference in rates of egg sensitization or OFC-proven egg allergy at age 1 year in standard-risk infants introduced to raw, pasteurized egg versus placebo at age 4 to 6 months (RR, 3.3; $P = .35$).[8] However, the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study of Japanese 4- to 5-month-old infants with eczema who consumed 50 mg/d heated egg powder from age 6 to 9 months of life, then 250 mg/d from age 9 to 12 months (vs placebo), noted a strongly protective effect in the early introduction group (RR, 0.22; 95% CI, 0.08-0.61; $P = .0012$; number needed to treat, 3.4), prompting early cessation of the trial by the data safety monitoring board equivalent after a preplanned interim analysis to assess sample size also noted the aforementioned large significant benefit. Of note, the children also had their eczema aggressively treated as part of the study design.[10] Lastly, the per-protocol analysis (but not the intention-to-treat analysis) of the EAT study also noted small, significant ARR differences for introduction of egg at age 3 months compared with introduction after age 6 months (ARR, 4.1%) in infants not at risk for the development of food allergy.[6] The meta-analysis performed by Ierodiakonou et al[11] also determined that there was a "moderate certainty" of evidence that introducing egg between age 4 and 6 months reduced the risk of developing egg allergy (RR, 0.56; 95% CI, 0.36-0.87) based on 5 RCTs (STAR, Starting Time for Egg Protection, Beating Egg Allergy Trial, HEAP, and PETIT) inclusive of 1915 children.[11] In terms of safety, the STAR trial

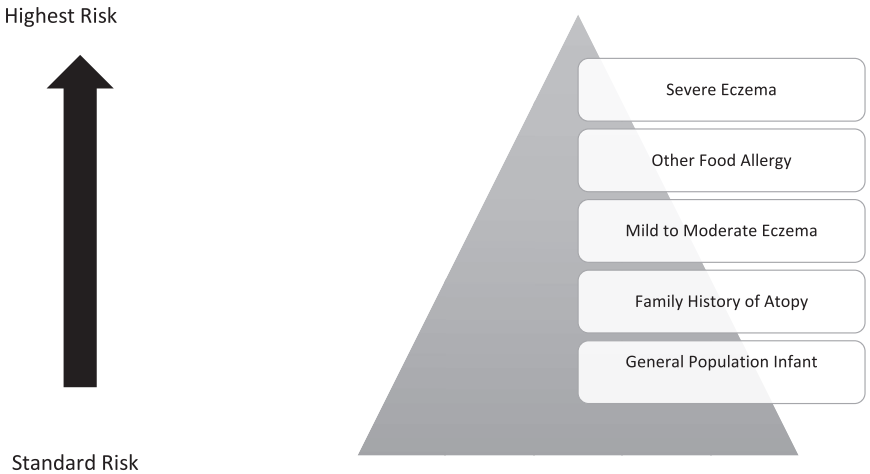

FIGURE 2. Ascending gradient of risk assessment for the development of food allergy among infants. The bottom of the pyramid represents standard risk and the peak the highest risk for developing food allergy.

was halted prematurely given one-third of the subjects experienced an allergic reaction (including anaphylaxis and FPIES) on initial exposure to the raw egg product.[4] A similar experience was noted in the HEAP trial in which 10 of 23 children excluded from the trial for having preexisting hen's egg specific IgE (sIgE) sensitization, who then underwent egg double-blind, placebo-controlled, food challenges, developed anaphylaxis (n = 23 excluded, n = 17 underwent double-blind, placebo-controlled, food challenges, during which 16 reacted to egg).[8]

Other major food allergens. There are fewer data regarding early introduction of other potentially allergenic complementary foods. No RCTs similar to LEAP/Beating Egg Allergy Trial/HEAP/Starting Time for Egg Protection/STAR/PETIT exist for the remaining 6 major food allergens, despite multiple observational studies that have been conducted.[11] Data from EAT (again, defined in a population felt by investigators not to be at high risk for food allergy development, but by older standards could have qualified as such) for CM, wheat, sesame, and codfish showed no significant association with reduced (or increased) rates of allergy development to these items (respectively) based on the early versus 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.[6] There are no known harmful associations between early CM protein exposure and the development of allergy/sensitization to CM.[11,68] Possible preventative benefit associated with early CM formula introduction within the first month of life has been suggested on the basis of 2 observational studies and nested data from the PETIT trial for egg allergy prevention. In a 13,000-infant Israeli cohort, Katz et al[62] found that the odds of developing cow's milk allergy (CMA) were 19.5-fold higher among infants having CM introduction between 105 and 194 days of life versus within the first 14 days of life, adjusted for breast-feeding. Onizawa et al[64] examined 51 children with CMA compared with 102 nonallergic controls and 32 egg-allergic children, noting the adjusted odds ratio of developing CMA associated with delayed (started >1 month after birth) or no regular CM formula (<once daily) was 23.7 (95% CI, 5.39-104.52) versus the control group, and 10.16 (95% CI, 2.48-41.64) versus the egg allergy group. Natsume et al[69] examined 114 subjects from the PETIT study for whom they had CM consumption data from birth to age 18 months, and noted a nonsignificant trend of a lower prevalence of CMA in those with continuous CM consumption from birth to 18 months versus delayed or less-continuous consumption (4% vs 20%; $P = .07$). Taken as a group, data from these observational studies suggest that delayed and/or irregular CM ingestion may be associated with an increased risk of developing CMA.[62,64,69] Notably, in the EAT study, there was no significant finding with respect to the timing of CM introduction.[6]

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.[11] Observationally, Du Toit et al[63] did note a lower rate of both tree nut allergy and sesame allergy in Jewish children in Israel compared with those in London, associated with reported introduction of these items in the first year of life versus later times.

Existing guidance. The 2013 AAAAI, 2013 CSACI, and 2014 EAACI guidelines did not make any specific recommendations for specific early introduction of any allergen.[13,14,21,22] The 2019 Canadian Paediatric Society Practice Point recommends introduction of commonly allergenic solids for high-risk infants at around 6 months, but not before 4 months.[17] The 2019 American Academy of Pediatrics (AAP) Clinical Report and the 2017 NIAID-AG make such a recommendation, restricted to peanut.[12,68] Infants in the highest risk criteria under the NIAID-AG guidelines and the AAP Clinical Report are recommended to undergo evaluation for preexisting peanut sensitization by sIgE or skin testing before introducing peanut (addendum 1).[12,68] However, this differs significantly from the recently published approaches advocated from the UK Department of Health and the Australasian Society of Clinical Immunology and Allergy, where all infants are recommended to have both peanut and egg introduced around age 6 months, without any risk stratification or recommendation for testing to either food

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TABLE IV. Summary of RCTs of early introduction of allergenic foods

Study	Full title	Study type	Population	Intervention	Primary outcome	Results
LEAP[5] (UK)	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 mo, through 60 mo of life	IgE-mediated peanut allergy based on OFC at month 60	• ITT analysis showed 13.7% prevalence of peanut allergy in the avoidance group vs 1.9% in the consumption group ($P <$ .001)
EAT[6] (UK)	Enquiring About Tolerance	Nonblinded RCT (n = 1303)	Standard risk: • Exclusively breast-fed until allergenic foods introduced	• Early introduction group (EIG) introduced 2 g of protein twice weekly at 3 mo of peanut, cooked egg, CM, sesame, whitefish, wheat • Standard introduction group (SIG) at 6 mo of above 6 foods	IgE-mediated food allergy to at least 1 of the 6 allergens at age 1 or 3 y based on OFC	• ITT analysis showed no difference in food allergy between EIG and SIG • PP analysis showed significantly less prevalence of peanut allergy (P = .003) and egg allergy (P = .009) in EIG vs SIG
STAR[4] (Australia)	Solids 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 mo • 0.9 g raw whole-egg powder daily (0.4 g protein/d) • Cooked egg at 8 mo	IgE-mediated egg allergy at 12 mo based on positive SPT result and egg OFC	• Study terminated early: one-third of patients reacted to egg at entry OFC • At 12 mo, 33% had egg allergy in the egg group vs 51% in the control group (not significant)
STEP[9] (Australia)	Starting Time for Egg Protein	Blinded RPCT (n = 820)	Intermediate risk: • Atopic moms (allergic disease + positive envir SPT result) • Infants: no allergic dz	• Daily consumption of egg vs placebo powder from 4 to 6.5 mo • 0.9 g raw whole-egg powder daily (0.4 g protein/d)	IgE-mediated egg allergy at 12 mo based on positive SPT result and egg OFC	• No significant differences in egg allergy between groups • No anaphylactic reactions at initial egg introduction
BEAT[7] (Australia)	Beating Egg Allergy Trial	Blinded RPCT (n = 319)	Intermediate risk: • Infants with first-degree relative with atopy • Infants: negative egg SPT result	• Daily consumption of egg vs placebo powder at 4 mo • 350 mg protein daily raw whole-egg powder • Cooked egg at 8 mo	Sensitization to egg by SPT at age 12 mo	• Subjects in the egg group vs placebo had significantly less egg sensitization (10.7% vs 20.5%; P = .03) • No harm with egg introduction
HEAP[8] (Germany)	Hens 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 age 4 to 6 mo until 12 mo	Sensitization to egg based on egg IgE ≥0.35 kU/L at age 12 mo	• No evidence of preventing egg sensitization or allergy • High rate of anaphylaxis at egg introduction at entry
PETIT[10] (Japan)	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 mo • Daily consumption of 250 mg heated egg from 9 to 12 mo	IgE-mediated egg allergy at age 12 mo based on OFC	• Prevalence of egg allergy 37.7% in placebo vs 8.3% in the egg group (P = .0013) • No SAEs

BEAT, Beating Egg Allergy Trial; *RPCT*, randomized placebo-controlled trial; *dz*, disease; *envir*, environment; *ITT*, intention-to-treat; *PP*, per-protocol; *SAE*, severe adverse effect; *STEP*, Starting Time for Egg Protection.

TABLE V. Comparison of existing early peanut and/or other potentially allergenic foods introduction guidelines

National Institutes of Allergy and Infectious Diseases[12]	British Society for Allergy and Clinical Immunology[15]	Australasian Society for Clinical Immunology and Allergy[16]
• Addendum 1: Infants with severe eczema, egg allergy, or both should have introduction of age-appropriate peanut-containing food as early as age 4 to 6 mo to reduce the risk of peanut allergy.	• Exclusive breast-feeding for around the first 6 mo of life.	• When your infant is ready, at around 6 mo, but not before 4 mo, start to introduce various solid foods, starting with iron-rich foods, while continuing breast-feeding.
• Addendum 2: Infants with mild to moderate eczema should have introduction of age-appropriate peanut-containing food around age 6 mo, in accordance with family preferences and cultural practices, to reduce the risk of peanut allergy.	• Foods containing peanut and hen's egg need not be differentiated from other complementary foods and should be introduced in an age-appropriate form from around age 6 mo, alongside continued breast-feeding, at a time and in a manner to suit both the family and individual child.	• All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products in the first year of life. This includes infants at high risk of allergy.
• Addendum 3: Infants without eczema or any food allergy have age-appropriate peanut-containing foods freely introduced in the diet, together with other solid foods, and in accordance with family preferences and cultural practices.	• The deliberate exclusion of peanut or hen's egg beyond age 6-12 mo may increase the risk of allergy.	• Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.
	• Once introduced, and where tolerated, these foods should be part of the infant's usual diet, to suit both the individual child and the family.	• No specific screening, testing, evaluation recommendations before introduction.
	• Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.	

before introduction (Table V).[15,16] At the time of finalization of this document, 2 additional draft copies of guidelines were released by the EAACI and the US Department of Agriculture, both also suggesting that peanut and egg in age-appropriate forms can be introduced after 4 months of life, to help reduce the risk of developing allergy to these foods.[18,20]

Assessment of stakeholder preferences for early allergen introduction. In formulating the NIAID-AG, there was no assessment done of parent preferences for any screening testing or possible observed feeding/graded OFCs for their infants. Similarly, there was no assessment of medical provider willingness to discuss early peanut introduction or to perform in-office observed feeding/graded OFCs in infants or investigation of the resource availability to implement such policy.[12,42,70] A recent nationally representative survey of 2000 pregnant and caregivers of children younger than 12 months noted poor support for peanut introduction before 6 months of life. Only 31% expressed willingness to introduce peanut before 6 months of life, and 40% expressed willingness to introduce peanut only after 11 months of life. In comparison, 60% reported willingness to introduce egg before 8 months of life. Only 49% reported willingness to allow their child to undergo preintroduction skin testing and 54% willingness to allow their child to undergo an OFC before 11 months of life.[71]

Assessment of the health and economic outcomes associated with early allergenic food introduction. There was no assessment of the potential health and economic outcomes related to the NIAID-AG recommendations at the time of their publication. Therefore, in support of the development of these guidelines, 3 specific cost-benefit analysis studies were performed to investigate the optimal health and economic benefits of early peanut and egg introduction strategies (the 2 foods with the clearest evidence of benefit), and whether younger siblings of peanut-allergic individuals should be screened. Markov modeling was used to simulate potential strategies for introduction of these allergens in both high-risk and not at-risk potential target populations, with effects modeled over a 10- to 20-year horizon for egg (given many cases of egg allergy resolve in childhood) and a 20-year horizon for peanut (because most patients with peanut allergy do not outgrow it) in a US infant population, using US costs. The probabilities for each outcome were determined from representative literature. The simulations compared "screening" approaches involving preintroduction allergy testing and reflexive in-office introduction based on such tests, versus a policy where early introduction of the allergens universally occurred for all infants without any screening assessment ("nonscreening" approach, eg, feeding the infant at home), versus a delayed introduction approach, for both allergens.[72,73]

For both egg and peanut introduction, a strategy of universal introduction to all infants (in both at-risk and not at-risk populations) without screening skin/sIgE testing and/or without in-office observed introduction or OFC dominated (eg, was associated with superior health benefits and lower costs) the other approaches of either screening or delayed introduction. Therefore, compared with the other options, universal introduction cost less, prevented more cases of the food allergy, and produced more net benefit to the patient (measured by gain in quality-adjusted life-years, a metric representing a year of perfect health relative to the health condition). Table V details these

TABLE VI. Cost-effectiveness of strategies for early introduction of peanut and egg*

Infant risk scenario	Cost per patient at risk	QALY per patient at risk	Allergic reactions per patient at risk	Incremental societal cost to screen
For peanut allergy (personal history of early-onset eczema and/or egg allergy)[72]				
No screening, early introduction	$6,557	19.63	0.4	—
Skin test screening before early introduction	$7,576	19.62	0.35	$654,115,322
sIgE screening before early introduction	$7,977	19.6	0.38	$911,211,774
Delayed introduction	$11,708	19.46	0.72	
For peanut allergy (sibling history of peanut allergy)[75]				
No screening before introduction	$3,278	19.72	0.2	—
Skin test screening with challenge before introduction	$3,984	19.72	0.2	Dominated
For egg allergy (early-onset eczema)[73]				
No screening, early cooked introduction	$2,235	19.78	0.03	—
Skin test screening before early cooked introduction	$9,100	19.59	0.12	$2,009,351,175
sIgE screening before early cooked introduction	$18,957	19.28	0.26	$4,894,445,790
Delayed cooked introduction	$10,615	19.53	0.13	

QALY, Quality-adjusted life-year.
*Model simulations over 20-y time horizons.

analyses, showing that compared with not screening, screening high-risk infants before peanut introduction cost an additional $654,115,322 and prevented 3,208 fewer cases of peanut allergy, and for egg was associated with additional costs of $2,009,351,175 and prevented 7% to 19% fewer cases of egg allergy (depending on the screening test used) (Table VI). Of note, screening for peanut cost less and prevented more cases than delayed introduction, comparatively, but overall, the approach of not screening these infants was the superior approach.[73,74]

Additional research into how the existing NIAID policy could be made more cost-effective found few realistic scenarios where this could occur. The situations that made screening cost-effective included either increased specificity of the diagnostic test, there being a very high underlying prevalence of peanut allergy, or there being a context where the parents strongly preferred screening (measured by health utility). Because the prevalence rate and the test specificity are unlikely to change, the health utility was the only context that could make screening cost-effective. However, even this is not entirely realistic to change. The authors noted that screening could be cost-effective only in a very unique context of families having a very strong concern for, fear of, or aversion to introducing the food(s) at home, defined as health disutility (eg, a negative or adverse state associated with an event or action). Screening became cost-effective when this disutility was equivalent to preferring to trade between a range of 76 and 148 days of life in a single year to have in-office screening rather than introduce this at home and avoid introduction without screening.[76] Restated, if there is a large population of parents who would be so distressed at the prospect that their infant would have a potentially severe reaction at home from early introduction, and were willing to trade a significant portion of a year of life to avoid this through the infant undergoing screening and having this very same reaction occur at a specialist office instead, then screening would be cost-effective. Outside of this strong desire to avoid such a situation, it would not be cost-effective.

For the question of the value of screening the younger sibling of a peanut-allergic child before early introduction, the results were similar in that at-home introduction without screening of these siblings dominated. However, in this analysis, if the prevalence of peanut allergy in the younger sibling was more than 11%, then skin testing before introduction was cost-effective, so long as an OFC was performed to confirm a true outcome, and the family was willing to trade off approximately 32.8 days (∼1 month) of life in a single year for the family to avoid having a reaction at home. If no OFC would be performed with the screening, then skin testing of the younger sibling was cost-effective only if the prevalence of peanut allergy in the younger sibling was more than 63%.[75] This reinforces a lack of utility of testing in situations in which the prevalence of the food allergy is low.

Recommendation 2. Introduce peanut-containing products to all infants, irrespective of their relative risk of developing peanut allergy, starting around 6 months of life, though not before 4 months of life. Introduction can occur at home when the infant is developmentally ready for complementary food introduction, in accordance with the family's cultural practice, but not before the infant demonstrates developmental readiness with eating a few other common starter foods. While screening peanut skin or sIgE testing and/or in-office introduction is not required for early introduction, this remains an option to consider for families that prefer to not introduce peanut at home; this decision is preference-sensitive and should be made taking into account current evidence and family preferences. Strongly consider encouraging either home introduction, or offering a supervised oral food challenge for any positive skin prick test (SPT) or sIgE result. Once peanut is introduced, regular ingestion should be maintained.

Recommendation: Strong; Strength of Recommendation: A; Evidence Category: Ia-III; Risk of Bias: moderate.

Agreement of workgroup. All 9 members agreed on this recommendation, and 6 of 9 agreed on the initial wording. Two members requested change to the wording regarding screening recommendation from "is not required" to "may not be required"; this was not changed because most preferred "is not

required." One member requested additional wording be added regarding an oral food challenge being offered to anyone with peanut sensitization detected; this change is reflected in the final recommendation.

Recommendation 3. Introduce egg or egg-containing products to all infants, irrespective of their relative risk of developing allergy, around 6 months of life, though not before 4 months of life. Use only cooked forms of egg and avoid administering any raw, pasteurized egg-containing products. Introduction can occur at home when the infant is developmentally ready for complementary food introduction, in accordance with the family's cultural practice, but not before the infant demonstrates developmental readiness with eating a few other common starter foods. While screening egg skin or sIgE testing and/or in-office introduction is not required prior to early cooked egg introduction, this remains an option to consider for families that prefer to not introduce egg at home; this decision is preference-sensitive and should be made taking into account current evidence and family preferences. Strongly consider encouraging home introduction, or offering a supervised oral food challenge for any positive SPT or sIgE result. Once egg is introduced, regular ingestion should be maintained.

Recommendation: Strong; Strength of Recommendation: A; Evidence Category: Ia-III; Risk of Bias: low.

Agreement of workgroup. Eight of 9 members agreed on this recommendation, and 7 of 9 agreed on the initial wording. The same 2 members requested change to the wording regarding screening recommendation from "is not required" to "may not be required"; this was not changed because most preferred "is not required." One member requested additional wording be added regarding oral food challenge being offered to anyone with egg sensitization detected; this change is reflected in the final recommendation.

Comments. There is strong evidence supporting that peanut-containing foods should be introduced into the infant's diet starting around 6 months of life, but not before 4 months of life, and that cooked egg/egg-containing products (eg, boiled, scrambled, or egg baked into a good, such as in a teething biscuit or muffin) should be introduced in a similar time frame.[11] It is unclear whether outcomes are truly superior for starting peanut introduction between 4 and 6 months versus at/after 6 months, though secondary analysis has shown a high rate of success for each age strata.[77] Introduction may be done at home for all infants regardless of risk, in accordance with family and cultural practices. However, if some families are less comfortable with the at-home approach, and prefer screening and in-office introduction, then this remains an option that can be considered. The timing of these introductions applies to all infants, independent of any high-risk or other categorization. There is no evidence supporting that screening for either allergen before early introduction improves health outcomes or prevents more cases of peanut or egg allergy, and such would be associated with costs in the hundreds of millions of dollars compared with universal introduction without screening.[72,73]

These guidelines evolve recommendations regarding assessing the high-risk child.[12] This is based on further evidence that has emerged since the publication of these documents, incuding multiple aforementioned clinical trials using different high-risk definitions, but also additional publications showing differential interpretation of the original value of testing in the LEAP study, a study of parent preferences regarding preassessment, and a cost-benefit analysis of preassessment to determine its associated health and economic outcomes.[6-11,71-73,77] However, this panel recognizes that the recommendations contained herein are just that—recommendations based on an ideal practice standard, and that such best practices will be subject to variable implementation in the real world. What is meant by saying screening is "not required" is just that—some families may still want this option, but not every family has to undergo screening for early introduction and for those families, they can introduce the food to their infant at home. It is anticipated that some clinicians and families may be hesitant or uncomfortable with an approach to just introduce the food at home. Thus, after using shared decision making to determine what the family wants, some may still prefer the option of sIgE/skin testing and/or facilitated in-office introduction before peanut introduction, as specified in the NIAID-AG in accordance with their risk categorization.[12] However, this recommendation also accommodates those who may not want a screening approach at all, and prefer at-home introduction. Therefore, the updated recommendation provides flexibility and incorporation of both preferences into the approach, rather than force one pathway. In the cost-benefit analysis, although the nonscreening approach had the lowest costs and the most cases of peanut or egg allergy prevented, the screening approach was still superior to a delayed introduction as a fallback option for peanut introduction, and is more preferred when compared with omitting early introduction of peanut altogether.[72,73] Recently published data from the Australian Early Nuts study has supported that an approach in which screening is not required is safe in terms of rates of severe reactions, and highly effective in terms of adherence to early introduction guidelines.[78]

Importantly, the panel also agreed that in infants undergoing preassessment, there may be many contexts and situations in which the risk to benefit ratio supports offering OFC regardless of the size of the positive skin test result or level of sIgE test to verify the presence of an allergy. The main benefit for such a consideration is the known issues with false-positive test results (specifically both the poor specificity and imperfect positive predictive values of these tests) when obtained in patients in the absence of a known symptomatic ingestion history, and a low rate of severe reactions on initial consumption from available data from infant OFCs.[3] However, such a decision with regard to an OFC in this context should also be a shared decision, made by the clinician taking into account current evidence and family preferences, after discussion of the risks and benefits. Although not all families may desire to exercise this option, some families may value a definitively proven outcome even if that results in objectively demonstrating their child is peanut allergic over an automatic precluded diagnosis made by an SPT exceeding a cutoff value that may potentially misclassify some tolerant individuals as allergic. We caution that the predictive cutoffs used in the NIAID guidelines were adapted from an unselected Australian population of slightly older children, and thus may potentially lack some generalization to the age group in question at the time of screening. We also strongly emphasize that food allergen panel testing for other allergens in association with assessing peanut sensitization is not recommended because of poor positive predictive value and potential for inappropriate diagnosis, in keeping with the NIAID guidelines and the Choosing Wisely initiative.[12,79]

Neither peanut nor egg should be the first food offered to an infant starting solid foods because it may be difficult to distinguish between an inability to manage complementary food, which may result in gagging, vomiting, or coughing in the infant; these symptoms may be incorrectly interpreted as an allergic reaction.[12,15,16] Peanut or egg should only be introduced to an infant soon after he or she has tolerated a few other typical starter foods such as stage 1 fruits, vegetables, or grains; the addition of these foods first can provide options in which to mix peanut powder/flour or peanut butter, which should not be fed unmodified.[12] Forms and dosages are discussed in this article's Online Repository and in Figure E1 in more detail in this article's Online Repository at www.jaci-inpractice.org.

We acknowledge that there are research gaps surrounding the knowledge translation of some of the net monetary benefits from a universal introduction approach, as well as gaps surrounding the use of the existing screening cutoffs for skin testing taken from the HealthNuts study (including whether screening is necessary and how applicable the HealthNuts cutoffs would be to a slightly younger population), and why the success of implementing early introduction in the United States contrasts with that of other countries such as Australia and Israel. Moreover, additional studies are needed to explore parental preferences on approaches to early introduction, provide shared decision support to these families, and understand variation at both the parent and clinician levels for why some may choose a screening approach and some may not.[80]

Recommendation 4. Do not deliberately delay the introduction of other potentially allergenic complementary foods (CM, soy, wheat, tree nuts, sesame, fish, shellfish), once introduction of complementary foods has commenced at around 6 months of life but not before 4 months. There may be potential harm in delaying the introduction of these foods based on past observational studies. There are no data showing harm in introducing these other allergenic foods within the first year of life, but also no data suggesting specific benefit. Prior to early introduction of these foods, screening skin or sIgE testing and/or in-office introduction is not required; however, the decision to screen or not is preference-sensitive and should be made by the clinician taking into account current evidence and family preferences. Strongly consider encouraging home introduction or offering a supervised oral food challenge for any positive SPT or sIgE result if screening is performed. Once introduced, regular ingestion should be maintained.

Recommendation: moderate; Strength of Recommendation: A/B; Category of Evidence: Ib-IV; Risk of Bias: moderate.

Agreement of workgroup. All 9 members agreed on this recommendation as was initially worded, which is reflected in the final recommendation.

Comment. The 2019 AAP recommendations on complementary feeding state that there is no benefit associated with the delay in introduction of any foods, including other major highly allergenic foods such as CM, soy, wheat, tree nuts, sesame, fish, or shellfish, beyond 4 to 6 months of life (a typical weaning age) for the deliberate prevention of food allergy.[68] However, there are no new RCTs outside of those mentioned for peanut and egg to better inform decision making regarding associations with introduction timing and prevention of food allergy.[11] Therefore, given this evidence gap, there is no recommendation to change or amend this practice for the purposes of prevention, nor any contraindications to these practices. The introduction of complementary foods, including CM, soy, wheat, tree nuts, sesame, fish, and shellfish (in nonchoking forms), should begin once the infant has tolerated other typical weaning foods. There is no set order in which these foods should be introduced, but their introduction should follow a logical progression of the infant's developmental stages, nutritional needs, as well as be aligned with cultural dietary practices (eg, there is no need to just introduce a food because it is a potential allergen if it is of low likelihood to be normally consumed in the diet). Once introduced, regular consumption of these foods is recommended according to cultural dietary practices and family preferences. There are no trial-based comparative data regarding quantity/frequency of allergen intake that are clearly associated with tolerance, though studies have suggested quantities and frequencies that were associated with positive outcomes in their trials, albeit without comparative efficacy data available.[68]

Despite the observational data support for early CM introduction for CMA prevention, there is insufficient evidence at present to support this as a formal CMA prevention recommendation. No data support that the introduction of CM-based products before age 1 year is harmful.[11] In fact, this is a routine and safe practice, and many infants are started on CM-containing formula at birth, though just not for the specific purposes of allergy prevention. This is an area requiring further study to establish whether this practice is associated with any benefit. Liquid CM as a beverage to substitute for breast milk or infant formula should not be introduced before age 1 year for reasons unrelated to allergy (ie, increased renal solute load, low iron content), but foods that contain CM as a minor ingredient, as well as CM-containing products such as yogurt and cheese, are safe to introduce.[81,82] Two studies have noted that early solid food introduction, including potentially allergenic solids, does not negatively impact growth and development.[83,84]

Question 3: Is there an association between early infant diet diversity and the development of food allergy?

Clinical context and background. Diet diversity is defined as the number of different foods or food groups consumed over a given reference period.[85,86] There are a total of 15 publications referring to 7 different studies that have investigated the effect of diet diversity on allergy outcomes (see Table E1 in this article's Online Repository at www.jaci-inpractice.org), but just 3 investigated food allergy as an outcome.[87-89]

In a study from 5 European countries (Austria, Finland, France, Germany, and Switzerland), Roduit et al[89] observed that decreased diet diversity in the first year of life was associated with increased risk of a reported doctor-diagnosed food allergy up to age 6 years (6 foods vs 4-5 foods: 1.85; 95% CI, 1.02-3.35; 6 vs 0-3 items: 4.43; 95% CI, 1.62-12.1), using a model that adjusted for potential confounders, but not a model that adjusted for both confounders and reverse causality. In applying this latter model, the results were no longer statistically significant. For each additional food in the diet, the risk of reported food allergy decreased significantly (0.70; 0.57, 0.86; $P < .05$), but lost significance when adjusted for a diagnosis occurring by age 1 year. There was a stronger protective association observed for diet

diversity when combining doctor-diagnosed food allergy with positive food sensitizations. Introduction of fish in the first year of life showed a reduction in the prevalence of food allergy in the first 6 years of life.

Roduit et al[89] also showed that decreased diet diversity during the first year of life was associated with an increased risk of sensitization to food allergens (specific IgE tests to egg, CM, peanut, hazelnut, carrot, and wheat) at age 4.5 or 6 years (6 foods vs 4-5 foods: 1.52; 95% CI, 0.83-2.76; 6 vs 0-3 items: 5.47; 95% CI, 1.91-15.67), again using a model that adjusted for potential confounders, but not a model that adjusted for both confounders and reverse causality. In this latter model, the results remained statistically significant for 6 foods versus 0 to 3 foods. Nwaru et al[90] reported that the introduction of 1 to 2 food items at 4 months and 4 or fewer food items at 6 months was associated with sensitization to egg, CM, fish, and wheat. However, this study also may be confounded by reverse causality. In the 15-year follow-up of the GINI study, Markevych et al[91] noted that higher food diversity during the first year of life was not associated with food sensitization (using the serologic FX5 test, which includes sIgE to CM, egg, peanut, soy, cod, wheat).

Grimshaw et al[87] measured dietary patterns (rather than diversity) based on prospective food diary data to investigate whether infant feeding patterns (rather than any specific food/food component) impacted food allergy development. In this small, nested case-controlled study of food-allergic (n = 41) and non−food-allergic (n = 82) children from a UK birth cohort, no such association was noted between the dietary pattern and development of food allergy, though the ongoing dietary pattern (after solid food introduction up to age 1 year) between the 2 groups was significantly different. This ongoing dietary pattern compared healthy versus unhealthy weaning foods, as defined by infant feeding guidelines, and found the "healthy infant diet" (identified as predominantly home-cooked diet during later infancy with high values for fruit, vegetable, fish, and poultry consumption and low values for highly processed adult foods, eg, ready meals, cook-in-sauces, potato-products, and bacon and the use of commercial baby foods more than once a day) was associated with less food allergy ($P = .002$). Another report from the same cohort showed that a lower "healthy infant pattern" score was associated with increased risk of all food allergy, including both IgE- and non−IgE-mediated food allergy at the age of 2 years.[88]

Lastly, a retrospective analysis of infant dietary patterns on the Isle of Wight in the food allergy intolerance research Birth Cohort noted a significant protective association between dietary diversity at both 6 and 9 months of life and lower odds of developing food allergy over the first decade of life.[92] Data from this study indicated that for each additional food introduced by 6 months, the odds of developing food allergy over the first 10 years of life reduced by 10.8%, even after correcting for significant factors. For each additional potentially allergic food introduced by 12 months, there was a significant reduction of 33.2% in the likelihood of food allergy over the first 10 years of life. Food allergen diversity did not negatively affect overall food diversity, and there was no association between eczema and age of introduction of solids.

Diet diversity studies to date have inherent limitations, including the following: (1) diversity is perhaps more important for typically allergenic than for nonallergenic foods, but these studies do not discriminate the 2 aspects; (2) the amount/regularity of exposure once introduced is not captured; (3) diversity among and also within food groups, for example, how many fruits and vegetables, is not described; and (4) diversity versus early potential allergen introduction is not differentiated. As well, there may be cultural differences to account for in the types of foods that may comprise a diverse diet for a particular infant.

Recommendation 5. Upon introducing complementary foods, infants should be fed a diverse diet, as this may help foster prevention of food allergy. There is observational evidence but not any RCTs supporting this recommendation, but this is balanced by no known harm in introducing a diverse range of foods. Future evidence may more conclusively demonstrate specific potential health benefits of diet diversity. In accordance with recommendation 4, do not deliberately delay the introduction of other potentially allergenic complementary foods (CM, soy, wheat, tree nuts, sesame, fish, shellfish) once introduction of complementary foods has commenced at around 6 months of life, but not before 4 months.

Recommendation: weak; Strength of Recommendation: C; Evidence Category: IIb-III Risk of Bias: high.

Agreement of workgroup. All 9 members agreed on this recommendation. Seven of 9 agreed with the recommendation as was initially worded. Two members requested change to the wording to strengthen the recommendation and emphasize the lack of harm of feeding a diverse diet despite unclear prevention benefit, as well as highlight that such advice is in concordance with recommendation 4 (do not delay introduction), which is reflected in the final recommendation.

Comments. Infants should be encouraged to try a broad variety of food, including potentially allergenic foods, once complementary food introduction has begun. This is consistent with recommendation 4 and with previous guidance from the AAAAI in 2013 and the AAP in 2019.[13,68] Although there is no harm in this practice, there is no RCT that has investigated the association between diet diversity and the prevention of food allergy. Better-designed studies, which can correct for potential reverse causality and cleaner time point assessments and assessments of health outcomes, are needed to help clarify the extent to which such a relationship may exist. Therefore, no recommendation can be made that deliberately advocates enhancing diet diversity to prevent food allergy development. However, this practice is not associated with any known harms, and culturally it is customary to have infants try various foods in the weaning period.

Question 4: What is the role for the use of hydrolyzed formula for the prevention of food allergy?

Clinical context and background. Hydrolyzed formulas (HFs), which include extensively hydrolyzed formula (eHF, typically casein-based in North America) and partially hydrolyzed formula (pHF, typically whey-based in North America), are marketed as having enhanced tolerability and reduced allergenicity, compared with intact CM formula.[53] These formulas are considered safe for use in at-risk and in not-at-risk infants.[93] However, HFs have been recommended in previous guidelines in both North America and elsewhere for the potential

prevention of allergic diseases in infants at high risk of allergy,[13,14,21,22] perhaps best established by the findings in the GINI study.[50-52]

The 2013 AAAAI guidelines state that although there is no conclusive evidence supporting HF use for prevention, for at-risk infants who cannot breast-feed over the first 4 to 6 months of life, an HF "appears to offer advantages to prevent allergic disease and CMA."[13] The 2013 CSACI guidelines recommend to use an HF only if necessary "for mothers who cannot or choose not to breastfeed," and that there is limited evidence of a protective effect associated with HF (eHF over pHF) for prevention specifically of atopic dermatitis.[14] The 2019 AAP Clinical Report states that there is lack of evidence that atopic disease may be prevented through the use of either eHF or pHF compared with a CM formula in at-risk infants who cannot breast-feed exclusively for 4 to 6 months.[68] This is a change from the previous 2008 AAP Guidelines, which had recommended HF for infants who could not breast-feed.[94]

The vast majority of data supporting HF use in at-risk infants are specific to the potential prevention of atopic dermatitis,[24,93] a topic that is both controversial due to inconsistent findings and also outside of the scope of this document. Few studies for either type of HF exist that have explored food allergy (let alone OFC-proven food allergy as opposed to reported food allergy) as an isolated outcome, apart from being grouped in with an amalgamated outcome of "atopic manifestations" along with other allergic diseases, including asthma, rhinitis, and atopic dermatitis. Many such studies are dated (performed before 1999).[24] Prevention of CMA in the first year of life as a specific outcome tends to predominate the bulk of the literature regarding food allergy—specific effects, but these studies are of low quality and use a questionable definition of CMA. Further complicating this are vacillating conclusions on the topic that have occurred in multiple meta-analyses, and retraction of a Cochrane review after publication when fraud was detected in a few included trials.[22,95] Another meta-analysis was critical overall of the lack of standardized definition as to what constituted a pHF or eHF, noting inconsistent definitions of both in the literature.[24] We noted only 1 study conducted observationally, but at a population level, the HealthNuts study, which found no association in the prevention of OFC-proven egg/peanut/sesame allergy development with the reported use of pHF before recruitment into the study at age 1 year.[96,97] The HealthNuts study did not explore CMA as an outcome.[98]

The most recent meta-analysis on this subject was published in the BMJ in 2016.[24] Boyle et al[24] examined 13 studies on the effects of HF and food allergy, noting no significant pooled difference in risk of the development of "any food allergy" attributable to pHF use (RR, 1.73; 0.79-3.8) or eHF use (RR, 0.86; 0.26-2.82) versus a standard CM formula at either age 0 to 4 or 5 to 14 years. Analysis of 19 studies noted no significant difference in the risk of allergic sensitization to food associated with HF use either. There is current debate whether all such eHFs and pHFs are equal as a class, or whether the preventative properties are specific only to particular brands, and this has been a criticism levied against this meta-analysis, given the groupings used by Boyle et al[24] assumed all pHFs and eHFs as equal for pooling.

Recommendation 6. Do not routinely prescribe or recommend the use of any HFs for the specific prevention of food allergy or development of food sensitization.

Recommendation: strong; Strength of Recommendation: A; Evidence Category: Ia-IV; Risk of Bias: moderate.

Agreement of workgroup. All 9 members agreed on this recommendation as was initially worded, which is reflected in the final recommendation.

Comment. There are no data regarding the use of an HF that have conclusively and consistently shown any protective benefit against the prevention of any specific food allergy, which was reaffirmed in a recent meta-analysis.[24] Previous guidelines hedged on very neutral to conditional recommendations regarding possible but not definitive benefit.[13,14,21] Given the lack of supporting data, use of any HF for specific prevention of food allergy is not recommended. This question is distinct from any associations that may exist for the use of HF for the prevention of atopic dermatitis, which is outside the scope of this guideline.

Question 5: What are the roles of prenatal food exposures, postnatal food exposures while breast-feeding an infant, and breast-feeding in general on the development of food allergy?

Clinical context and background. Exclusive breast-feeding is recommended by both the AAP Committee on Nutrition for 4 to 6 months of life, as well as by the World Health Organization for the first 6 months of life.[68,94,99] There are multiple health outcomes that such practice provides benefit for, including infectious immunity, but there are no data that suggest that breast-feeding is conclusively associated with the prevention of any food allergy. A 2004 systematic review did suggest possible benefit against prevention of CMA (but not other food allergies), and was the rationale behind the 2013 AAAAI guidelines suggesting this may have possible preventative benefit.[13,99] The 2019 AAP Clinical Report suggests that no conclusions can be made about the role of breast-feeding in preventing or delaying any specific food allergy.[68] However, because the World Health Organization and AAP both recommend, when possible, to preferentially breast-feed an at-risk or not-at-risk baby as a first feeding option, the recommendation to preferentially breast-feed an infant would likely not be enhanced by any specific food allergy prevention outcome. RCTs to explore preventative effects of breast-feeding versus alternative options regarding the development of food allergy are difficult to conduct, and likely unethical, which hampers the ability to provide high-certainty evidence to address this question.

The role of concurrent breast-feeding while introducing allergens in the development of food allergy is unclear. Poole et al[100] published data on the association between the timing of introduction of wheat and development of wheat allergy. In this study, introduction of wheat while breast-feeding was associated with decreased risk of parent-reported wheat allergy, but duration of breast-feeding was not.[87,100] Following from this, Grimshaw et al[88] indicated that concurrently breast-feeding while introducing CM-containing foods/drinks had a protective effect against the development of food allergy (not just CMA per se). The duration of concurrent feeding had no effect on the outcomes. Venter et al[101] found that there was no effect of concurrent breast-feeding alongside CM introduction on the development of CMA or introduction of food allergens on the development of food allergy.[102] Using retrospective, nested data,

Pitt et al[103] found in the high-risk Canadian Childhood Asthma Primary Prevention Study birth cohort that the combination of maternal peanut consumption while breast-feeding followed by infant peanut introduction in the first year of life was associated with a protective effect against peanut sensitization at age 7 years, compared with either exposure in isolation. Further information on whether allergens should be introduced while breast-feeding is needed. In the most recent review of the topic, Garcia-Larsen et al[104] noted no evidence of an association between breast-feeding, exclusive breast-feeding, or the timing of solid food introduction during breast-feeding and food allergy outcomes in a meta-analysis of 1 interventional and 259 observational studies.

Avoidance diets during pregnancy are a controversial practice. In particular, although earlier 2000 AAP guidance suggested that peanuts and other high-risk allergens should be avoided in mothers while breast-feeding infants at risk for developing atopy,[53] the latest study with respect to peanut consumption from a large, retrospective, and nested cohort suggested that consumption was protective, although outcomes were not determined by OFC in all subjects.[105] The 2013 AAAAI and CSACI and the 2019 AAP Clinical Report specifically state there is a lack of evidence to support deliberate maternal exclusion of high-risk allergens during pregnancy and while breast-feeding for the purposes of preventing allergic diseases, including food allergy, in the diets of their infants.[13,14,68] The Garcia-Larson meta-analysis noted no association with avoidance diets (CM, egg, CM/egg, or multiple foods) in pregnancy, lactation, or both, as well as what these authors described as "multifaceted interventions" where avoidance was included, and any food-allergic outcome.[104]

Evidence regarding other interventions, such as prenatal and postnatal vitamin D and probiotic supplementation, is an emerging area of investigation to determine whether there is any beneficial effect with these measures and a reduced rate of food allergy. There are limited data on vitamin D at this time with respect to food allergies, though a prospective trial is underway outside North America.[104] For probiotics, the GLAD-P guidelines currently conditionally recommend probiotic supplementation in both pregnant and breast-feeding mothers with baseline conditions that place the child at risk, mainly due to the potential preventative effects for atopic dermatitis, and not specifically for food allergy or specific prevention of a particular food allergy.[106] Garcia-Larsen et al[104] did find a significant protective association for fish oil supplementation (omega-3 fatty acid) during pregnancy and lactation against egg sensitization from 19 interventional trials (RR, 0.69; 95% CI, 0.53-0.9), but not with egg allergy or allergy or sensitization to other foods, and no association with omega-6 fatty acids. They also noted a protective association from 28 interventional trials of probiotic supplementation (single and multiple organisms given at doses between 1 and 10 million colony-forming units) for reduced CM sensitization between ages 1 and 2 years, but no other association with CMA (RR, 0.59; 95% CI, 0.36-0.96), or allergy or sensitization to other foods.[104]

Recommendation 7. We do not recommend maternal exclusion of common allergens during pregnancy and lactation as a means to prevent food allergy. We offer no recommendation to support any particular food or supplement in the maternal diet for the prevention of food allergy in the infant in either the prenatal period or while breast-feeding. While exclusive breast-feeding is universally recommended for all mothers, there is no specific association between exclusive breast-feeding and the primary prevention of any specific food allergy.

Recommendation: weak; Strength of Recommendation: B/C; Evidence Category: Ia-IV Risk of Bias: high.

Agreement of workgroup. All 9 members agreed on this recommendation. Eight of 9 as was initially worded. One member requested change to the wording to incorporate evidence from a meta-analysis regarding the effects of omega-3 fatty acid supplementation, which is reflected in the final recommendation.

Comment. Although there is some theoretical concern that *in utero* exposure to maternally consumed allergen could potentially sensitize the developing fetus and be associated with the development of food allergy in childhood, there is no conclusive nor consistent evidence that the specific exclusion of particular foods or inclusion/dietary enrichment of certain foods in the diets of pregnant mothers is associated with the development or prevention of food allergy in either at-risk or not at-risk children. There are few studies that have supported that allergens consistently pass through breast milk and has been attributed to objectively and conclusively inducing food allergy in the breast-feeding infant in controlled studies.[3] There is no conclusive evidence that the specific exclusion of particular foods, inclusion/dietary enrichment of certain foods, or the specific use of supplements or probiotics in the diets of breast-feeding mothers is associated with the development or prevention of food allergy in either at-risk or not at-risk children, which was recently confirmed in a meta-analysis.[104] Moreover, there is no evidence that formula-fed infants or nonexclusively breast-fed infants are at a greater or lesser risk of developing food allergy compared with exclusively breast-fed infants. Protective associations with omega-3 fatty acids (in the form of fish oil) and probiotic supplementation have not been associated with preventing food allergy, but have been associated with reduced the risk of egg and CM sensitization, respectively.[104]

HOW TO IMPLEMENT THESE RECOMMENDATIONS

Rectifying differences in multiple published guidelines

The authors would like to acknowledge the recent and rapidly changing landscape regarding food allergy prevention, as well as potential for confusion among parents and health care providers with multiple new recommendations and inertia to abandon formerly recommended practices. Guidance has shifted no less than 4 times now since 2000 and continues to do so in successive iterations.[12-14,53,68]

There will be many challenges in dissemination, education, and adoption of these recommendations. Primary care clinicians will have the greatest opportunity to engage all families with newborns and ideally find ways to include discussion of food allergy prevention along with other anticipatory guidance recommendations provided at each age. Repetition, confidence, and practical advice for parents will be needed to gain trust and adoption of these recommendations. To achieve this, partnerships between allergists and primary care clinicians will be important not only for timely referrals and evaluation, when indicated, but also to allow for questions and feedback

surrounding the many nuances that will surely arise. Allergists can be proactive within their communities and educate their colleagues in primary care and other specialties (eg, dermatology). In areas with limited access to allergists, outreach efforts from professional organizations may be needed to support primary care clinicians. Ultimately, a coordinated and sustained effort from all fronts will be necessary to implement these recommendations on a population level.

Accumulating evidence suggests that early introduction of peanut and cooked egg with subsequent regular inclusion in an infant's diet is likely the most effective, current strategy to prevent these food allergies from developing. Previous recommendations to avoid specific foods until after age 1 year are still followed and possibly are preferred by many parents and medical providers (eg, pediatricians, family medicine physicians, or other primary care providers), which must be actively addressed and reversed.[80] A recent nationally representative survey noted poor willingness to introduce many foods in the first year of life, which may be indicative of the extent to which this former recommended and out-of-date practice may exist.[71] All medical providers should be aware of the significant paradigm shift from avoidance to active, early feeding.

These recommendations herein build upon the recent NIAID-AG, but expand and modify that document significantly in accordance with recently published data to cover a broader range of topics for which additional but crucial data were unavailable for inclusion at the time. To successfully help decrease the prevalence of food allergy among children, these early introduction recommendations will need to be implemented on a population level, which will require ongoing education, support, and evaluation of the process, along with collaboration among primary care providers and subspecialists. A paradigm shift will be needed at the public health and primary care level for full implementation in the general population. In Australia, the EarlyNuts study provided evidence of a 3-fold increase in peanut introduction by age 1 year, with 88.6% (95% CI, 86.1%-90.7%) in the period 2017 to 2018 compared with 28.4% (95% CI, 27.2%-29.7%) in the period 2007 to 2011, largely attributed by the authors to maternal and child health nurses providing the majority of education to parents (eg, maternal and child health nurses see new parents 10 times in the first $3^1/_2$ year).[78] Although neither the United States nor Canada has this extent of public health resources, an example of a large-scale change in the general population is a simple, focused public health campaign by federal health agencies (eg, the 2020 US Department of Agriculture guidelines, which recommend early introduction of peanut and egg without mention of screening).[18] Recruiting more implementation science researchers into the field, devoting more research funding to implementation, incorporating best practices from other successful countries, and other strategies are needed, which are beyond the scope of this document. General discussion points for medical providers are provided in Table VII.

Although at a population level, universal allergen introduction at home without screening is associated with far superior health and economic outcomes compared with preassessment screening tests and in-office OFCs for these allergens, some parents and providers may still insist on this despite these not being required as per this guidance.[72,73,75,76] Therein lies the difficulty in implementing a policy that unambiguously shows superior societal benefit while balancing the reality that there may be preference-sensitive care options that patients desire (no screening, screening, and delayed introduction). The role of the allergist is to facilitate early introduction, but also to ensure that how that is accomplished fits with the family values and preferences. Therefore, we would not recommend turning away a family requesting screening before introduction, though attempts should be made to minimize any screening procedures if a family is insistent on having these done.[15,16] However, it is understood that some families, after consideration of their options, will prefer the screening approach, and may be uncomfortable with at-home introduction.[12] Again, data suggest that many families may not prefer their child to undergo preintroduction skin testing and/or undergo an OFC before 11 months of life.[71] However, if testing before anticipated introduction is performed, every effort should be made to offer an in-office introduction, either as an observed ingestion or as a graded OFC supervised by an allergist, if the parent and/or clinician is not comfortable introducing these items at home on the basis of test results. Clinicians should be aware that even for highly sensitized children, some families may still desire to introduce peanut via OFC and not rely on a cutoff value for preemptive diagnosis.

The authors would also like to acknowledge the previous inconsistency in recommendations for screening from different countries (Table V).[12,15-17] These updated recommendations should now align the guidelines across multiple different countries and professional societies. As discussed in this document, as

TABLE VII. General discussion points for parents and caregivers regarding early introduction of allergenic foods

Concept of early introduction
• Primary care providers should implement talking points surrounding early introduction into all well-child visits, beginning at birth and repeated at age 2, 4, 6, and 9 mo.
• Allergists seeing infants for conditions such as atopic dermatitis should discuss concepts surrounding early introduction with families.
• Obstetricians can introduce these concepts with expecting parents to help them increase awareness and understanding.
Benefits of early introduction
• Medical providers who discuss timing and method of solid food introduction should include discussion of the benefits of incorporating allergenic foods into the diet.
• Medical providers should also discuss that early introduction has not been associated with increased harm or risk for food allergy development.
Risk stratification
• Medical providers should identify infants at highest risk to develop food allergies and discuss that risk, along with benefits of early introduction, with families.
• Medical providers should help parents of infants at low risk to develop food allergy understand that special precautions are not necessary surrounding the early introduction of allergenic foods and encourage them to diversify their infant's diet.
Testing
• Medical providers should understand and discuss the pitfalls associated with overuse and misinterpretation of food sIgE tests.
• When deemed appropriate, medical providers should discuss the role of IgE testing before introduction of foods as a method to determine whether the food will be introduced at home or under supervision in the office setting.
• Medical providers should discuss with families that food sIgE testing in an infant who has never ingested a food is not diagnostic for food allergy and should not be used as a routine screening test.

a policy, widespread screening of all infants is not required, especially those at low risk for development of food allergy before introduction. If specific IgE testing is used, the results should guide the most appropriate manner in which to introduce the food, and the NIAID-AG recommendations are reasonable to follow in these circumstances though there should be consideration to offering in-office introduction to anyone, irrespective of the test size. Again, it is important enough to repeat that any allergen-specific IgE testing should only be used by those providers with sufficient understanding of how to interpret such results, or that these infants with positive test results should be referred to an allergist for consultation and possibly further testing (eg, skin testing and/or graded OFC). These tests have high sensitivity but poor specificity, and there are risks of overinterpreting the positive test results in infants with less robust pretest probability of a clinically significant risk.[58,107] If screening is desired by the family, a discussion of the risks and benefits of how screening skin or sIgE testing result may be interpreted in the absence of ingestion of a food is needed. This should include specific discussion with the family regarding home introduction or performing an OFC if testing result is positive, as expanded options in addition to just avoiding the food on the basis of how a large SPT wheal size may be interpreted. The vast majority of infants with positive skin or sIgE test results should still be offered consideration for an OFC, because the OFC is an essential step in verifying the significance of sensitization detected in screening, given the issue of low positive predictive value of screening tests in the absence of previous ingestion and clinical allergic reaction. It is also imperative that there is urgency for these infants with positive test results to be prioritized to have an OFC performed as soon as possible (ie, not weeks or not months later), if the parents elect to pursue this option.

Practical feeding advice for counseling parents regarding weaning and how to introduce peanut, egg, and other major allergens

The AAP Committee on Nutrition recommends exclusive breast-feeding until age 4 to 6 months in healthy, term infants.[68] Beginning no sooner than age 4 months and no later than age 6 months, and when the infant has exhibited developmental readiness, complementary foods should be offered. Developmental signs of readiness include infants holding their head up when sitting, showing interest in what others are eating, and opening mouth when food approaches.[68]

Parents may offer a single ingredient food at a time and gradually expand the variety of foods and textures offered to the infant to help balance the diet and promote acceptance of a wide variety of flavors and textures of natural foods. Typically, 1 new food may be introduced every 3 days, although there are no data to critically assess this practice as necessary, and it could prolong the introduction of new foods. Breast milk should remain the main source of nutrition in these early months. Iron is the main nutrient of concern for infants who are breast-fed or partially breast-fed (>50% of daily feeds), because breast milk alone does not meet the infants' needs for iron after age 4 months; therefore, iron-rich foods, such as pureed meat, poultry, greens, and whole grains, should be included in the early weaning diet.[108]

For the purposes of this recommendation, a peanut-containing product is meant to imply any age-appropriate peanut item that can be administered mixed in other baby foods or by itself. Infant-safe forms of peanut include diluted peanut butter. Whole-peanut kernels and chunks of peanut butter are potential choking hazards and should not to be given to children younger than 4 years.[109,110] Peanut-containing products, such as powders/flours and snacks (eg, peanut puffs), have also been used as safe forms of peanut for infants. Although Bamba was specifically used as a peanut snack in the LEAP trial and provides a dissolving textured food, it is not necessarily a long-term, healthy weaning food option; therefore, thinned, natural peanut butter or peanut flour is preferred as early weaning food.[12] Please see Appendix A in this article's Online Repository at www.jaci-inpractice.org for a list of recommended age-appropriate items and recipes.

Although a dose of 2 g protein administered 3 times a week has been recommended in the NIAID-AG on the basis of the LEAP study, and up to 250 mg of cooked egg daily was administered in the PETIT study, there is no known dose relationship to either peanut allergy or egg allergy outcome.[5,6,10] Thus, there is insufficient evidence to support a precise dose and frequency necessary to support tolerance, and we recommend parents focus on feeding amounts and types of peanut- or egg-containing foods that their child likes and tolerates with some frequency. Regular exposure for several years is felt to be more important than focusing on a particular fixed dosing interval or amount. A reasonable amount and frequency, such as 1 to 2 teaspoons of peanut butter or egg (or their equivalents—see Appendix A) at least once weekly, should be encouraged, and larger amounts if the child enjoys the food.[12]

Importantly, once peanut has been introduced into the infant's diet, consumption should not be stopped unless there are signs/symptoms of an allergic reaction (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). If an allergic reaction is suspected, the infant should be evaluated by an allergist who can perform specific testing and possibly an OFC, if necessary, to confirm the presence of true reactivity.[12] Evaluation by an allergist experienced in childhood food allergy is important in these cases because some infants in the LEAP study did go on to develop reactions at home after initial introduction was tolerated. Some of these infants were found to then be peanut-allergic, but some were not, with their apparent allergic reaction, for example, urticaria, being alternatively related to urticaria from a viral infection or contact reaction to food and not a true IgE-mediated food allergy, which is not uncommon with certain acidic fruits in which peanut (or other foods) may be mixed.[5] It is therefore important that there is urgency for infants referred under these circumstances to be seen as soon as possible, within days, to prevent any unintended downstream harm from removing a food from the infants' diet and having them wait weeks to months for a visit.

Egg or egg-containing products should be introduced in a well-cooked form. Introduction of raw forms of egg (including ingestion of raw, pasteurized dehydrated egg white) is not recommended, because these may be associated with a higher risk of reactivity compared with more cooked forms of egg.[16] There is no evidence that baked egg is protective, though this is an age-appropriate form for infants once egg tolerance is demonstrated. As with peanut, tree nuts in the shelled form should not be introduced until age 4 years because of choking hazard, but tree nut butters are available as a safe alternative for infants. Tree nut choices should be reflective of the cultural dietary preferences, and it is unclear whether particular tree nuts are more

important to be exposed to than others. Sesame can be introduced in a safe form, such as hummus or tahini paste mixed with other pureed foods. Fish and shellfish may be introduced when an infant is tolerating appropriate staged foods (see Appendix A for suggested foods containing these major allergens); more guidance on fish consumption can be found at the US Foof and Drug Administration website.[111] Once these foods are eaten and tolerated, they should be incorporated regularly into the infant's diet, again in accordance with family and cultural preferences, because there are no data to determine the amounts and frequencies of which to consume these other foods.[6,16]

CONCLUSIONS

There is strong evidence that early introduction of peanut and egg within the first year of life can prevent the development of food allergy to these respective foods. Screening infants for evidence of sensitization to peanut and/or egg before initial introduction is not required, though this may be a preference-sensitive care choice for some families. If screening is performed, the clinician should encourage consideration for offering all sensitized infants an OFC to determine an objective outcome of allergy or tolerance, rather than rely on poorly predictive values of sensitization. The key is to minimize delay when peanut is to be introduced, in particular if in-office introduction cannot be done promptly after screening. If considered, an OFC should be prioritized to be done shortly after testing, to minimize delays and maximize benefit. With respect to other potentially allergenic foods (CM, soy, wheat, tree nut, sesame, fish, shellfish), there are observational data suggesting harm from intentional delayed introduction, and although no RCT suggests benefit from early introduction of these items, there are no data suggesting that doing so beginning at around 6 months of life is harmful. Along these lines, observational data support a potentially beneficial preventative effect for a diverse and varied infant diet in the first year of life without suggestion of harm, which would be in accordance with not delaying the introduction of any potentially allergenic food. There is no clear preventative role for the use of any form of HF for the specific prevention of food allergy as opposed to the prevention of other potential atopic manifestations. Exclusive breast-feeding for at least 4 to 6 months has not been associated with protection against the development of food allergy (with or without excluding any food in the maternal diet while doing so), though exclusive breast-feeding has multiple other health benefits to the child and is universally encouraged. Prenatal or perinatal maternal or infant use of supplements also has no clear role in the prevention of food allergy, though maternal probiotic omega-3 fatty acid supplementation may protect against the development of milk and egg sensitization in the infant.

These recommendations are aimed to help inform the primary care and allergy practicing clinician regarding the best current practices for infant feeding and food allergy prevention. These have evolved considerably since the last AAAAI update in 2013, as well as the NIAID-AG in 2017, and likely will continue to do so, requiring an iterative process to maintain an up-to-date knowledge base to best advise all stakeholders, with a focus on the United States and Canada as represented in this consensus document.

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ONLINE REPOSITORY

Appendix A
Common questions regarding early peanut and other major allergen introduction

1. I thought peanuts can cause choking in children younger than 5 years; can I give it to my baby?

Yes—that is true—whole, shelled peanuts and lumps of peanut butter should not be given to children younger than 5 years due to the risk of choking; this is pretty much a recommendation all across the world. The new NIH guidelines recommend that you give your baby peanut puffs (eg, Bamba), smooth peanut butter mixed with hot water and then cooled down, peanut flour, or peanut powder.

2. Why 2 g peanut protein, 3 times per week?

The amount of peanut used in the LEAP study was based on the median monthly consumption of 7.1 g peanut protein in Israeli children where peanut allergy prevalence is relatively low, when recalled by parents up to several years after the fact. It is an approximate target to achieve, rather than a rigid requirement that has to be met.

3. What does 2 g of peanut look like, or is it actually 2 g of peanut protein?

It is 2 g of peanut protein. The NIH guidelines list the following options for giving 2 g of peanut protein:

- 17 g Bamba (another peanut puff that is very similar to Bamba is called Cheeky Monkey)
- 9-10 g peanut butter depending on the brand
- 8 g of ground peanuts
- 4 g defatted peanut flour (eg, defatted peanut flour from the Golden Peanut Company) or peanut butter powder (eg, PB2 powder or PB fit)

4. I don't have kitchen scales …does that matter?

No—these amounts do not have to be that exact. Remember, these are all approximate dosing targets.

- 17 g of peanut puffs is about two-third of a bag of Bamba
- 9-10 g peanut butter is either 2 level measured teaspoons or a "round full" teaspoon
- 8 g of ground peanuts is $2\frac{1}{2}$ level measured teaspoons
- 4 g of peanut flour or peanut butter powder is 2 level measured teaspoons

5. What if my baby is sick and won't eat, or if they are full and have not eaten the full portion?

We just do not know if smaller amounts or less frequent feeds will be as protective against the development of peanut allergy. Although there is certainly no evidence that lesser amounts would be a problem, there is no evidence to suggest lesser amounts would not be a problem, making a definitive recommendation here difficult to make. According to the LEAP study authors, some of the babies got ill (as babies do) and some did not actually finish every feed, though most did, so it is unclear if this truly made a difference. The main thing is to be as consistent as possible with regular peanut intake, even if your baby does not eat the full dose. The dosing amount and frequency are targets, and based on data of what worked in a trial, but were not otherwise specifically chosen from evidence suggesting that these recommendations compared with others were proven to work better.

6. What if my baby/child loves the peanut puffs and want to eat more?

Yes! Some babies are good eaters and love peanut flavor. Eating more is allowed; I also think that older children (peanut was given up to age 5 years in the LEAP study) may not be happy if you remove the bag of Bamba once two-third of the bag is eaten. In the LEAP study, the median amount of peanut protein in the consumption group was 7.7 g (interquartile range, 6.7-8.8 g).

7. I don't think my baby will eat the peanut-containing foods in the NIH guidelines; is there anything else I can try?

We would say first try different options of the foods listed in the NIH guidelines. Peanut powder mixed with mango puree tastes very differently from diluted peanut butter mixed with baby rice or carrot puree. You could also try to crush the Bamba, dissolve it in water, and mix it into the baby's pureed foods.

During the development of the NIH guidelines, we looked at other options, such as peanut-containing breakfast cereal or peanut-containing candy (chocolate) and found that either the portion sizes would be too large (eg, up to 6 cups of cereal) or the fat, sugar, or salt content would be unsuitable for young children to meet the 2 g peanut protein target. If you are adventurous in the kitchen, try to bake low-sugar peanut cookies/biscuits—1 cookie contains about 0.8 g of peanut protein, which means 2 to 3 cookies should give around 2 g of protein—or cook peanut soup!

Any dietitian (irrespective of their knowledge of food allergy) can help you to find out what the peanut protein content of a food is by calculating it from the label (if peanut is the only ingredient) or from information obtained from the manufacturer. I am sure they will be happy to help ensure that you use foods that are culturally accepted and favorites of the family!

8. Which solid foods are best to start with?

In terms of introduction of solid foods, just use the usual advice about starting solid foods as suggested by the country in which you live. In most situations, this will be vegetable or fruit purees or infant fortified-cereal-rice/oat.

9. What about other major allergens?

We suggest introducing other allergens once a number of solid foods have been introduced and peanut-containing foods are eaten without any reactions. Introducing new allergenic foods one at a time over a 3-day period is a common recommendation (that fits a more common sense than evidence-based approach) that may be relevant for some children, and we suggest that you discuss this with your physician. There is no specific order in which the other allergens should be introduced, and no specific wait time between new foods that is required or shown to work. In the EAT study, wheat was always introduced last. For ways to introduce the other allergens, see our suggestions at the end of the post.

- Milk—If you have not given your baby infant formula, we suggest to start with milk in baked foods or yogurt (cheese can be given later in infancy from around 6 to 7 months).
- Egg—Give fully cooked/baked egg to start with (such as low-sugar cookies, muffins, or pancakes) rather than soft boiled egg/poached egg/raw egg powder/pasteurized egg, which have led to reactions in young infants in previous studies. Under-cooked egg is also not recommended for children younger than 1 year.
- Soy—Offer you baby soy milk, soy yogurt, or tofu (there is not much protein left in soy sauce, and the salt content is very high— best to avoid these).
- Fish/Shellfish—Did you know that there are more than 700 species of fish and shellfish in the sea? It is therefore impossible to give all these to your baby just to be able to tick the "fish box." We suggest that give your baby a few portions of the fish/shellfish species that you tend to eat as a family and continue with regular intake. (Don't give more than 2 portions of fatty fish per week according to the Food and Drug Administration [USA]) and Food Standards Agency [UK] guidance.)
- Sesame—Try some hummus and tahini (sesame-containing sweets/candy can be given to older children on occasion but be aware of the sugar content).
- Wheat—Softly cooked pasta (which also makes a great finger food), bread fingers (if you already started to give wheat in egg-containing baked goods such as sugar-free cookies/pancakes, feel free to continue with these as well).

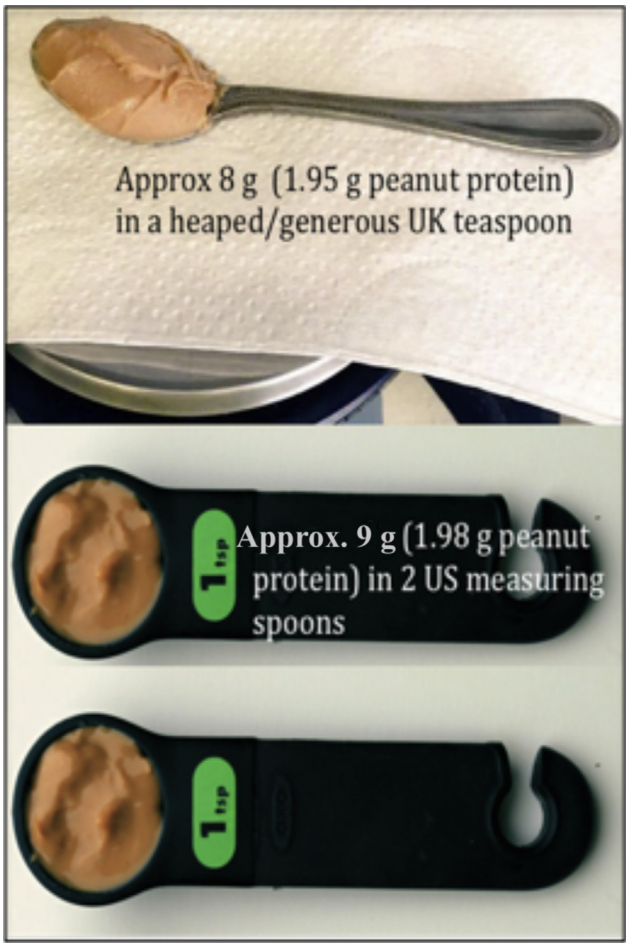

FIGURE E1. Dosing quantity conversion for measuring spoons for peanut butter. Photo courtesy of Dr George DuToit.

TABLE E1. Diet diversity studies with associated diet diversity definitions

Reference	Diet diversity definition
Austria, Finland, France, Germany, and Switzerland Roduit et al,[E1,E2] 2012 and 2014	To define diet diversity, parents indicated the food item that was given to the child in the last 4 wk. Food diaries were completed monthly between age 3 and 12 mo. The diversity score was based on major food items, defined as food introduced in the first year of life to at least 80% of the children over these 5 countries. The food diversity score is a total count of the number of different food items included in the child's diet. Diet diversity for the analysis shown was based on introduction of 6 food items (vegetables or fruits, cereals, bread, meat, cake, and yogurt) introduced in the first year of life.
New Zealand Fergusson et al,[E3-E5] 1981, 1982, 1990 Fergusson and Horwood,[E6] 1994	Intake of CM, cereals, vegetables, dairy products, meat, fruit, egg/related products, other foods determined at 1 time point.
Germany GINI study Schoetzau et al,[E7] 2002 Filipiak et al,[E8] 2007	Food groups: dairy products, egg, cereals, legumes, vegetables, fruits, nuts, meat products, fish, and other foods—determined once at 4 mo and 6 mo.
Germany LISA study Schoetzau et al,[E7] 2002 Zutavern et al, 2006[E9] Zutavern et al,[E10] 2008 Markevych et al,[E11] 2017	Timing of introduction of 48 solid food items into child's diet was collected at age 4 and 6 mo and at 1 y. Forty-eight food items were grouped into 8 food groups: (1) vegetables (avocado, cauliflower, beans, broccoli, peas, cucumbers, carrots, potatoes, white cabbage, turnip, cabbage, lenses, celery, asparagus, spinach, tomatoes, onion, vegetable juices); (2) fruits (apples, pineapples, apricots, bananas, pears, strawberries, peaches, citrus fruit, fruit juices); (3) cereal (bread/pretzels/rolls, cookies/cakes/rusk, rolled oats, muesli, millet, cornmeal/corn starch, wheat semolina/starch, noodles, rice/rice starch, spelt); (4) meat (poultry, lamb, veal/beef, pork, sausages); (5) egg; (6) dairy products (cow milk/cream, yogurt/quark/cheese); (7) fish; and (8) other (nuts, soy products, cocoa/chocolate).
Finland Nwaru et al,[E12,E13] 2014 and 2013	Food groups: CM and infant formula; potatoes; carrots; turnip; fruits and berries (as a combined variable); cereals (rye, wheat, oats, and barley as a combined variable); other cereals (maize, rice, millet, and buckwheat as a combined variable), meat; fish; egg; cabbage; spinach; and lettuce—determined at multiple time points.
Italy Turati et al,[E14] 2016	Food groups: vegetables, legumes, or roots (potatoes, carrots, tomatoes, and beans), fruits (apples, pears, peaches, apricots, plums, citrus fruits, red fruits), cereals (maize/tapioca, rice, pasta, and gluten-free pasta), meat (poultry, pork, and beef), dairy products (cheese, and other dairies), fish, eggs, and nuts/cacao/chocolate. Determined at multiple time points.
UK Venter et al,[E15] 2020	Diet diversity was measured using 21 foods commonly introduced in the first year of life including fruits, vegetables, meat and poultry, grains, egg and milk products as well at the major food allergens.

GINI, German Infant Nutritional Intervention.

TABLE E2. Signs and symptoms of an allergic reaction in infants[E16-E19]

Target organ	Signs and symptoms
Skin/subcutaneous tissue*	Systemic urticaria, angioedema, flushing
Upper respiratory tract	Rhinorrhea, sneezing, nasal congestion
Lower respiratory tract	Cough, wheeze, stridor, shortness of breath, respiratory distress (intercostal retractions, accessory muscle use)
Gastrointestinal tract	Persistent profuse vomiting, diarrhea
Cardiovascular	Tachycardia, hypotension
Central nervous system	Behavioral change (irritability, inconsolable crying, clinging to caregiver, lethargy)

Working definition of anaphylaxis applies to children of all ages, including infants.[E19]

*Most common organ system involved in allergic reactions in infants.

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