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Special Article

Introduction of food in the first year of life and food allergy prevention: what is the evidence?

Introdução dos alimentos no primeiro ano de vida e prevenção da alergia alimentar: quais as evidências?

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ABSTRACT

Objective: The incidence of allergic diseases has increased in recent decades. In an attempt to contain the increase in food allergy (AA) over the years, prevention strategies have been implemented. To promote a better understanding of the dilemmas that permeate the introduction of food in the first year of life, this article deals with a narrative literature review on the introduction of complementary foods in the first year of life and possible associations with the primary prevention of food allergy. **Data source:** Relevant publications were searched in the Cochrane Library, MEDLINE, PubMed, Guidelines International Network, National Guidelines Clearinghouse, and revised recommendations from the national food allergy guide and consensus. **Results:** Several observational studies and randomized controlled trials are available, as well as recommendations. published by scientific organizations; however, of variable quality. Recommendations from clinical practice guidelines classified as high quality and recent publications not yet systematically categorized in their quality, but internationally recognized as relevant to primary care, were considered. **Conclusion:** To date, there is no consistent evidence that the early introduction, before 6 months, of allergenic foods contributes to the prevention of food allergy in the general population.

Keywords: Primary prevention, food hypersensitivity, infant food, child development, eating.

RESUMO

Objetivo: A incidência das doenças alérgicas cresceu nas últimas décadas. Na tentativa de conter o aumento da alergia alimentar (AA) ao longo dos anos, estratégias de prevenção vêm sendo implementadas. Para promover um melhor entendimento dos dilemas que permeiam a introdução alimentar no primeiro ano de vida, esse artigo trata de uma revisão bibliográfica narrativa sobre a introdução dos alimentos complementares no primeiro ano de vida e possíveis associações com a prevenção primária da alergia alimentar. **Fonte dos dados:** Publicações relevantes foram pesquisadas nas bases de dados Cochrane Library, MEDLINE, PubMed, Guidelines International Network, National Guidelines Clearinghouse e revisadas recomendações do guia e do consenso nacional de alergia alimentar. **Resultados:** Estudos observacionais diversos e ensaios clínicos randomizados estão disponíveis, bem como recomendações publicadas por organizações científicas; no entanto, de qualidade variável. Foram consideradas as recomendações de diretrizes de prática clínica classificadas como de alta qualidade e publicações recentes ainda não categorizadas de forma sistemática em sua qualidade, mas internacionalmente reconhecidas como relevantes para a atenção primária. **Conclusão:** Até o momento, não há evidências consistentes de que a introdução precoce, antes dos 6 meses, dos alimentos alergênicos, contribua para a prevenção de alergia a alimentos na população geral.

Descritores: Prevenção primária, hipersensibilidade alimentar, alimentos infantis, desenvolvimento infantil, ingestão de alimentos.

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The incidence of pediatric atopic diseases has increased in recent decades.[1] Genetic and environmental factors, in constant interaction since the intrauterine period, constitute the pathophysiological basis of these diseases.[2] AtIn an attempt to contain the increase in food allergy (AA) over the years, prevention strategies have been implemented, among them, changes ins eating habits, notably in the introduction of food in the first year of life.[3]

In the 1990s, delaying the introduction of the most allergenic foods in the child's diet was the strategy adopted.[4] However, these recommendations have not been scientificallysustained as new studies emerged and suggesting if it would not be early consumption of allergenic foods the best way for the induction of oral tolerance.[5]

Clinical trials were designed to test the "Allergen Exposure Route Hypothesis", according to which early consumption of food allergens could induce oral tolerance, while allergic sensitization to food allergens could occur transcutaneously.[6-12] However, the methodological diversity of these trials brought conflicting results, andthe incorporation of the new recommendations has become a challenge in regions with prevalence of AA, socioeconomic conditions and different eating habits.[13]

To promote a better understanding of the dilemmas that permeate the introduction of food in the first year of life, this article deals with a narrative literature review on the introduction of complementary foods in the first year of life and possible associations with the primary prevention of food allergy, through questions and answers on the main controversies on the subject, adapting scientific evidence to clinical practice.

Is the definition of early or late introduction of complementary feeding uniform in literature?

The results of the studies still show controversies about the ideal moment[14] and few conclusions can be assumed to be definitive.

In 2001, the World Health Organization (WHO) published a systematic review with the objective of evaluating the scientific evidence about the ideal period for the practice of exclusive breastfeeding. The authors concluded that exclusive breastfeeding for six months should be instituted, instead of the previous orientation, for four to six months, in view of the numerous evidences of short- and long-term benefits for the mother-child binomial and for society.[15] In agreement, the "Food Guide for Brazilian Children Under 2 Years Old" by the Ministry of Health, published in 2019,[16] and the "Practical Feeding Guide for Children 0 to 5 Years Old – 2021", prepared by the Brazilian Society of Pediatrics,[17] recommend exclusive breastfeeding until the 6th month of life.

From six months of age, other foods should be part of the child's meal. The transition to family meals should occur around 12 months.[16,17] With these milestones, we can define, for our population, early introduction as the offer of foods complementary to breast milk before six months of age. On the other hand, in the light of current knowledge, the offer of potentially allergenic foods after 12 months of age would be considered a late offer. However, these definitions are no longer so evident in situations where breastfeeding is not possible, or is insufficient.

Recommendations from other countries and entities may differ from those recommended by the WHO[15] and Brazil.[16,17] The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends starting the introduction of complementary foods between four and six months of age (17th and 26th weeks of life), and should not be introduced before four or delay beyond of six months.[18]

The early introduction of complementary feeding may have a role in the development of food allergy?

Two decades ago, it was believed that allergic sensitization to foods occurred through oral exposure and, therefore, preventing AA translated into delaying the introduction of potentially allergenic foods.[19] However, despite the delay in this introduction, the prevalence of AA continued to increase, which led specialists to reassess the recommendations and develop new prevention strategies, one of which focused on the ideal time to introduce allergenic foods into the diet of children.[20]

Observational and in vitro studies in animals and humans have demonstrated transcutaneous sensitization to food allergens through inflamed skin, with eczema.[21-23] Data published by Fox et al. suggested that high levels of environmental exposure to peanuts during childhood could promote sensitization rather than tolerance.[24] An ecological study evaluating the prevalence of peanut allergy in infants in Israel and the UK found a significantly higher rate in the UK (1.85% vs. 0.17%). An explanation for this difference, favoring tolerance, would have been

the early consumption and in greater amounts of peanuts in Israeli children.[25]

Based on previously published data, researchers have developed the "Allergen Exposure Route Hypothesis" as one of the new prevention strategies. She suggested that the balance of exposures during the first year of life, whether through the skin or the intestine, would prepare the immune system for allergy or tolerance, respectively.[26]

Clinical trials were needed to test the new hypothesis. The Learning Early about Peanut Allergy (LEAP) study was the first clinical trial designed to demonstrate whether the introduction of peanuts before one year of age could serve as effective primary and secondary prevention strategies in peanut allergy.[6] The introduction of peanuts, between 4 and 11 months of age, significantly reduced the frequency of peanut allergy among children, sensitized or not, classified as high risk, due to egg allergy and/or severe atopic dermatitis.[6] The results demonstrated raised questions: would the benefit of the early introduction of peanuts also be found with other foods and in the general population?

The Enquiring About Tolerance (EAT) study evaluated whether the introduction of six common allergenic foods (peanuts, milk, egg, wheat, fish and sesame) could prevent AA in 1,303 infants from the general population, exclusively breastfed up to three months of age.[7] According to the intention-to-treat analysis, 5.6% of infants with early introduction, between three and six months of age, developed AA to at least one of the six foods at three years of age, whereas in the standard group , fed solids from 6 months of age, the rate was 7.1%, a difference not statistically significant. However, in the per-protocol analysis, a significant reduction in allergy was demonstrated between different foods (2.4% vs. 6.4%), more specifically to egg and peanut, in the early introduction group, between 3-6 months, suggesting that the introduction of food in a "time window" could prevent food allergy[7].

Unfortunately, the dropout rate from the EAT study was very high, 69.1% of infants recruited, representing an important bias in the per-protocol analysis. Analyzing the protocol adherence rate for each food, the lowest value was found for the egg (43.1%), suggesting that the consumption of boiled egg could be the main factor for abandonment.[27]

Randomized placebo-controlled clinical trials were designed to assess the preventive effect of early egg introduction in AA7-12 (Table 1). Among the evidence, there were methodological differences related to the type of food chosen, the form of presentation of the food, the dose of allergenic protein consumed, and the outcome sought (Table 1). These differences generated varied conclusions, sometimes antagonistic, and not always comparable.[2]

Currently, although the strength of evidence is greater for the introduction of peanuts in a high consumption population, such as the United States, studies with other allergenic foods, such as eggs, have also shown a benefit in not delaying their offer during the food transition. However, further studies are needed in larger populations, with different diets and environmental exposures to generalize and assess the safety of this potential preventive strategy.

In which populations does the age of introduction of potentially allergenic foods deserve consideration in the food allergy scenario?

Genetics have a strong influence on the prevalence of food allergies. A child has a sevenfold increased risk of peanut allergy if they have an affected parent and/or sibling.[28] Monozygotic twins have a 64% probability of peanut allergy if their twin is allergic.[29] However, research substantiates that, by themselves, alterations or genetic factors do not explain the increasing prevalence of AA.[28,29]

According to international recommendations, a child at high risk for developing food allergy is defined as when one or more family members (parents and/or siblings) have eczema, food allergy, asthma or allergic rhinitis.[2] The LEAP study in 2015 considered two factors as high risk for peanut sensitization and allergy: severe eczema and/or egg allergy.[6]

In groups at risk for atopy, not delaying the introduction of allergenic complementary foods has been shown to protect against the development of food allergy.[6,8-12] However, a concern is the possibility of previous sensitization to the food to be introduced, including the chance of immediate clinical manifestations.[6] Although some allergic reactions were observed in the LEAP[6] study, there is no recommendation for tests to search for specific IgE in foods, as a routine for food introduction. The exceptionality of food allergy, in this situation, would not justify the recommendation of this conduct, which is difficult to implement in terms of public health and

which could even bring harm due to the delay in food introduction.[30]

Other aspects are cultural issues, family preferences and specific risks, such as the parents' fear of introducing food when the other child has this type of allergy. It is important to establish a trusting doctor-family relationship and guide the family that a child considered to be at "high risk" for developing food allergy will not necessarily develop it.

Do formulas for artificial breastfeeding have an impact on the outcome of food allergy?

Given the impossibility of exclusive breastfeeding, polymeric infant formulas should be introduced to children without allergy symptoms, in accordance with international and national recommendations.[15-17] However, a recent guideline updated by the European Academy of Allergy and Clinical Immunology (EAACI) reinforces the need to avoid supplementation of breast milk with infant formula in the first week of life, which is associated with a greater chance of developing allergy,[31,32] in addition to increasing the risk of early weaning, according to the WHO.[15]

The main considerations regarding infant formula and food allergy prevention are derived from the German GINI (German Infant Nutritional Intervention Study). In this study, 2252 children at risk for allergies (one allergic first-degree relative) were randomized (blinded for the first three years) to receive either standard cow's milk formula or hydrolyzed formula (partially or extensively hydrolyzed whey protein). or extensively hydrolyzed casein formula) in the first four months of life, when exclusive breastfeeding was not possible. Allergic outcomes of this study have been evaluated for the last 20 years. In the last publication, the authors concluded that extensively hydrolyzed

Table 1
Clinical trials on egg introduction and allergy prevention

Test name, country	Population	Type of food	Proteins	Intervention period months (m)	Result in the analysis by ITT (P value)
EAT[7], UK	General	Milk, peanuts, eggs, sesame, fish and wheat	4 g/week	3 to 6 m	RR, 0.69 (95%CI, 0.40-1.18); p = 0.17
STAR[8], Australia	High risk (child with moderate eczema)	Pasteurized raw egg	0.9 g/day	0-8 m	RR, 0.65 (95%CI, 0.38-1.11); p = 0.11
HEAP[9], Germany	General	Pasteurized raw egg	2.5 g 3 times/week	4 to 12 m	RR, 2.2 (95%CI, 0.68-7.14); p = 0.24
STEP[10], Australia	Moderate risk (atopic mothers)	Pasteurized raw egg	0.4 g/day	4-10 m	Adjusted RR, 075 (95%CI, 0.48-1.17); p = 0.20
BEAT[11], Australia	Moderate risk (first-degree relatives with allergies)	Pasteurized raw egg	0.35 g/day	4-8 m	OR, 0.46 (95%CI, 0.22-0.95); p = 0.3
PETIT[12], Japan	High risk	Freeze-dried boiled egg	0.175 mg/day ai-3 months 0.875 mg/day ai-3 months	4-12 m	RR, 0.222 (95%CI, 0.22-0.95); p = 0.0012

EAT = Enquiring About Tolerance, STAR = Solids Timing for Allergy Research, HEAP = Hen's Egg Allergy Prevention, STEP = Starting Time of Egg Protein, PETIT = Prevention of Egg Allergy with Tiny Amount Intake, BEAT = Beating Egg Allergy Trial, ITT = analysis by intention to treat, OR = odds ratio, RR = relative risk, 95%CI = 95% confidence interval.

casein formulas and partially hydrolyzed whey protein formulas reduced the prevalence of eczema and asthma.[33] However, a systematic review in 2018 concluded that there was no substantial evidence proving that the use of hydrolyzed formulas prevents allergic diseases.[34]

Therefore, we should encourage exclusive breastfeeding up to six months of life, avoid the use of polymeric formulas in the first week of life, even if it is for the purpose of complementation. There is still no evidence that hydrolyzed formulas prevent allergies when breastfeeding cannot be maintained. There is also no evidence that delaying the introduction of cow's milk protein intake prevents allergy.

Should early introduction for allergy prevention be instituted for all foods?

Clinical trials have provided evidence that the early introduction of peanuts and chicken eggs decreased the incidence of peanut and egg allergy in infants at high risk of developing AA. Studies on prevention of other food allergens have been less robust and have shown evidence of safety, but not necessarily efficacy.[35]

Regarding the introduction of cow's milk (CM), whether in the form of infant formula, raw milk or yogurt, there is no robust evidence that early introduction plays any protective role. Its introduction in the first days of life can contribute to the development of food allergy,[32] however, the introduction from 3-4 months or after 6 months did not show any difference in effect in relation to food allergy.[36] Likewise, there is no evidence to justify the delay in the introduction of CM proteins after 12 months of life.[37] Regarding special infant formulas, partially or extensively hydrolyzed, data published in a systematic review no longer justify their use for the prevention of allergy to cow's milk proteins (CMPA).[34,38] Numerous international societies are revising the recommendations of introducing special hydrolyzed formulas for the prevention of CMPA, instead of using conventional infant formulas. However, in the last GINI publication in 2021, the authors concluded that extensively hydrolyzed casein and partially hydrolyzed whey protein formulas reduced the prevalence of eczema and asthma.[33]

Regarding the introduction of eggs, studies vary greatly in terms of the recommended dose, the type of exposure (whether whole egg, or raw or cooked pasteurized whites) and the selected population (presence of atopic dermatitis or increased risk of atopy).[2,6,40] A systematic review and meta-analysis, published in 2016, involving the grouping of five studies, with 1,915 participants, showed that the early introduction of eggs (between 4 and 6 months) was associated with a significant reduction in egg allergy.[39]

According to the position of the European Food Safety Authority, this evidence is of low to moderate confidence, and therefore insufficient to support the introduction of the egg at 3-4 months of age in all infants, for the prevention of allergy. In the studies, no serious adverse reactions were observed with the boiled egg, but when the intervention consisted of pasteurized raw egg powder, some anaphylactic reactions occurred. Therefore, products containing raw eggs, even if pasteurized, should be avoided.[30,41] Boiled eggs should be introduced into children's diets, similarly to other complementary foods, around 6 months of age.[30,41]

British Society of Allergy and Clinical Immunology (BSACI) guidelines suggest that eggs and peanuts can be introduced as part of the family diet in high-risk infants between 4-6 months of age. However, they recommend the introduction of the egg before the introduction of peanuts, because sensitization to the egg seems to occur earlier.[42]

Regarding the introduction of peanuts, a meta-analysis showed moderate evidence from two studies (1,550 participants) that the introduction of peanuts between 4 and 11 months was associated with a reduction in peanut allergy.[40] According to the position of the European Food Safety Authority, there is evidence that introducing peanuts during the first year of life, compared with avoiding them until 5 years of age, reduced the risk of developing peanut allergy. However, evidence is insufficient to conclude whether, when comparing infants who were introduced to peanuts at ≤ 6 months of age with those who were introduced at > 6 months but still within the first year of life, a similar effect.[41] American guidelines recommend the introduction of peanuts to infants between 4 to 6 months of age in countries with the highest peanut consumption.

The HealthNuts study reported that cashew nut intake for high-risk patients (severe atopic dermatitis and/or egg allergy)[27] before 1 year of age (n = 140) was associated with no cases of cashew allergy at 6 years.[44] There are no studies available on the safety or efficacy of the early introduction of other nuts, soybeans or shellfish.[35]

In light of current knowledge, there is no consistent evidence that the early introduction, before 6 months, of allergenic foods contributes to the prevention of allergy to these foods in the general population.[30,40]

Can the recommendations for the complementary introduction of external studies be widely applied in Brazil?

It is known that the introduction of complementary foods together with breast milk reduces the amount ingested and, consequently, all its immunological benefits, such as the prevention of infections and reduction of infant mortality, and non-immunological benefits, such as the optimized absorption of iron and zinc. via breast milk by the infant, which will be reduced.[16,17] The literature does not allow establishing whether breastfeeding has any protection in relation to AA.[45] It is suggested that the introduction of allergenic foods while the child is breastfed may have a protective effect, but there is insufficient evidence in this regard.[45] Although the results of the EAT study showed that there was no reduction in breastfeeding rates with the introduction of solid foods from 3 months of age, there are no proven data on the risk nor on benefit of the reduction of exclusive breastfeeding in a country like Brazil, with high poverty rates, food insecurity and malnutrition, where breast milk guarantees effective nutrition security for the infant.

The first motor skills indicative of developmental readiness for spoon feeding can be observed between 3 and 4 months of age. At this age, it can be assumed that the search and extrusion reflexes may also have diminished in some babies. In preterm infants, the developmental milestones required for feeding are also reached around the same age group (post-term), depending on the severity of the illness experienced during the neonatal period, the degree of prematurity, and any sequelae.[41]

Accordingly, the EAT was the only early introduction trial (3 months) with multiple allergens simultaneously.[7] Parents should offer their children, from 3 months of age, along with breastfeeding, boiled eggs, peanut butter, cow's milk yogurt, cooked white fish, sesame paste and wheat-based cereal.[7] However, the adherence of the intervention group was much lower than that of the control group (31.9% vs. 92.9%).[7] The likely reasons for the low adherence were the difficulty in cooking certain foods and the palatability.[7]

There is no evidence that the order of introduction of the various solid foods contributes to a greater or lesser risk of food allergy.[47] Thus, timely food introduction should follow the dietary habits of families, allowing the child to have contact with all food groups between 6 and 12 months of age.[17] There is no reason to delay the introduction of potentially allergenic foods (eggs, cereals, milk proteins, meat and fish) beyond 1 year of age, nor to advance exposure to potentially allergenic foods to before 6 months of age.[47] Nuts, peanuts and seafood can also, and ideally should, be introduced to the child during this period.[17]

For children at high risk of developing food allergies, those with severe eczema, egg allergy, or both, guidance from the US Institute of Allergy and Infectious Diseases, in relation to peanuts, its introduction between 4 and 6 months of age, occurs after performing the prick test or serum IgE specific for peanuts and, when necessary, performing the oral provocation test.[48] However, this would imply that all high-risk children have access to a specialized allergy service for testing the main allergens – in this case, peanuts, which is unfeasible in most countries, including Brazil.[46] So this is yet another question that remains open, waiting for more evidence.

What other factors, in addition to complementary feeding, can interfere with the outcome of food allergy?

Genetic, environmental and dietary factors can influence the occurrence of food allergy.[49] Among the genetic factors, those that predispose to defects in the filaggrins and, consequently, in the skin barrier, facilitate transcutaneous sensitization.[50] In this rationale, we sought to assess whether the use of moisturizers was likely to reduce early transcutaneous sensitization, thus preventing the development of food allergy.[12] To date, the results have not confirmed this hypothesis, as evidenced in a systematic review. However, it is argued that perhaps more specific moisturizers can bring more promising results.[50]

Living with animals and other people can be considered protective environmental factors, while the use of antibiotics, cesarean delivery and acid secretion inhibitors are risk factors.[51] Regarding diet,has been studied as protective factors for breastfeeding, use of probiotics and preference for foods prepared at home and with high fiber content.[49] A study with 1,628 children showed that a maternal diet during pregnancy rich in processed and sugary products, combined with a longer period of breastfeeding, may

favor food allergy, suggesting a harmful effect of trans fats in children.[51] More studies with supplementation of short-chain fatty acids and fiber are needed,[52,53] in addition to studies to confirm the immunomodulatory effects of vitamin D and antioxidants in the prevention of food allergy.[54,55]

Regarding the effect of probiotics,it is known that may have a role in inducing regulatory T cells in the mucosa, reinforcing the epithelial barrier and protecting against sensitization to food allergens.[56] It is not clear what the ideal time for intervention would be, but according to a multicenter study, perhaps the age of 3 to 6 months is a window during which the intestinal microbiota can influence food allergy.[53] Clearer definitions of healthy and allergenic microbiomes are needed, taking into account that they vary across different ages, regions, risk groups and social classes. Although probiotics show promise in preventing food allergy, a recent systematic review by the European Academy of Allergy[57] and the World Allergy Organization concluded that data are insufficient to recommend supplementation with probiotic, prebiotic, symbiotic or fecal transplant in food allergy, due to the limited and low level of quality of evidence, whether in the child or the pregnant woman.[58]

Roduit et al. evaluated that, in a cohort of 301 children, consumption of yogurt, fish, vegetables and fruits in the first year of life was associated with an increase in butyrate, a metabolite of the healthy microbiota, in the feces of children at age 1 year and reduced sensitization to food allergens up to the age of 6,[59] reinforcing the concept that a varied and healthy diet is important for the development of oral tolerance.[60]

Conclusion

Although in the literature there is no more evident standardization of what we consider early food introduction, we already have enough data to demonstrate that delay in food introduction is strongly associated with a higher risk of food allergies and, considering the various benefits of breastfeeding, it is suggested that the timely introduction of complementary feeding should not be carried out before six months of age, and that, from that age onwards, even potentially allergenic foods can be introduced into the diet, ideally within the first year of life, preferably while breastfeeding and maintaining a routine consumption, respecting the family's eating habits.

References

1. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention and management. J Allergy Clin Immunol. 2018;141:41-58.
2. Baker MG, Nowak-Wegrzyn A. Food allergy prevention: current evidence. Curr Opin Clin Nutr Metab Care. 2020;23(3):196-202.
3. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129(5):1187-97.
4. Fiocchi A Assa'ad A, Bahna S; Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. Food allergy and the introduction of solid foods to infants: a consensus document. Ann Allergy Asthma Immunol. 2006;97(1):10-20.
5. Du Toit G, Foong R-XM, Lack G. Prevention of food allergy- Early dietary interventions. Allergology International. 2016;65(4):370-7.
6. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803-13.
7. Perkin MR, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, et al. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol. 2016;137:1477-86.
8. Tan JWL, Valerio C, Barnes EH, Van Asperen PP, Kakakios AM, Campbell DE. Early introduction of dietary egg reduces egg sensitization at 12 months of age in infants at risk of allergic disease. J Allergy Clin Immunol. 2017;139:1621-8.
9. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Keil T, Niggemann B, et al. Early introduction of hen's egg during weaning results in frequent allergic reactions: first results from a randomized placebo-controlled trial on hen's egg allergy prevention. Allergy. 2015;70(101):111.
10. Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. J Allergy Clin Immunol. 2013;132:387-92.
11. Palmer DJ, Sullivan TR, Gold MS, Prescott SL, Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. J Allergy Clin Immunol. 2017;139:1600-7.
12. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M; PETIT Study Team. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. Lancet. 2017 Jan 21;389(10066):276-86.
13. Heine RG. Food Allergy Prevention and Treatment by Targeted Nutrition. Ann Nutr Metab. 2018;72:27-39.
14. Tran MM, Lefebvre DL, Dai D, Dharma C, Subbarao P, Lou W, et al. Timing of food introduction and development of food sensitization in a prospective birth cohort. Pediatr Allergy Immunol. 2017;28(5):471-7.
15. World Health Organization. Report of the expert consultation on the optimal duration of exclusive brestfeeding. Genebra: World Health Organization; 2001.
16. BRASIL, Ministério da Saúde. Guia alimentar para crianças menores de 2 anos. Brasília-DF: Ministério da Saúde; 2019. p. 265.
17. Sociedade Brasileira de Pediatria - Departamento de Nutrologia. Guia Prático de Alimentação da Criança de 0 a 5 anos. São Paulo: SBP - Departamentos Científicos de Nutrologia e Pediatria Ambulatorial; 2021. p. 74.
18. Agostoni C, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, et al. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2008;46(1):99-110.
19. Sansotta N, Piacentini GL, Mazzei F, Minniti F, Boner AL, Peroni DG. Timing of introduction of solid food and risk of allergic disease development: Understanding the evidence. Allergol Immunopathol (Madr). 2013;41(5):337-45.

20. Ferraro V, Zanconato S, Carraro S. Timing of Food Introduction, and the Risk of Food Allergy. Nutrients 2019;11:1131.
21. Lack G, Fox D, Northstone K, Golding J. Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. N Engl J Med. 2003;348:977-85.
22. Brough HA, Santos AF, Makinson K, Penagos M, Stephens AC, Douiri A, et al. Peanut protein in household dust is related to household peanut consumption and is biologically active. J Allergy Clin Immunol. 2013;132:630-8.
23. Brough HA, Simpson A, Makinson K, Hankinson J, Brown S, Douiri A, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. J Allergy Clin Immunol. 2014;134:867-75.
24. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. J Allergy Clin Immunol. 2009;123:417-23.
25. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. 2008;122:984-91.
26. Du Toit G, Sampson HA, Plaut M, Burks W, Akdis CA, Lack G. Food allergy: Update on prevention and tolerance. J Allergy Clin Immunol. 2018;141:30-40.
27. Caffarelli C, Di Mauro, D, Mastrorilli C, Bottau P, Cipriani F, Ricci G. Solid Food Introduction and the Development of Food Allergies. Nutrients. 2018;10(11),1790.
28. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. BMJ. 1996;313(7064):1046.
29. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. N Engl J Med. 2003;348:977-85.
30. Fleischer DM, Chan ES, Venter C, Spergel JM, Abrams EM, Stukus D, et al. A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. J Allergy Clin Immunol Pract. 2021;9(1):22-43.
31. Halken S, Muraro A, de Silva D, Khaleva E, Angier E, Arasi S, et al. EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol. 2021;32:843-58.
32. Urashima M, Mezawa H, Okuyama M, Urashima T, Hirano D, Gocho N, et al. Primary prevention of cow's milk sensitization and food allergy by avoiding supplementation with cow's milk formula at birth: a randomized clinical trial. JAMA Pediatr. 2019;173:1137-45.
33. Gappa M, Filipiak-Pittroff B, Libuda L, von Berg A, Koletzko S, Bauer CP, et al. Long-term effects of hydrolyzed formulae on atopic diseases in the GINI study. Allergy. 2021;76(6):1903-7.
34. Osborn DA, Sinn JK, Jones LJ. Infant formulas containing hydrolysed protein for prevention of allergic disease and food allergy. Cochrane Database Syst Rev. 2017 Mar 15;3(3):CD003664.
35. Schroer B, Groetch M, Mack DP, Venter C. Practical Challenges and Considerations for Early Introduction of Potential Food Allergens for Prevention of Food Allergy. J Allergy Clin Immunol Pract. 2021 Jan;9(1):44-56.e1.
36. Royal C, Gray C. Allergy Prevention: An Overview of Current Evidence. Yale J Biol Med. 2020 Dec 29;93(5):689-98.
37. D'Auria E, Peroni GP, Sartorio MUA, Verduci E, Zuccotti GV, Venter C. The role of diet diversity and diet indices on allergy outcomes. Front Pediatr. 2020;8:545.
38. Szajewska H, Horvath A. A partially hydrolyzed 100% whey formula and the risk of eczema and any allergy: an updated meta-analysis. World allergy Organ J. 2017;10(1):27.
39. Roberts G. Another step towards prevention of food allergy. Lancet. 2017;389(10066):230-1.
40. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. JAMA. 2016;316(11):1181-92.
41. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Castenmiller J, de Henauw S, Hirsch-Ernst KI, Kearney J, Knutsen HK, Maciuk A, et al. Appropriate age range for introduction of complementary feeding into an infant's diet. EFSA J. 2019 Sep 12;17(9):e05780. doi: 10.2903/j.efsa.2019.5780.
42. Turner PJ, Feeney M, Meyer R, Perkin MR, Fox AT. Implementing primary prevention of food allergy in infants: New BSACI guidance published. Clin Exp Allergy. 2018;48(8):912-5.
43. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141:4-58.
44. Peters RL, Barret DY, Soriano VX, McWilliam V, Lowe AJ, Ponsonby AL, et al. No cashew allergy in infants introduced to cashew by age 1 year. J Allergy Clin Immunol. 2021;147(1):383-4.
45. Greer FR, Sicherer SH, Burks AW; Committee on Nutrition; Section on Allergy and Immunology. The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Foods. Pediatrics. 2019 Apr;143(4):e20190281.
46. Fisher HR, Du Toit G, Bahnson HT, Lack G. The challenges of preventing food allergy: Lessons learned from LEAP and EAT. Ann Allergy Asthma Immunol. 2018;121(3):313-9.
47. D'Auria E, Peroni GP, Sartorio MUA, Verduci E, Zuccotti GV, Venter C. The role of diet diversity and diet indices on allergy outcomes. Front Pediatr. 2020; 8;545. doi.org/10.3389/fped.2020.00545.
48. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract. 2013;1(1):29-36.
49. Berni Canani R, Paparo L, Nocerino R, Di Scala C, Della Gatta G, Maddalena Y, et al. Gut Microbiome as Target for Innovative Strategies Against Food Allergy. Front Immunol. 2019;15(10):191.
50. Kelleher MM, Cro S, Van Vogt E, Cornelius V, Lodrup Carlsen KC, Ove Skjerven H, et al. Skincare interventions in infants for preventing eczema and food allergy: A cochrane systematic review and individual participant data meta-analysis. Clin Exp Allergy. 2021;51(3):402-18.
51. Kim YH, Kim KW, Lee SY, Koo KO, Kwon SO, Seo JH, et al. Maternal Perinatal Dietary Patterns Affect Food Allergy Development in Susceptible Infants. J Allergy Clin Immunol Pract. 2019;7(7):2337-47.
52. Schindler T, Sinn JK, Osborn DA. Polyunsaturated fatty acid supplementation in infancy for the prevention of allergy. Cochrane Database Syst Rev. 2016:28;10.
53. Bunyavanich S, Shen N, Grishin A, Wood R, Burks W, Dawson P, et al. J Allergy Clin Immunol. 2016;138(4):1122-1130.
54. Shu SA, Yuen AWT, Woo E, Chu KH, Kwan HS, Yang GX, et al. Microbiota and Food Allergy. Clin Rev Allergy Immunol. 2019 Aug;57(1):83-97.
55. Venter C, Agostoni C, Arshad SH, Ben-Abdallah M, Du Toit G, Fleischer DM, et al. Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology. Pediatr Allergy Immunol. 2020;31(8):889-912.
56. Sampson HA, O'Mahony L, Burks AW, Plaut M, Lack G, Akdis CA. Mechanisms of food allergy. J Allergy Clin Immunol. 2018;141(1):11-9.
57. de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, et al. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. Pediatr Allergy Immunol. 2020;31(7):813-26.

58. Fox A, Bird JA, Fiocchi A, Knol J, Meyer R, Salminen S, et al. The potential for pre-, pro- and synbiotics in the management of infants at risk of cow's milk allergy or with cow's milk allergy: An exploration of the rationale, available evidence and remaining questions. World Allergy Organ J. 2019;12(5):100034.
59. Roduit C, Frei R, Ferstl R, Loeliger S, Westermann P, Rhyner C, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy. 2018;74(4):799-809.
60. Bunyavanich S, Berin MC. Food allergy and the microbiome: Current understandings and future directions. J Allergy Clin Immunol. 2019;144(6):1468-77.

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