

Evolution of Guidelines on Peanut Allergy and Peanut Introduction in Infants

A Review

Sara Anvari, MD, MS; Niti Y. Chokshi, MD; Qurat ul Ain Kamili, MD; Carla McGuire Davis, MD

IMPORTANCE The reported prevalence of peanut allergy among children in the United States has increased more than 3-fold in the last 20 years. Medical guidelines on the introduction of peanut as well as other allergenic foods have evolved with the emerging evidence that an early introduction to these foods is more beneficial than a delayed introduction. This review highlights the studies that have led to the evolving guidelines on peanut introduction in infants.

OBSERVATIONS The prevalence of peanut allergy has increased despite the publication of guidelines from the American Academy of Pediatrics in 2000, which recommended a delayed introduction of peanut. Since the 2000 guidelines, studies have provided evidence to support an earlier rather than delayed introduction. As a result, the American Academy of Pediatrics updated their guidelines in 2008 to promote peanut introduction during infancy. Current evidence continues to support the benefits of an earlier rather than delayed introduction.

CONCLUSIONS AND RELEVANCE Over the years, guidelines on the introduction of peanut have evolved, and recent literature suggests that an earlier rather than delayed introduction is beneficial to prevent peanut allergies in infants.

JAMA Pediatr. doi:10.1001/jamapediatrics.2016.2552
Published online November 7, 2016.

Author Affiliations: Division of Immunology, Allergy and Rheumatology, Texas Children's Hospital, Houston (Anvari, Davis); Baylor College of Medicine, Houston, Texas (Anvari, Davis); Division of Pediatric Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, New York (Chokshi); Allergy Partners of North Texas, Dallas (Kamili).

Corresponding Author: Carla McGuire Davis, MD, Baylor College of Medicine, 1101 Bates Ave, Ste 330, Houston, TX 77030 (cmdavis@texaschildrens.org).

Food allergies constitute a major public health concern, and the prevalence of food allergies over the past decade has doubled.¹⁻⁴ Foods that most commonly cause allergic reactions include milk, eggs, peanuts, tree nuts, shellfish, fish, wheat, and soy.²⁻⁹ Peanuts account for the most food-induced anaphylaxis and fatal reactions.^{4,10,11} Furthermore, the reported prevalence of peanut allergy has nearly tripled in the last 10 years.^{2,4,6,9} Peanut allergy occurs early in life, and based on published reports, 18.3% to 21.5% of children may outgrow their peanut allergy.^{12,13} Thus, the persistence of peanut allergy is a concerning issue.

Since the 1990s, studies have provided evidence that led to guidelines on the timing of peanut introduction. In 1999 and 2000, guidelines from the European Society for Pediatric Allergology and Clinical Immunology, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN),¹⁴ and the American Academy of Pediatrics (AAP) Committee on Nutrition¹⁵ suggested delaying the introduction of peanut. However, because of the increasing prevalence of peanut allergy, more studies, including the more recent Learning Early About Peanut Allergy (LEAP)¹⁶ study and the Effect of Avoidance on Peanut Allergy After Early Peanut Consumption (LEAP-On)¹⁷ study, report convincing evidence suggesting that early peanut introduction can help reduce the incidence of peanut allergy (Table). These studies highlight the potential of an early peanut introduction to prevent peanut allergy and provide

evidence to support recent recommendations on the timing of peanut introduction.

This review discusses the earlier guidelines, highlights challenges to those guidelines, and reviews the new recommendations on early peanut introduction.

Previous Guidelines

The European Society for Pediatric Allergology and Clinical Immunology and ESPGHAN¹⁴ in 1999 and the Nutritional Committee of the AAP¹⁵ in 2000 provided recommendations for the prevention of food allergies in infants, including those at high risk. The European Society for Pediatric Allergology and Clinical Immunology and ESPGHAN¹⁴ guidelines focused primarily on the treatment and prevention of food allergies in the first 6 months of life. Based on previous prospective studies in high-risk infants (defined as having 1 first-degree family member with atopy), the European committees recommended preventive dietary measures to reduce the cumulative incidence of atopic disease. This included exclusive breastfeeding for the first 4 to 6 months of life, supplementation with extensively hydrolyzed formula when breastfeeding was not possible, and avoidance of complementary (ie, solid) foods and cow's milk protein for infants 5 months and younger.²⁰⁻²⁴

Table. Evolution of Guidelines for the Introduction of Peanut

Intake of Allergenic Foods ^a	ESPGHAN (1999) ¹⁴ and AAP (2000) ¹⁵	ESPGHAN (2008) ¹⁸ and AAP (2008) ¹⁹	LEAP Guidelines (2015) ¹⁶
Mother			
During pregnancy	Avoid consuming peanuts	No restriction	No recommendation
During breastfeeding	Avoid consuming peanuts, tree nuts, and fish	No restriction	No recommendation
Infant			
When aged 4 to 6 mo	Avoid consumption of allergenic foods when younger than 12 mo	Begin consumption of allergenic foods at 4 to 6 mo	Introduce peanut to infants aged 4 to 11 mo with early-onset atopic disease
After 1 y	Avoid consuming milk when younger than 1 y, eggs, 2 y, peanuts, tree nuts, and fish, 3 y	Consume allergenic foods regularly after 4 to 6 mo	No recommendation

Abbreviations: AAP, American Academy of Pediatrics; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; LEAP, Learning Early About Peanut Allergy.

^a Allergenic foods defined as milk, eggs, peanuts, tree nuts, fish, and shellfish.

Similarly, the AAP strategy focused on the treatment and prevention of food hypersensitivity, and this was published in the 2000 guidelines.¹⁵ In contrast to the European committees, the AAP definition for an infant at high risk for atopic disease was defined as having 2 family members with a strong history of allergic disease.¹⁵ The AAP recommendations were derived from previous studies, in particular the findings reported from a prospective randomized clinical study performed by Zeiger et al²⁵ that evaluated the development of allergic disease, including food allergies, in high-risk infants who were observed for 7 years. The study demonstrated that avoiding milk, eggs, and peanuts during pregnancy and lactation and delaying solid food introduction until 6 months, cow's milk until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years reduced food sensitization and food allergy during the first year of life. However, the benefit was reduced at 2 years and absent by 3 to 4 years.²⁵ Although the reduction of food sensitization was only significant in the first year of life, the cumulative prevalence of food allergy remained lower in the control group compared with the food avoidance group at 7 years.²⁵ Thus, while a slight decrease in incidence in sensitization may have occurred in the study by Zeiger et al,²⁵ it was a temporary effect at best.

Subsequent retrospective studies demonstrated that maternal consumption of allergenic foods during pregnancy and lactation could be associated with the development of food sensitization in infants.²⁶⁻³⁰ Given the possibility of at least a temporary diminishment of food allergy and sensitization, the AAP recommended avoiding peanuts during pregnancy and peanuts, tree nuts, eggs, milk, and fish while nursing.¹⁵ The AAP also recommended breastfeeding for at least 12 months and supplementation with hypoallergenic formula when nursing was not possible in high-risk infants. Furthermore, they recommended delaying solid food introduction for infants until age 6 months, dairy until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years.¹⁵ For nonhigh-risk patients, no specific recommendations were provided regarding prophylactic maternal or infant elimination of allergenic foods, unless the infant became symptomatic. In 2006, the American College of Allergy, Asthma, and Immunology provided a consensus document³¹ to further support the 2000 AAP recommendations of a delayed introduction of allergenic foods to infants. Despite the preventive measures outlined by the European and AAP guidelines, the incidence of food allergies continued to rise.

Challenges to Previous Guidelines

In contrast to the preventive measures suggested by the earlier European and AAP guidelines, there was emerging evidence in the following years that suggested against maternal avoidance and a delayed introduction of peanut and rather suggested that maternal peanut consumption during pregnancy and lactation was not associated with an increased risk of peanut allergy in offspring. A study by Tariq et al³² evaluated a birth cohort of 1218 children born on the Isle of Wight between 1989 and 1990 to estimate the prevalence of nut allergy and evaluate the routes of sensitization. They observed that maternal peanut consumption during pregnancy and lactation did not increase the risk of peanut allergy in children. Furthermore, they demonstrated that there was no difference in the duration of breastfeeding and the age at introduction to formula milk in children with and without peanut sensitization.

A subsequent study by Lack et al³³ was able to evaluate the risk factors associated with the development of peanut allergy. The study used a geographically defined cohort of 13 971 preschool children in southwest England and identified children younger than 38 months with a convincing history of peanut allergy. A total of 49 children with a diagnosis of peanut allergy were identified and underwent a double-blind placebo-controlled peanut challenge, of which 23 were found to be positive for peanut allergy. Retrospectively, Lack et al³³ found no significant difference between mothers of children with and without peanut allergy and consumption of peanuts during pregnancy and lactation. This observation suggested that maternal peanut consumption during pregnancy and lactation did not increase the risk of peanut allergy in children. Furthermore, the study also found that a positive family history, the presence of atopic eczema, and the use of topical preparations containing peanuts and soy could be contributing factors to the sensitization to peanut and the development of peanut allergy.³³

Further studies also demonstrated that there was no evidence of an association between maternal peanut consumption or avoidance during pregnancy and lactation with the development of peanut allergy in the child.³⁴⁻³⁷ In 2012, a meta-analysis³⁸ evaluating food allergies and maternal allergen avoidance during pregnancy and/or lactation showed no significant evidence of a protective effect against peanut allergy with a maternal exclusion diet. More recently, a study

published by Frazier et al³⁹ examined the association of peripregnancy consumption of peanuts and tree nuts with the development of peanut and tree nut allergy in 10 907 participants born between 1990 and 1994 in the Growing Up Today Study 2. The study determined a higher peripregnancy consumption of peanuts and tree nuts was associated with a lower risk of nut allergy in offspring (odds ratio, 0.31; 95% CI, 0.13-0.75; $P = .004$), thus supporting that early allergen exposure increases tolerance and reduces the risk of childhood food allergy.³⁹

In addition to perinatal exposure, other prospective studies^{40,41} demonstrated that delaying the introduction of allergenic food beyond age 6 months did not prevent the development of atopic disease in infants. To evaluate the early introduction of peanut, Du Toit et al⁴² conducted a comparison study on Jewish children living in Israel and in the United Kingdom. The study evaluated the association of peanut allergy with infant and maternal peanut consumption, as it was known that peanuts were introduced earlier in infancy and were consumed more frequently in Israel. Using a questionnaire-based study, Du Toit et al⁴² showed that the rate of peanut allergy in Jewish children in the United Kingdom was 1.85% compared with 0.17% in Israel ($P < .001$), suggesting a protective effect with an early introduction of peanut.

Two prospective German birth cohort studies,⁴³ the German Infant Study on the Influence of Nutrition Intervention Plus Environmental and Genetic Influences on Allergy Development and the Influence of Lifestyle Factors on the Immune System and Allergies in East and West Germany Plus the Influence of Traffic Emissions and Genetics, which enrolled 9088 infants between 1995 and 1999, investigated the effects of feeding patterns in early life and the risk of allergy development. The results of both studies supported that a delayed introduction of solid foods or the avoidance of highly allergenic foods during the first year of life was not beneficial in the prevention of allergies.⁴³ However, the study authors concluded that the introduction of solid foods before age 17 weeks may increase the risk of allergy.⁴³

These studies provided strong evidence against earlier recommendations regarding delaying the introduction of allergenic foods and led to the issuing of new recommendations by ESPGHAN and the AAP in 2008.

Updates to Guidelines

Based on the evidence, the 2008 ESPGHAN¹⁸ and AAP¹⁹ guidelines recommended exclusive breastfeeding for the first 4 to 6 months and stated that there was no evidence suggesting a protective effect against developing atopic disease by delaying solid foods after 4 to 6 months. Furthermore, there was no evidence that maternal diet restriction during pregnancy or lactation prevented allergy in offspring.^{18,19} Soon after, the National Institute of Allergy and Infectious Diseases (NIAID)⁴⁴ and the American Academy of Allergy, Asthma, and Immunology⁴⁵ published guidelines that further supported the new AAP and ESPGHAN recommendations. The NIAID and American Academy of Allergy, Asthma, and Immunology highlighted that there were insufficient data to demonstrate that delaying complementary foods, including allergenic foods, beyond 6 months could have a protective effect on the development of atopic disease.^{44,45}

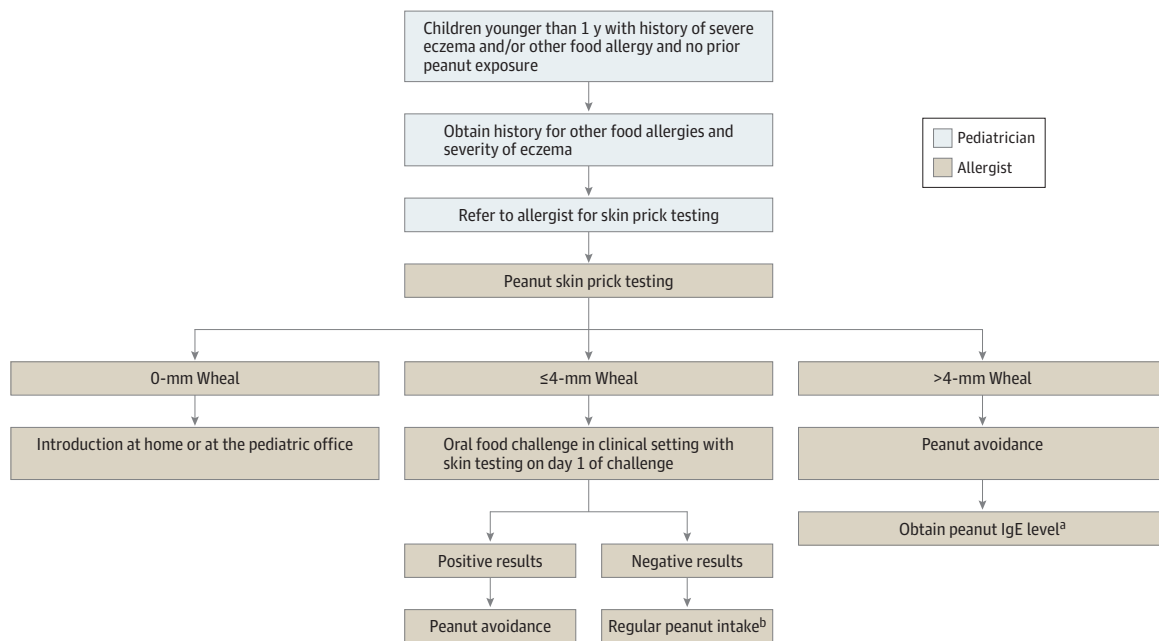
Ultimately, the findings from the 2015 LEAP study¹⁶ provided groundbreaking level 1 evidence, highlighting perhaps the most significant findings to date concerning the prevention of peanut allergy in infants. This single-site study from the United Kingdom was an open-labeled randomized clinical trial involving 640 high-risk infants (ie, defined as having severe atopic dermatitis and/or egg allergy).¹⁶ The study compared the effects of early (ie, aged 4 to 11 months) high-dose (ie, 6 g/wk) peanut protein consumption with strict avoidance in children over a 5-year period. All children underwent skin prick testing, and those with a skin wheal of 4 mm or less were included in the study. The small skin test inclusion criterion was chosen to include patients with peanut sensitization but not clinical allergy. Overall, the results demonstrated a significant reduction in the prevalence of peanut allergy among the consumption group compared with the avoidance group.¹⁶ The prevalence of peanut allergy for children aged 5 years who tested negative in the skin test (ie, no wheals) was 13.7% in the avoidance group vs 1.9% in the consumption group ($P < .001$), and the prevalence of peanut allergy for those who tested positive (ie, a wheal sized 1 to 4 mm) was 35.3% in the avoidance group vs 10.6% in the consumption group ($P < .004$).¹⁶

Furthermore, tests to find immunoglobulin levels associated with allergen-specific tolerance (ie, IgG4 levels) as well as allergic sensitization (ie, IgE levels) were performed, and the results demonstrated higher peanut-specific IgG4 levels and lower peanut-specific IgE levels in the consumption groups. The authors concluded that a larger skin prick wheal response to peanut and a lower ratio of peanut-specific IgG4:IgE levels was associated with peanut allergy.¹⁶ An additional observation was that peanut IgE levels in peanut-tolerant infants were more likely to be positive compared with skin testing. Therefore, using peanut IgE levels alone as opposed to skin testing to determine sensitization could lead to numerous unnecessary oral peanut challenges. Furthermore, they concluded that an early introduction of peanut significantly reduced the risk of developing peanut allergy among children at high risk and modulated the immune responses.¹⁶

The LEAP study¹⁶ precipitated yet another update to the food allergy guidelines in 2015. Based on the results of the LEAP study, a consensus guideline⁴⁶ on the early introduction of peanut and prevention of peanut allergy in high-risk infants was published, highlighting evidence on the potential benefits of an early rather than delayed peanut introduction during a period of complementary food introduction in high-risk infants. The interim guidance provided by this report⁴⁶ recommended infants with early-onset atopic disease (eg, infants with severe atopic eczema and/or egg allergy) aged 4 to 11 months might benefit from an early evaluation for food allergies by an allergist. Evaluation would include skin testing and may include an oral food challenge in the clinical setting, which could be performed to confirm whether the patient demonstrated clinical reactivity to peanuts before the introduction of peanut at home (Figure).

Although noted to be an excellent study, the consensus report⁴⁶ highlighted that the LEAP study had limitations and did not address the alternative doses of peanut that could be consumed to maintain tolerance, the minimal duration of therapy necessary to achieve tolerance, and the potential risks of premature discontinuation or sporadic feeding of peanut. Additionally, the study did not address whether the children with evidence of mild to moderate

Figure. Suggested Algorithm for the Introduction of Peanut



A suggested algorithm derived from the Learning Early About Peanut Allergy consensus guidelines¹⁶ outlining an approach for pediatricians and allergists to use to evaluate for peanut allergy in infants with atopic disease (ie, severe eczema and/or egg allergy).

^a Yearly trends in peanut IgE levels can help determine whether the patient

develops a peanut tolerance in the future.

^b To prevent a choking hazard, thin out peanut butter and avoid whole peanuts until older than 4 years.

atopic eczema could benefit from a similar protocol. The study defined severe eczema as having an eczematous rash with a Scoring of Atopic Dermatitis of 40 or greater and requiring the application of topical creams, ointments, or both containing corticosteroids or calcineurin inhibitors as well as skin manifestations lasting at least 12 of 30 days on 2 occasions. Overall, the consensus report provided updated recommendations based on the scientific evidence found in the LEAP study, still emphasizing that the forthcoming extensive guidelines by the NIAID and the European Academy of Allergy and Clinical Immunology would consider all supporting evidence to clarify and provide the best guidelines on preventive strategies for the population at large (Table).

To further supplement the LEAP study, the LEAP-On study¹⁷ demonstrated that the prevalence of peanut allergy did not increase following a 12-month period of peanut avoidance in all participants of the LEAP study. The LEAP-On trial demonstrated that the overall prevalence of peanut allergy was 74% lower in the group that consumed peanuts compared with the group that avoided peanuts,¹⁷ suggesting that an early introduction of long-term peanut exposure can have a clinically significant and durable effect.

In addition to determining whether similar findings as seen in the LEAP studies could also be observed with other foods, the Enquiring About Tolerance Trial⁴⁷ observed infants aged 3 months who were introduced early to 6 allergenic foods alongside continued breastfeeding as well as control infants aged 6 months and compared food allergy prevalence rates. Infants participating in the study were randomized into an early introduction group (EIG) or a standard introduction group (SIG). Parents of infants in the EIG who

tested negative on skin testing or tested positive but had negative results on food challenge were asked to introduce 6 allergenic foods: cow's milk (yogurt) first, followed (in random order) by hard-boiled hen's egg, peanut, sesame, and whitefish, with wheat being introduced last.⁴⁷ The infants consumed 2 g of the food protein twice a week. Infants in the SIG were exclusively breastfed and did not consume allergenic foods before age 6 months. The infants were observed until aged 3 years.

Overall, the intention-to-treat analysis demonstrated that the efficacy of the early introduction of allergenic foods was not significant and did not significantly reduce the prevalence of food allergy compared with a standard introduction (EIG, 5.6% vs SIG, 7.1%; $P = .32$).⁴⁷ However, only 42.8% of participants adhered to the early intervention protocol and thus were accounted for in the primary outcome of the study, whereas 92.9% of the SIG were adherent to the protocol. Thus, the per-protocol analysis, which analyzed those who adhered to the protocol, demonstrated that infants in the EIG had a significantly lower prevalence of any food allergy than those in the SIG (EIG, 2.4% vs SIG, 7.3%; $P = .01$), suggesting a 67% lower relative risk of food allergy. Furthermore, in the per-protocol analysis, a significantly lower relative risk of peanut allergy (EIG, 0% vs SIG, 2.5%; $P = .003$) and egg allergy (EIG, 1.4% vs SIG, 5.5%; $P = .009$) were also observed in the EIG vs SIG comparison.⁴⁷ Although the per-protocol analysis demonstrated significant findings, the authors of the study stated that the results of the per-protocol analysis should be interpreted with caution, as the differences in results could have been due to biological effects or hidden bias.

Conclusions

As guidelines have changed, we can anticipate that results from current and future studies will provide additional insights into the prevention and treatment of food allergies and encourage future investigations that will facilitate their understanding. Furthermore, with additional studies, it will remain imperative for a consensus to be achieved concerning the safe introduction of allergenic foods into infants' diets. At this time, the current guidelines on food allergy prevention no longer suggest mothers avoid peanut consumption during pregnancy or lactation, and recent studies have provided evidence to support the updated recommendations on the introduction of allergenic foods for infants aged 6 months without delayed introduction.

The LEAP and LEAP-On trials provided new insights and consensus recommendations on the early introduction of peanut in high-risk infants. Based on the evidence from LEAP, consensus recommendations suggest that infants with severe atopic eczema and/or

egg allergy should undergo a food allergy assessment by an allergist to determine whether they may benefit from an early introduction of peanut.⁴⁵ A suggested algorithm derived from the LEAP consensus guidelines in the Figure outlines an approach that can be used by pediatricians and allergists evaluating infants for peanut allergy. Based on the recent recommendations, it is anticipated that an expanded consensus document from the NIAID-sponsored Working Group and the European Academy of Allergy and Clinical Immunology will be published and provide further guidance in this area.

The changes anticipated as a result of current and future studies will provide additional insights into the development and prevention of food allergies. Furthermore, research from these studies will provide more clarity about the underlying immune mechanisms that regulate the development of food hypersensitivity and tolerance in infants. The reported rising prevalence of food allergies has facilitated current knowledge about risk factors for disease, and there is great potential for future investigative studies to elucidate methods to reduce the incidence of allergies and increase allergen tolerance through preventive measures.

ARTICLE INFORMATION

Accepted for Publication: July 15, 2016.

Published Online: November 7, 2016.
doi:10.1001/jamapediatrics.2016.2552

Author Contributions: Drs Anvari and Davis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Anvari, Chokshi, Kamili.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: All authors.

Study supervision: Davis.

Conflict of Interest Disclosures: None reported.

REFERENCES

- Chafen JJ, Newberry SJ, Riedl MA, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA*. 2010;303(18):1848-1856.
- Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol*. 2010;125(6):1322-1326.
- Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol*. 2002;110(5):784-789.
- Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics*. 2009;124(6):1549-1555.
- Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol*. 2011;127(3):594-602.
- Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-e17.
- Osborne NJ, Koplin JJ, Martin PE, et al; HealthNuts Investigators. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127(3):668-76.e1-2.
- Boyce JA, Assa'ad A, Burks AW, et al; NIAID-sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 suppl):S1-S58.
- Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007;120(3):638-646.
- Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. *J Allergy Clin Immunol*. 2007;120(3):491-503.
- Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol*. 1989;83(5):900-904.
- Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study. *BMJ*. 1998;316(7140):1271-1275.
- Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107(2):367-374.
- Høst A, Koletzko B, Dreborg S, et al. Dietary products used in infants for treatment and prevention of food allergy: joint statement of the European Society for Paediatric Allergy and Clinical Immunology (ESPAI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child*. 1999;81(1):80-84.
- American Academy of Pediatrics. Committee on Nutrition: hypoallergenic infant formulas. *Pediatrics*. 2000;106(2, pt 1):346-349.
- Du Toit G, Roberts G, Sayre PH, et al; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
- Du Toit G, Sayre PH, Roberts G, et al; Immune Tolerance Network LEAP-On Study Team. Effect of avoidance of peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443.
- Agostoni C, Decsi T, Fewtrell M, et al; ESPGHAN Committee on Nutrition. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2008;46(1):99-110.
- Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics*. 2008;121(1):183-191.
- Saariinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet*. 1995;346(8982):1065-1069.
- Oldaeus G, Anjou K, Björkstén B, Moran JR, Kjellman NI. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child*. 1997;77(1):4-10.
- Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. *Pediatrics*. 1990;86(4):541-546.
- Zeiger RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol*. 1989;84(1):72-89.
- Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet*. 1992;339(8808):1493-1497.
- Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol*. 1995;95(6):1179-1190.

26. Høst A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants: incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. *Acta Paediatr Scand*. 1988;77(5):663-670.
27. Frank L, Marian A, Visser M, Weinberg E, Potter PC. Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol*. 1999;10(1):27-32.
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(7056):518-521.
29. Sicherer SH, Wood RA, Stablein D, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol*. 2010;126(6):1191-1197.
30. DesRoches A, Infante-Rivard C, Paradis L, Paradis J, Haddad E. Peanut allergy: is maternal transmission of antigens during pregnancy and breastfeeding a risk factor? *J Invest Allergol Clin Immunol*. 2010;20(4):289-294.
31. 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.
32. Tariq SM, Stevens M, Matthews S, Ridout S, Twiselton R, Hide DW. Cohort study of peanut and tree nut sensitisation by age of 4 years. *BMJ*. 1996;313(7056):514-517.
33. 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(11):977-985.
34. 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(2):417-423.
35. Dean T, Venter C, Pereira B, Grundy J, Clayton CB, Higgins B. Government advice on peanut avoidance during pregnancy: is it followed correctly and what is the impact on sensitization? *J Hum Nutr Diet*. 2007;20(2):95-99.
36. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol*. 2007;119(2):307-313.
37. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol*. 2005;116(1):49-55.
38. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev*. 2012;(9):CD000133.
39. Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC. Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. *JAMA Pediatr*. 2014;168(2):156-162.
40. Tromp II, Kiefte-de Jong JC, Lebon A, et al. The introduction of allergenic foods and the development of reported wheezing and eczema in childhood: the Generation R study. *Arch Pediatr Adolesc Med*. 2011;165(10):933-938.
41. Zutavern A, Brockow I, Schaaf B, et al; LISA Study Group. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics*. 2008;121(1):e44-e52.
42. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122(5):984-991.
43. Sausenthaler S, Heinrich J, Koletzko S; GINIplus and LISAplus Study Groups. Early diet and the risk of allergy: what can we learn from the prospective birth cohort studies GINIplus and LISAplus? *Am J Clin Nutr*. 2011;94(6 suppl):2012S-2017S.
44. Burks AW, Jones SM, Boyce JA, et al. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. *Pediatrics*. 2011;128(5):955-965.
45. Sampson HA, Aceves S, Bock SA, et al; Joint Task Force on Practice Parameters; Practice Parameter Workgroup. Food allergy: a practice parameter update—2014. *J Allergy Clin Immunol*. 2014;134(5):1016-25.e43.
46. Fleischer DM, Sicherer S, Greenhawt M, et al; American Academy of Allergy, Asthma & Immunology; American Academy of Pediatrics, American College of Allergy; Asthma & Immunology, Australasian Society of Clinical Immunology and Allergy; Canadian Society of Allergy and Clinical Immunology; European Academy of Allergy and Clinical Immunology; Israel Association of Allergy and Clinical Immunology; Japanese Society for Allergology; Society for Pediatric Dermatology; World Allergy Organization. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol*. 2015;136(2):258-261.
47. Perkin MR, Logan K, Tseng A, et al; EAT Study Team. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733-1743.