

Prevention of Food Allergies



Jennifer J. Koplin, PhD^a, Rachel L. Peters, PhD^{a,b},
Katrina J. Allen, MBBS, FRACP, PhD^{a,b,c,d,e,*}

KEYWORDS

- Food allergy • Prevention • Peanut allergy • Egg allergy • Eczema • Vitamin D
- Infant feeding • Probiotics

KEY POINTS

- There is now good evidence that timely introduction of peanut into the infant diet reduces the risk of peanut allergy in high-risk infants.
- There is also some evidence that timely introduction of egg might reduce the risk of egg allergy, whereas the role of timing of introduction of other allergenic foods has not yet been established.
- Additional food allergy prevention strategies currently under investigation include optimizing infant vitamin D levels, modulating the gut microbiota through use of probiotics, and preventing eczema to reduce the risk of food sensitization through a damaged skin barrier.

INTRODUCTION

A population-level approach to food allergy prevention moved one step closer in 2015 to 2016, with a successful trial of early peanut introduction for preventing peanut allergy. This widely lauded landmark study resulted in definitive changes to infant feeding guidelines around the world. As a result of this successful trial and subsequent development and dissemination of new infant feeding recommendations, there is a very real possibility that new generations of infants born in countries with high food

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^a Centre of Food and Allergy Research, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, Victoria 3052, Australia; ^b Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Victoria 3052, Australia; ^c Department of Allergy and Clinical Immunology, Royal Children's Hospital, Melbourne, Victoria 3052, Australia; ^d Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Victoria 3052, Australia; ^e Institute of Inflammation and Repair, University of Manchester, Oxford Road, Manchester M13 9PL, UK

* Corresponding author. Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville, Melbourne, Victoria 3052, Australia.

E-mail address: katie.allen@rch.org.au

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allergy prevalence, such as the United Kingdom, the United States, and Australia, will have less food allergy than the generation before. However, further targeted research is still required to bridge some important knowledge gaps. This research includes the following:

- Monitoring the impact on prevalence of changed guidelines
- Developing prevention strategies for foods other than peanut
- Developing strategies to prevent cases of peanut allergy that do not respond to earlier allergen introduction

In this review, the authors discuss the current state of food allergy prevention. They highlight topics of ongoing research as well as areas where prevention strategies may continue to evolve as new research findings emerge.

THE CURRENT BURDEN OF IMMUNOGLOBULIN E-MEDIATED FOOD ALLERGIES AROUND THE WORLD

Food allergy is estimated to affect around 5% to 10% of infants and young children in developed countries. Data show that the incidence of food-induced anaphylaxis increased between the 1990s and 2010, particularly in children,^{1–3} although it remains unclear to what extent this is due to an increase in food allergy prevalence, an increase in severe reactions among allergic individuals, or an increased number of reactions in the same pool of allergic people. A recent acceleration in rates of adolescent anaphylaxis supports the concept of a cohort effect with children born in the early stages of the increase in food allergy prevalence in the early 2000s now reaching adolescence.¹

There are increasing published reports on food allergy prevalence from around the world, which reveal emerging significant differences in the prevalence between countries, although the reasons for these differences are not yet established. The Europrevall birth cohort study was designed to compare food allergy prevalence between countries by using a standardized study protocol in multiple European centers. Around 12,000 infants from 9 countries were recruited into a series of birth cohorts in 2005 to 2010, with approximately 9000 infants followed up to 2 years of age. The prevalence of egg allergy was reported to range from 0.07% in Greece to more than 2% in Germany and the United Kingdom,⁴ whereas cow's milk allergy ranged from 0% in Greece to 1.3% in Lithuania.⁵ Outside of Europe, the HealthNuts study in Australia recruited 12-month-old infants around the same time as Europrevall (2007–2011). Of the 5300 participating infants, 3.0% were peanut allergic, 9.0% egg allergic, and 0.8% sesame allergic.⁶

Recently, there have been new publications reporting the prevalence of food allergy in infants in South Africa and China, both countries where food allergy was previously considered to be rare. The South African Food Sensitization and Food Allergy study (SAFFA) used a population-based sampling frame to recruit an unselected cohort of infants aged 12 to 36 months.⁷ In an interim analysis of the first 544 participants, the prevalence of challenge-proven immunoglobulin E (IgE)-mediated allergy was 2.5% (95% confidence interval [CI] 1.2–3.9), with a 1.8% prevalence of allergy to egg, 1.2% to peanut, and 0.2% to cow's milk. A study in Chongqing, China recruited 497 infants from 9 districts of Chongqing attending the Children's Hospital of Chongqing Medical University for routine health checks, with a participation rate of 96% (477 of 497). The prevalence of challenge-proven food allergy was 3.8% (95% CI 2.5–5.9), with a 2.5% prevalence of egg allergy and 1.3% to cow's milk. Only 2 infants (0.4%) were sensitized to peanut and 1 to fish and shrimp; there were no positive challenges to peanut, fish, or shrimp.⁸

These recent studies of challenge-confirmed food allergy have provided strong baseline prevalence data. These data are a vital first step to measuring changes in food allergy prevalence in the future. Importantly, these baseline data will allow us to measure the extent to which new interventions, including a shift toward earlier introduction of dietary peanut, alter the prevalence of food allergy.

PREVENTION OF FOOD ALLERGY THROUGH TIMELY INTRODUCTION OF ALLERGENIC FOODS

In the late 1990s, most expert guidelines for prevention of allergic disease internationally recommended delayed introduction of allergenic solids, such as egg and peanut, until after 2 to 4 years of age, based on theoretic concerns regarding immaturity of the infant immune system. Later studies suggested that this was not effective in reducing increasing rates of food allergy; by 2008 there was increasing interest in earlier introduction of allergenic solids in a bid to engage an allergen-specific immune response and oral tolerance earlier in infancy.⁹

In 2008, Du Toit and colleagues¹⁰ also observed that the common practice of earlier peanut consumption in Israel seemed to be associated with very low rates of peanut allergy. Jewish children in Israel had very little peanut allergy compared with Jewish children in the United Kingdom; most infants in Israel started eating peanut in the first year of life, whereas most infants in the United Kingdom avoided peanut until after 1 year of age. To test the hypothesis that earlier introduction of peanut could prevent peanut allergy in high-risk children, the group then mounted an intervention trial (the Learning Early About Peanut allergy [LEAP] study) whereby children with severe eczema and/or egg allergy were randomly assigned to either start eating peanut from 4 to 11 months of age or completely avoid peanut until 5 years of age.¹¹ Infants were first screened for possible peanut allergy by skin prick testing, and 11% of the screened infants were excluded from the study because they were already likely to be peanut allergic at 4 to 11 months of age (skin prick test wheal size >4 mm). In the remaining group of 640 infants, those who had consumed peanut starting from 4 to 11 months of age had an 81% relative reduction in peanut allergy compared with those who had avoided peanut. This study provided the first evidence from a randomized trial that delayed introduction of peanut into the diet of high-risk infants increased the risk of peanut allergy.

The results of trials for early introduction of other foods have been less clear. In an egg allergy trial, giving high doses of egg powder at 4 to 6 months of age to high-risk children (with eczema) seemed to be associated with some reduction in egg allergy risk compared with egg avoidance until 8 months of age; however, the difference between groups did not reach statistical significance and 31% of infants in the early egg introduction group had a reaction when the egg powder was first given, suggesting that egg allergy was already present at this early age in a significant proportion of infants with eczema.¹² A large trial of multiple allergenic food introductions from 3 to 6 months of age, compared with standard introduction from 6 months of age, did not find a significant difference in food allergy risk between the two groups in the primary intention-to-treat analysis.¹³ There are several possible explanations for this finding, including low compliance with the intervention protocol, because a per-protocol analysis showed a possible protective effect of earlier introduction of both egg and peanut in those who were compliant with the intervention. Other studies of earlier egg introduction have also mostly reported a nonsignificant reduction in egg allergy with earlier egg consumption.¹⁴ A recent systematic review and meta-analysis combined data from all of these studies and reported a reduction in egg allergy with

introduction at 4 to 6 months of age compared with later introduction (risk ratio [RR] 0.56; 95% CI 0.36–0.87, $P = .009$). The same meta-analysis showed a potentially greater reduction in peanut allergy with early introduction (RR 0.29; 95% CI 0.11–0.74), with early introduction defined as 4 to 11 months of age.¹⁴

HOW MUCH FOOD ALLERGY CAN WE PREVENT THROUGH TIMELY INTRODUCTION OF ALLERGENIC FOOD?

Despite the great success of the early peanut introduction trial, likely peanut allergy (defined as a skin prick test wheal size >4 mm) was already present in around 11% of high-risk infants screened at 4 to 11 months of age. These infants were excluded from the intervention; early introduction of peanut is not a feasible intervention strategy for this group, because most are likely to react on consumption of peanut. Similarly, egg allergy prevention trials found relatively high levels of egg allergy already present by 4 months of age. The authors recently modeled the potential reduction in peanut allergy that could be expected if the LEAP study protocol was implemented for peanut allergy prevention in the general population. Their models predicted that around 40% to 60% of peanut allergy might be preventable under optimal conditions.¹⁵ Although this is a substantial reduction in peanut allergy, there remains a need to identify strategies for individuals who do not benefit from early introduction.

To achieve even this level of reduction in peanut allergy, several questions regarding the optimal prevention strategy will need to be answered. One aspect that remains unanswered by LEAP is how much allergen exposure is enough to prevent food allergy. The editorial article¹⁶ accompanying the publication of the trial results suggests that infants include 2 g of peanut protein 3 times a week for at least 3 years based on the intervention protocol, but little is known about the impact of variations in dosage of allergen exposure. Secondly, LEAP does not yet provide sufficient information about the critical window of opportunity of timing because peanut introduction occurred during a wide window from 4 to 11 months. Analysis of peanut introduction by restricted time windows and the impact of this on the risk of peanut allergy will be valuable as will mechanistic studies assessing immunologic and epigenetic differences based on the age of recruitment. Finally, there is as yet no evidence as to whether early introduction of peanut is equally effective in infants without eczema or egg allergy in infancy, a population in which approximately one-quarter of all peanut allergy cases occur.¹⁵

PREVENTING FOOD ALLERGY THROUGH TIMELY INTRODUCTION OF ALLERGENIC FOODS: ARE ALL FOOD ALLERGIES THE SAME?

It is not clear that timely introduction of allergens into the diet will be equally effective for preventing all food allergies. There are differences in allergic responses to different food allergens, and differences in the natural history of food allergy, with individuals more likely to outgrow their milk and egg allergy early in life compared with peanut allergy.¹⁷ There is also some evidence of a variation in risk factors for different food allergy phenotypes.¹⁸ In addition, the usual timing and amount of allergen given in the infant diet differs for different foods, with foods such as tree nuts and shellfish, often not given until later in childhood. Observational studies also suggest potentially different windows of opportunity for optimal introduction of different foods, with cow's milk introduction potentially needing to be earlier than egg or peanut.^{19,20} There may not be a one-size-fits-all approach to preventing all food allergy, and the definition of timely introduction may be allergen specific.

Tree nuts are some of the most common foods to cause IgE-mediated allergic reactions and account for around 18% to 40% of all fatal food reactions.²¹ Despite

this, there have been far fewer studies of tree nut allergy prevalence and risk factors compared with peanut allergy. The authors recently reported that tree nuts were the second most common cause of food allergy in the adolescent age group after peanut, affecting 2.3% of the population.²² There have been no studies of tree nut allergy in infants or young children; thus, it is not known whether tree nut allergy, like peanut allergy, also develops during infancy and whether it shares similar risk factors to peanut allergy. To date there have also been no prevention trials for tree nut allergy, with existing research focusing on peanut, egg, and cow's milk allergies.

HOW RELEVANT IS EARLY PEANUT INTRODUCTION IN COUNTRIES WITH LOW PEANUT ALLERGY PREVALENCE?

In countries with a low prevalence of peanut allergy where peanut is already introduced early, such as Israel, changes are unlikely to be required because the current practice seems to be safe and effective. It is not clear what to recommend for countries with a low prevalence of peanut allergy and low peanut consumption in infancy, which seems to be the case in Singapore.²³ Other areas of Asia also report low rates of peanut allergy, although data on infant peanut consumption have not yet been reported.⁸ Although changes to infant feeding practices in these countries currently seem unnecessary, it may be advisable to continue to monitor any changes in peanut allergy prevalence with increases in industrialization.

BARRIERS TO ACHIEVING OPTIMAL TIMING OF INTRODUCTION OF ALLERGENIC FOODS

In order for infant feeding guidelines to be effective in reducing the population prevalence of peanut allergy, these guidelines need to result in changes in behavior. It is not yet clear to what extent parents will follow new guidelines recommending earlier peanut introduction. This change is the second major change in recommendations around peanut introduction in the past 10 years. In the late 1990s and early 2000s, many guidelines recommended delaying introduction of peanut until 1 to 3 years of age.⁹ This advice was removed from most of these guidelines around 2008. The authors previously documented an evolving significant shift toward earlier introduction of peanut and egg 1 year after the removal of advice to delay peanut introduction in 2008.²⁴ Overall, however, less than 10% of the population changed their practices between 2007 and 2011; there was no significant change in the group with a family history of allergy, who might benefit the most from early allergen introduction because of their increased food allergy risk.

There may now have been a larger shift toward earlier introduction of allergenic foods, because updated guidelines specifically recommend early introduction, including for those at high risk of food allergy, and because of widespread media reporting of the trial results showing early introduction of peanut is protective. However, it will be important to monitor both awareness and uptake of these recommendations to ensure high compliance with earlier peanut introduction, particularly among infants with eczema or egg allergy.

The issue of whether high-risk infants should undergo screening for peanut sensitization before the first introduction of peanut into the diet remains the subject of debate.²⁵ Currently, some countries, such as Australia, recommend early introduction of peanut for all infants without screening, in a setting where infants at highest risk (particularly those with other food allergies) are often already under the care of an allergist. By contrast, recommendations in the United States by the National Institute of Allergy and Infectious Disease are for evaluation with peanut-specific IgE and/or a

skin prick test and, if necessary, an oral food challenge before peanut introduction for the highest-risk infants (those with severe eczema, egg allergy, or both). Arguments for screening center around reducing the risk of reactions on first peanut consumption and promoting early introduction in high-risk groups when parents may be less willing to introduce peanut because of a fear of an allergic reaction. Arguments against screening include the difficulty in accommodating screening demands within the existing allergy workforce and a potential detrimental delay in the introduction of peanut while parents await specialist evaluation for their infant. The relative efficacy of these different strategies for both promoting timely peanut introduction and preventing peanut allergy remains to be seen.

IS THERE A ROLE FOR OTHER PREVENTION STRATEGIES APART FROM TIMING OF INTRODUCTION OF ALLERGENIC FOODS?

Changing the age at which infants are exposed to individual allergenic foods, such as peanut, has been shown to have an allergen-specific protective effect for peanut allergy but is unlikely to have a broader protective effect for all food allergies. In addition, the infants shown to benefit from early peanut introduction for peanut allergy prevention already had other manifestations of allergic disease (eczema and egg allergy). Therefore, development of other strategies that modulate the immune system to more broadly protect against the development of allergic responses to all food allergens remains an important research focus. Strategies that are currently under investigation include optimizing infant vitamin D levels, use of probiotics, as well as eczema prevention.

Vitamin D

Both ecological and epidemiologic evidence suggest a role of vitamin D in the development of food allergy. Several studies have shown higher rates of food allergy, adrenaline-autoinjector prescriptions, and hospital admissions for food-related anaphylaxis in children living further from the equator and those born in winter/autumn compared with summer/spring, both proxies of low vitamin D levels.^{26–32} Vitamin D is associated with immune functioning, and it has been shown to suppress the T-helper type 2 (Th2) response, which is associated with B-cell production of IgE antibodies and food allergy; however, the exact immunologic mechanisms driving the role of vitamin D in the development of food allergy have not been established.

Direct evidence assessing vitamin D levels in infants and the risk of food allergy has only recently become available. The HealthNuts study in Australia provided the first evidence that a directly measured vitamin D level is associated with the risk of food allergy; infants with vitamin D levels less than 50 nmol/L at 1 year of age had an increased risk of challenge-confirmed peanut allergy at 1 year of age by 11-fold (adjusted odds ratio [aOR] 11.51; 95% CI 2.01–65.79) and egg allergy nearly 4-fold (aOR 3.79; 95% CI 1.19–12.08).³³ However, a smaller (n = 274) case-control study also in Australia did not find an association between vitamin D insufficiency at birth or 6 months of age and food allergy at 1 year of age.³⁴ A cross-sectional study in New Zealand reported a 2-fold increased risk of parent-reported doctor-diagnosed food allergy in children aged 2 to 5 years with vitamin D levels greater than 75 nmol/L compared with those with vitamin D levels of 50 to 74 nmol/L, although measurement of vitamin D levels occurred after 2 years of age rather than in infancy when food allergy is likely to have developed.³⁵ There may be a U-shaped association, that is, an increased risk in individuals with both low and high levels of vitamin D, as has been suggested for high IgE levels.³⁶

Well-designed randomized controlled trials (RCTs) are needed to assess the role of vitamin D supplementation as a preventative strategy for food allergy and to establish whether vitamin D has a causal role in the development of food allergy. Several studies assessing maternal and postnatal vitamin D supplementation have failed to demonstrate a protective benefit against respiratory and allergic outcomes in their offspring.^{37–39} This lack of beneficial effect may be because maternal administration of vitamin D is not the optimal route to impact on child outcomes. To date, there are no completed RCTs assessing vitamin D supplementation in infancy to prevent food allergy. The VITALITY study, an RCT investigating the use of vitamin D supplementation in infancy to prevent food allergy, is currently underway.⁴⁰

Probiotics

Observational studies have shown that factors associated with increased microbial exposure, such as exposure to pet dogs, living on a farm, childcare attendance, and the presence of older siblings, may have a protective effect against developing food allergy.^{41,42} The role that microbial exposure may play in the development of food allergy is described by the hygiene hypothesis, which postulates that a lack of exposure to microbes and infections in early childhood increases susceptibility to allergic disease by modulating the development of the immune system.⁴³ The gut microbiota plays an important role in the development and healthy functioning of the immune system, and its role in the development of food allergy has been a subject of interest in the scientific community. Disruption of the gut microbiota in infancy when the immune system is developing alters the Th1/Th2 balance in the intestinal mucosa and may contribute to the development of Th2-dependent allergic disease.^{44–46}

Probiotics are live microorganisms, such as bacteria belonging to the *Lactobacillus* and *Bifidobacterium* groups, and can modulate the immune response by stimulating production of Th1 cytokines, suppressing the Th2 allergic response. Therefore, probiotic supplementation is another plausible target for both the prevention and treatment of allergic disease. Studies assessing probiotic supplementation have tended to use food sensitization as an outcome rather than challenge-proven food allergy. In 2014, the World Allergy Organization conducted a systematic review and meta-analysis of RCTs assessing probiotic supplementation for allergy prevention. They found no evidence to support that probiotic supplementation reduced the risk of food allergy, although probiotic use in pregnancy, breastfeeding, and infancy reduced the risk of eczema in infants, with low-certainty evidence requiring caution in interpretation of these findings.^{47,48} In 2016, another meta-analysis found that probiotic supplementation when administered both prenatally and postnatally reduced the risk of food sensitization (RR 0.77; 95% CI 0.61–0.98), although there was no protective effect demonstrated when probiotics were administered only prenatally (RR 1.01; 95% CI 0.66–1.55) or only postnatally (RR 1.43; 95% CI 0.94–2.18).⁴⁹ Further studies on the use of probiotics as a prevention strategy for food allergy using challenge-proven outcomes are needed.

Eczema Prevention

A history of eczema is one of the strongest known risk factors for food allergy. A recent population-based study of more than 5000 infants showed that those with eczema were approximately 5 times more likely to develop food allergy than infants without eczema. One in 5 infants with eczema had challenge-confirmed allergy to egg white, peanut, or sesame by 12 months of age, compared with only 1 in 25 infants without eczema.⁵⁰ The risk of food allergy increased with an earlier age at onset and increasing severity of eczema, with approximately 50% of infants whose eczema started in the

first 3 months of life and required treatment with topical corticosteroids developing a food allergy.

Skin barrier dysfunction is a feature of eczema and is thought to play an important role in the initiation of allergic sensitization and subsequent progression to food allergy and other allergic disease.^{51–53} Therefore, prevention of eczema in early life may have a follow-on effect of preventing food allergy and other allergic diseases later in childhood.

One of the primary targets for eczema prevention is improving skin barrier integrity through regular application of a moisturizing cream in infants. RCT evidence supports efficacy of this intervention for reducing eczema.^{54,55} However, it is yet to be determined whether prevention of eczema in early life will subsequently prevent allergic sensitization and food allergy. In an RCT of 118 high-risk infants, moisturizer was applied daily for the first 32 weeks of life ($n = 59$) and reduced the incidence of eczema by 32%. However, this trial failed to show an effect of the intervention on reducing egg sensitization at 32 weeks of age. Sensitization to other food and inhalant allergens was not measured.⁵⁴ A recent pilot RCT ($n = 80$) of twice-daily application of a ceramide-dominant moisturizing cream for the first 6 months of life showed a trend toward reduced eczema in the intervention group at 12 months of age (RR 0.32; 95% CI 0.07–1.51), although this did not reach statistical significance. Per protocol analysis showed a significant reduction in food sensitization at 12 months of age in the intervention group (0% vs 19.4%, $P = .04$), although this was not significant on intention-to-treat analysis.⁵⁶ The results of this pilot study are promising; further larger trials are needed, incorporating challenge-proven food allergy outcomes, to assess the potential of eczema prevention as a preventive strategy for food allergy.

SUMMARY

New food allergy prevention strategies, focused on promoting timely introduction of allergenic foods (predominantly peanut) into the infant diet, have been introduced in several countries. Additional prevention strategies are currently under investigation and are likely to expand our knowledge for foods other than peanut and how to prevent cases that are not preventable through timely allergen introduction in the infant diet. It will be important to monitor population responses to, and effectiveness of, existing and new prevention strategies as they are implemented and to have mechanisms in place to allow rapid adaption of prevention guidelines if necessary as new data come to light.

REFERENCES

1. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998–1999 to 2011–2012. *J Allergy Clin Immunol* 2015;136(2):367–75.
2. Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000–2009. *J Allergy Clin Immunol* 2014;134(4):960–2.
3. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol* 2015;135(4):956–63.
4. Xepapadaki P, Fiocchi A, Grabenhenrich L, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life - the EuroPrevall birth cohort study. *Allergy* 2016;71(3):350–7.
5. Schoemaker AA, Sprickelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children - EuroPrevall birth cohort. *Allergy* 2015;70(8):963–72.

6. Koplin JJ, Wake M, Dharmage SC, et al. Cohort profile of the HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol* 2015;44(4):1161–71.
7. Basera W, Botha M, Gray CL, et al. The South African food sensitisation and food allergy population-based study of IgE-mediated food allergy: validity, safety, and acceptability. *Ann Allergy Asthma Immunol* 2015;115(2):113–9.
8. Chen J, Hu Y, Allen KJ, et al. The prevalence of food allergy in infants in Chongqing, China. *Pediatr Allergy Immunol* 2011;22(4):356–60.
9. Koplin JJ, Allen KJ. Optimal timing for solids introduction - why are the guidelines always changing? *Clin Exp Allergy* 2013;43(8):826–34.
10. 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):984–91.
11. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372(9):803–13.
12. Palmer DJ, Metcalfe J, Makrides M, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. *J Allergy Clin Immunol* 2013;132(2):387–92.
13. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374(18):1733–43.
14. Ierodiakonou D, Garcia-Larsen V, Logan A, 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.
15. Koplin JJ, Peters RL, Dharmage SC, et al. Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy. *J Allergy Clin Immunol* 2016;138(4):1131–41.
16. Gruchalla RS, Sampson HA. Preventing peanut allergy through early consumption—ready for prime time? *N Engl J Med* 2015;372(9):875–7.
17. Peters RL, Koplin JJ, Gurrin LC, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. *J Allergy Clin Immunol* 2017;140(1):145–53.
18. Peters RL, Allen KJ, Dharmage SC, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. *Clin Exp Allergy* 2015;45(5):953–63.
19. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126(1):77–82.
20. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126(4):807–13.
21. McWilliam V, Koplin J, Lodge C, et al. The prevalence of tree nut allergy: a systematic review. *Curr Allergy Asthma Rep* 2015;15(9):54.
22. Sasaki M, Koplin JJ, Dharmage SC, et al. Prevalence of clinic-defined food allergy in early adolescence: the SchoolNuts study. *J Allergy Clin Immunol* 2017. [Epub ahead of print].
23. Tham EH, Lee BW, Chan YH, et al. Low food allergy prevalence despite delayed introduction of allergenic foods-data from the GUSTO cohort. *J Allergy Clin Immunol Pract* 2017. [Epub ahead of print].
24. Tey D, Allen KJ, Peters RL, et al. Population response to change in infant feeding guidelines for allergy prevention. *J Allergy Clin Immunol* 2014;133(2):476–84.

25. Tang MLK, Koplin JJ, Sampson HA. Skin testing is necessary before early introduction of peanut for prevention of peanut allergy: pro-con debate. *J Allergy Clin Immunol Pract* 2017 [Epub ahead of print].
26. Camargo CA Jr, Clark S, Kaplan MS, et al. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007;120(1):131–6.
27. Hoyos-Bachiloglu R, Morales PS, Cerda J, et al. Higher latitude and lower solar radiation influence on anaphylaxis in Chilean children. *Pediatr Allergy Immunol* 2014;25(4):338–43.
28. Mullins RJ, Camargo CA. Latitude, sunlight, vitamin D, and childhood food allergy/anaphylaxis. *Curr Allergy Asthma Rep* 2012;12(1):64–71.
29. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol* 2009;103(6):488–95.
30. Mullins RJ, Clark S, Katelaris C, et al. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 2011;22(6):583–9.
31. Oktaria V, Dharmage SC, Burgess JA, et al. Association between latitude and allergic diseases: a longitudinal study from childhood to middle-age. *Ann Allergy Asthma Immunol* 2013;110(2):80–5.
32. Vassallo MF, Banerji A, Rudders SA, et al. Season of birth and food allergy in children. *Ann Allergy Asthma Immunol* 2010;104(4):307–13.
33. Allen KJ, Koplin JJ, Ponsonby AL, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;131(4):1109–16.
34. Molloy J, Koplin JJ, Allen KJ, et al. Vitamin D insufficiency in the first 6 months of infancy and challenge-proven IgE-mediated food allergy at 1 year of age: a case-cohort study. *Allergy* 2017;72(8):1222–31.
35. Cairncross C, Grant C, Stonehouse W, et al. The relationship between vitamin D status and allergic diseases in New Zealand preschool children. *Nutrients* 2016; 8(6).
36. Hypponen E, Berry DJ, Wjst M, et al. Serum 25-hydroxyvitamin D and IgE - a significant but nonlinear relationship. *Allergy* 2009;64(4):613–20.
37. Chawes BL, Bonnelykke K, Stokholm J, et al. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. *JAMA* 2016;315(4):353–61.
38. Goldring ST, Griffiths CJ, Martineau AR, et al. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. *PLoS One* 2013;8(6): e66627.
39. Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin d on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. *JAMA* 2016;315(4):362–70.
40. Allen KJ, Panjari M, Koplin JJ, et al. VITALITY trial: protocol for a randomised controlled trial to establish the role of postnatal vitamin D supplementation in infant immune health. *BMJ Open* 2015;5(12):e009377.
41. Marrs T, Bruce KD, Logan K, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 2013; 24(4):311–20.
42. Koplin JJ, Dharmage SC, Ponsonby AL, et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012; 67(11):1415–22.

43. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299(6710): 1259–60.
44. Shreiner A, Huffnagle GB, Noverr MC. The “microflora hypothesis” of allergic disease. *Adv Exp Med Biol* 2008;635:113–34.
45. Aitoro R, Paparo L, Amoroso A, et al. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. *Nutrients* 2017;9(7).
46. Tsabouri S, Piftits KN, Chaliasos N, et al. Modulation of gut microbiota downregulates the development of food allergy in infancy. *Allergol Immunopathol (Madr)* 2014;42(1):69–77.
47. Cuello-Garcia CA, Brozek JL, Fiocchi A, et al. Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2015;136(4):952–61.
48. Fiocchi A, Pawankar R, Cuello-Garcia C, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. *World Allergy Organ J* 2015;8(1):4.
49. Zhang GQ, Hu HJ, Liu CY, et al. Probiotics for prevention of atopy and food hypersensitivity in early childhood: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine* 2016;95(8):e2562.
50. Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015; 45(1):255–64.
51. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121(6): 1331–6.
52. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(6 Suppl):S118–27.
53. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol* 2017;139(6):1723–34.
54. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;134(4): 824–30.e6.
55. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;134(4):818–23.
56. Lowe AJ, Su JC, Allen KJ, et al. A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation: the PEBBLES pilot study. *Br J Dermatol* 2017. [Epub ahead of print].