

Prospects for Prevention of Food Allergy



Katrina J. Allen, MD, PhD^{a,b,c,d}, and Jennifer J. Koplin, PhD^{a,c} Melbourne, Australia; and Manchester, United Kingdom

A rise in both prevalence and public awareness of food allergy in developed countries means that clinicians and researchers are frequently asked to explain reasons for the increase in food allergy, and families are eager to know whether they can take steps to prevent food allergy in their children. In this review, we outline leading theories on risk factors for early life food allergy. We summarize the leading hypotheses to explain the increase in food allergy as “the 5 Ds”: dry skin, diet, dogs, dribble (shared microbial exposure), and vitamin D. We discuss currently available evidence for these theories and how these can be translated into clinical recommendations. With the exception of dietary intervention studies, evidence for each of these theories is observational, and we describe the implications of this for explaining risk to families. Current infant feeding recommendations are that infants should be introduced to solids around the age of 4 to 6 months irrespective of family history risk and that allergenic solids do not need to be avoided, either by infants at the time of solid food introduction or by mothers whilst pregnant or lactating. Additional potential strategies currently being explored include optimization of early life skin barrier function through a decrease in drying soaps and detergents and an increase in the use of nonallergenic moisturizers. The investigation of the role of microbiota and vitamin D is ongoing and cannot yet be translated into clinical recommendations. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:215-20)

Key words: Food allergy; Peanut allergy; Eczema; Hygiene hypothesis; Microbial exposure; Vitamin D; Migration

WHY IS FOOD ALLERGY ON THE RISE?

The rise in food allergy in developed countries is an intriguing phenomenon that has captured the attention of both the medical research community and the media. Although we need to be circumspect about the extent to which it has risen and which countries are most affected, there is little doubt that IgE-mediated food allergy and anaphylaxis were rarely reported 50 years ago but are now commonly described. The drivers for this modern-day epidemic are poorly understood, and indeed it is not clear whether this phenomenon is part of a second wave of allergy epidemic¹ following on from the general rise in allergic disease that was noted around the world at the end of the 21st century or whether the new food allergy epidemic is due to a new set of unique factors.

The possibility remains that this second wave of allergy epidemic has its roots in events that occurred when the parents of current children were *in utero*, and we are witnessing the expression of an epigenetic effect that has been transmitted through to the next generation—through a heritable epigenetic mechanism. Against this hypothesis is emerging evidence that postnatal factors, which are both common and modifiable, are associated with an increased risk of food allergy. If these factors that we describe in detail below are found to be causal, they will provide an important underpinning of new public health guidelines. However, evidence of causality needs to be generated through carefully controlled randomized trials or through elucidation of biological mechanisms that point to plausibility of such hypotheses, and as such there is currently insufficient data for informed public health guidelines for several of these factors.

In the meantime, as allergy clinicians and researchers, we are routinely asked whether food allergy is on the rise and why. Families are eager to know whether there are factors under their control that may have contributed to the development of food allergy in their children. They are also keen to know what steps they can take to prevent food allergy in subsequent children. Below we outline the emerging evidence for risk factors of early life food allergy. With the exception of the Learning Early about Peanut Allergy study,² evidence to date is primarily epidemiological or ecological. As such a word of caution is required in explaining risk to families. Careful adjustment for confounding is central to good quality epidemiological studies. For instance, families at high risk of allergic disease are more likely to breast-feed because guidelines inform them that breastfeeding may be protective. If researchers do not adjust their analysis for family history risk of allergy (the real reason why offspring are likely to be more allergic), it can appear that breastfeeding actually increases the risk of allergic disease that is of course spurious. This is called “reverse causation” and is one of the reasons why randomized controlled trials (RCTs) are required to provide level 1 evidence that a factor is indeed a risk factor. Even with the best intention, observational studies can be undermined by unmeasured confounders and as such clear high-quality data for a risk

^aCentre of Food and Allergy Research, Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia

^bDepartment of Allergy and Clinical Immunology and Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia

^cDepartment of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia

^dInstitute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom

No funding was received for this work

Conflicts of interest: K. J. Allen has received speakers' honoraria from Nutricia, Wyeth, Pfizer, AspenCare, Nestle, Abbott, and Danone; and is an unpaid board member for Ilhan Food Allergy Foundation. J. J. Koplin declares that she has no relevant conflicts.

Received for publication September 10, 2015; revised October 13, 2015; accepted for publication October 16, 2015.

Available online January 2, 2016.

Corresponding author: Katrina J. Allen, MD, PhD, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville 3052, Victoria, Australia. E-mail: katie.allen@rch.org.au.

2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.10.010>

Abbreviations used

EAT- Early introduction of allergenic foods to induce tolerance in infants
EHF- Extensively hydrolyzed formula
GINI- German Infant Nutritional Intervention
PHF- Partially hydrolyzed formula
RCT- Randomized controlled trial

factor must be evident before recommendations are incorporated into public health guidelines. With these qualifications in mind, clinicians can still provide carefully framed information to individual patients about emerging evidence and allow families to decide for themselves whether to act on the information or not.

When asked by a curious member of the public why food allergy is on the rise, we often find we have long-winded academic responses. So we have summarized our response to this question with an overview of the emerging hypotheses in an easily digestible way. This overview is not meant to be exhaustive but provides information for consumers that helps to explain that there is a rapidly emerging body of research attempting to elucidate the cause of food allergy. It is not yet clear whether there is one main hypothesis that accounts for the epidemic or whether a number of factors act in concert. Alternatively, there may be multiple pathways to disease.

In the next sections, we outline 5 current leading hypotheses (dubbed the “5 Ds”: dry skin, diet, dogs, dribble, and vitamin D) for the rise in food allergy and then conclude with an interesting and perhaps illuminating observation that offspring of migrants moving from developing to developed countries have the highest risk of food allergy if the offspring are born in the developed country. We conclude with some simple recommendations that families might consider whilst waiting for level 1 evidence to emerge to inform the construction of updated public health guidelines.

DRY SKIN

Clinicians have recognized for many years a strong association between eczema and food allergy. Not only are infants with eczema 5 times more likely to develop IgE-mediated food allergy but also more than half of those with moderately severe early-onset eczema (defined as onset before age 3 months and requiring treatment with topical corticosteroids) will develop challenge-proven food allergy by age 1 year.³ This association led researchers to investigate whether the filaggrin gene (which is strongly associated with an increased risk of eczema) independently increases the risk of food allergy. Although some studies suggested that this is the case,⁴ others have found that the real risk that filaggrin confers is probably an increased risk of food sensitization rather than food allergy itself.⁵ The presence of a filaggrin gene mutation does not appear to distinguish between those who are sensitized to foods but clinically tolerant and those who are both sensitized and allergic.

In 2008, Gideon Lack proposed a mechanism to explain the role of skin barrier function in the development of food allergy that he termed the “dual allergen hypothesis”—often now referred to as the “Lack” hypothesis.⁶ The Lack hypothesis proposes that allergic sensitization to foods may occur through exposure to low doses of allergen through the skin because of food allergens absorbed through a damaged skin barrier (such as

in eczema or presence of filaggrin loss-of-function mutations). A second aspect of this hypothesis suggests that oral exposure to these allergens through the consumption of allergenic foods early in infancy can abrogate the development of sensitization and instead result in the development of oral tolerance and prevention of the development of food allergy. Mechanistic evidence supporting this hypothesis comes from mouse models showing that sensitization can be induced following the application of allergen to damaged skin, and that this can be reduced by prior high-dose oral allergen exposure.⁷ Further support of this hypothesis comes from a recent study demonstrating that higher exposure to environmental peanut antigens found in households increases the risk of peanut allergy in children with either filaggrin loss-of-function mutations⁸ or atopic dermatitis.⁹

Two exciting new studies were recently published that both undertook RCTs of daily moisturizing from birth in an attempt to reduce infantile eczema and potentially sensitization to foods. The first demonstrated an impressive 50% reduction in eczema but unfortunately did not examine the protective effect on the development of food allergy.¹⁰ The second assessed both eczema and egg sensitization, and although it also showed a decrease in eczema prevalence in those applying topical moisturizers, it did not appear to have the power to show a statistically significant decrease in food sensitization.¹¹ A number of larger trials are in progress to pursue this concept and inform public health guidelines.

DIET

Allergen exposure

The Lack hypothesis was first promulgated after the publication of a paper by Du Toit et al¹² that found a 5-fold higher prevalence of peanut allergy in Jewish children in the UK versus Jewish children in Israel. Although the dietary history of children in this observational study was not ascertained, the authors reported a significant difference in dietary patterns between the 2 populations. At the time, it was common practice in Israel to introduce a peanut snack (Bomba) as a weaning food into the diet of infants around the age of 4 to 6 months. By contrast, UK guidelines at the time recommended avoidance of peanut until after the age of 3 years. Lack and colleagues² subsequently embarked on a large and ambitious RCT to formally assess whether the early introduction of peanut prevented the development of peanut allergy at age 5 years. The results of this landmark trial were recently published and are the first level 1 evidence to show that the early introduction of peanut (between 4 and 11 months) is protective against peanut allergy in infants who are at high risk (as defined by early-onset eczema or coexistent egg allergy).² A note of caution has been sounded however, as an earlier RCT by Palmer et al¹³ that assessed the role of the early introduction of egg in a similar high-risk group of infants was abandoned because of adverse events at study entry point during egg challenges. This suggests that care needs to be taken at the time of introduction in high-risk infants, and this sentiment is reflected in recently published interim international consensus guidelines.¹⁴ These emerging trials add weight to previous observational studies that delayed timing of introduction of egg,¹⁵ cow's milk,¹⁶ and wheat¹⁷ is associated with an increased risk of those respective food allergies. Of course, the interplay between the timing of introduction of one allergenic solid and another is difficult to tease out both observationally and

in single allergen trials and so the results of trials such as EAT (early introduction of allergenic foods to induce tolerance in infants) that aim to introduce a variety of solids into an infant's diet as early as 3 months are eagerly awaited. In the meantime, there is now strong consensus that delaying the introduction of allergenic solids is unnecessary and may even be harmful. It should be noted that the World Health Organization continues to recommend introduction of solids after the age of 6 months that is in contradistinction to expert body allergy guidelines.¹⁸ Consensus of infant feeding guidelines across different expert bodies would be helpful to the consumer and ensure that fidelity of the recommendation is maintained.

Diet quality and variety

In addition to allergen exposure, the nature and quality of an infant's diet may also play a role in food allergy development with evidence that there have been substantial changes in dietary patterns (both in mothers and their infants) over the period of time that food allergy has risen. A recent prospective birth cohort study of 856 children from rural areas in 5 European countries (the Protection against Allergy: Study in Rural Environments [PASTURE]/Mechanisms of Early Protective Exposures on Allergy Development [EFRAIM] study) followed up to 6 years of age reported that increased diversity of complimentary foods introduced in the first year of life was associated with a reduced risk of doctor diagnosed food allergy and food sensitization.¹⁹ A second nested case-control study of 41 food allergic infants (predominantly egg and milk allergic) and 82 controls within a prospective longitudinal cohort using prospective food diaries also found that dietary patterns in the first year of life consisting of more fresh fruit and vegetables and home-prepared meals were associated with less challenge-proven food allergy by the age of 2 years.²⁰ There was no difference in the age that egg or milk was introduced into the diet of infants with food allergy compared with control infants in this study, suggesting that these differences might not be explained by timing exposure to these foods. The findings from these 2 studies generate interesting hypotheses, although the mechanisms for a protective effect, whether through improved nutrient levels, differences in microbial diversity or microbial products related to higher dietary fiber intake,²¹ or other mechanisms, are currently not clear. Further studies including intervention trials will be required to confirm and extend these findings.

Breastfeeding

Systematic analyses of observational studies on the protective effect of breastfeeding have shown conflicting results, and many of the studies included were conducted decades ago when food allergy was uncommon and methods of assessment were limited.²² An early review by Muraro et al²³ including 15 observational and 14 intervention studies concluded that breastfeeding for at least 4 months was associated with a reduced cumulative risk of cow's milk allergy in high-risk infants over the first 18 months of age. None of these studies were either randomized or prospective, and most systematic reviews since have failed to find a specific beneficial effect on food allergy.^{24,25} Several more recent cohort studies suggested that extended exclusive breastfeeding may increase the likelihood of sensitization or food allergy^{26,27} in infants at high risk (reviewed in Ref. 25). This may relate to the delayed timing of first complementary foods rather than the effects of breast milk per se.

Alternatively, these more recent findings of increased risk of breastfeeding may simply relate to reverse causation, whereby infants already at high risk of food allergy are breastfed for longer because of a perceived benefit for allergic disease and as a result are spurious. In a recent systematic review and meta-analysis,²⁸ there was no evidence that breastfeeding was protective against food allergy. This was despite some evidence that breastfeeding is protective for asthma in children and weaker evidence for a protective effect for eczema up to 2 years of age and allergic rhinitis up to 5 years of age. However, the interpretation of these results should be treated with some caution because many of the studies are low quality (partly because it is unethical to randomize to breast feed or not and therefore RCTs are not available) and there is a high level of heterogeneity across the different studies.

Partially hydrolyzed formula

There has been significant interest in the use of modified infant formulas—especially partially (PHF) and extensively hydrolyzed cow's milk formula (EHF)—for prevention of early childhood allergic disease. Intense expectations from families with a history of allergy seeking readily available primary prevention interventions have been responded to by industry with the development of a range of “allergy prevention” formulae, leading peak expert bodies to provide recommendations regarding the use of formula for prevention of allergies. Current infant feeding guidelines in Europe,²⁹ the USA,³⁰ and Australia all recommended that hydrolyzed formula can be considered as primary prevention therapy for allergic diseases. These guidelines were informed by the conclusions of the Cochrane review, the last update of which occurred in 2009, which supports the use of hydrolyzed formula for the prevention of allergy especially in high-risk infants who are unable to be completely breast fed.³¹ The authors themselves recommend further larger trials because of the methodological concerns and inconsistency of the findings of the studies included in the review. We have recently demonstrated that the Cochrane review suffers from small-study publication bias (scarcity of small negative studies),³² and thus is likely to have overestimated the beneficial effect of PHF. The findings of the Cochrane review were heavily influenced by the reported benefits of PHF demonstrated by the largest study included in the review, the German Infant Nutritional Intervention (GINI) study, a double-blind randomized controlled trial of 2252 infants with a family history of allergy allocated to one of 4 formula types as a milk substitute for the first 4 months of life, if breastfeeding was insufficient. An intention to treat analysis did not demonstrate a difference in eczema up to age 3 years in infants fed partially hydrolyzed whey formula compared with cow's milk formula, although a per-protocol analysis suggested a reduction in eczema in infants fed partially hydrolyzed whey formula.³³ It is important to note that intention to treat is the preferred reporting analysis for RCTs. Since the last update of this review, new evidence from a large intervention trial of high-risk infants (the Melbourne Atopic Cohort Study) has emerged challenging the effectiveness of PHF.³⁴ Additionally, although the results of the large GINI study up until the 6-year follow-up were promising, subsequent results have shown little evidence of an ongoing preventive effect between the ages of 7 and 10 years.³⁵ These more recent findings have also not yet been incorporated into the Cochrane review.³¹ Interestingly, the most recent recommendations from GINI suggest that casein-

predominant EHF might be expected to have a more profound biological effect because the formula is more extensively modified.³⁶ However, most guideline recommendations are based on the fact that PHF is both cheaper and more palatable than EHF and therefore should be considered in place of EHF. Additionally, in some countries, EHF can only be medically prescribed, which significantly increases costs to the health care system.

DRIBBLE AND DOGS (MICROBIAL EXPOSURES)

As described in the landmark paper by David Strachan in 1989,³⁷ the traditional concept of the “hygiene hypothesis” described a protective effect of an increasing number of siblings in a household on the risk of developing allergic rhinitis. This was thought to potentially relate to the shared exposure to common childhood infections transmitted through direct contact with older siblings or by maternal contact with her older children prenatally. Although a protective sibling effect has been confirmed for various food sensitization and allergy outcomes³⁸ including in our own infant cohort study (Healthnuts),³⁹ it is by no means clear as to the underlying mechanism of this phenomenon. Although a protective effect of siblings is interesting and reproducible, changes to postwar houses and sanitation and sizes of families as well as the emergence of national immunization programs with high uptakes moderate our interpretation of the mechanisms underlying the protective effects of siblings. However, sharing of microbiota between siblings may still contribute to this protective effect. A potentially protective effect of shared oral microbiota was suggested by a small study of 184 children in Sweden where children whose parents sucked on their pacifier had both different oral microbiota and less eczema than children whose parents did not suck on their pacifiers.⁴⁰

Further evidence of a protective effect of dog ownership on food allergy risk in Healthnuts³⁹ may point to sharing of microbes or even parasites—the latter underpinning the “old friends hypothesis” that is predicated on the teleological emergence of the IgE antibody immune mechanism as primary protection against parasite infestation.

In pursuit of therapeutic outcomes, a number of trials have assessed the role of probiotics in allergy prevention following on from the concept of the hygiene hypothesis and microbial diversity. However, an overview review (a systematic review of systematic reviews) concluded that there is currently insufficient evidence that probiotics protect against food allergy.³⁹

VITAMIN D

Ecological and epidemiological evidence suggest a potential link between low vitamin D and food allergy risk. Prescriptions of adrenaline autoinjectors and hypoallergenic formulas in children are more common in regions further from the equator, and these findings appear to be independent of longitude, physician density, or socioeconomic status.^{41–44} Pediatric hospital admissions and emergency department visits for food allergy events appear to rise with distance from the equator and among children born in autumn and winter, potentially reflecting lower vitamin D exposure.^{45,46} In Australia, children residing in the south (further from the equator) have twice the odds (95% CI 1.2, 5.0) of peanut allergy at age 4 to 5 years and 3 times (95% CI 1.0, 9.0) the odds of egg allergy than those in the northern states.⁴⁷

We recently described that infants with vitamin D insufficiency were 3 times more likely to have either peanut or egg

allergy, the odds increasing to 4-fold among those with 2 or more food allergies. Furthermore, among food-sensitized infants, those with vitamin D insufficiency were 6 times more likely to be food allergic than tolerant.⁴⁸ These effects were observed among infants with Australian-born parents but not those with parents born outside Australia. The investigation of genetic risk factors may help to explain these differences in associations between populations. Genetic polymorphisms contribute to the variation in vitamin D binding protein levels, explaining almost 80% of variation in levels. Binding protein levels in turn alter the biological availability of serum vitamin D, with lower levels increasing the availability of serum vitamin D (25OHD3). We also found that polymorphisms resulting in lower binding protein levels appeared to compensate for the adverse effects of low serum vitamin D on food allergy risk,⁴⁹ presumably by increasing the ability to utilize available vitamin D.

As well as supporting a potentially causal link between vitamin D and food allergy, these findings suggest that reference ranges to define low levels of serum vitamin D with a detrimental effect on food allergy risk may need to take into account differences in binding protein level. It is also suggested that there may be a need to consider stratification of risk factors by genetic risk—a concept consistent with personalized or precision public health guidelines.

EFFECT OF MIGRATION

We have recently noted an interesting and illuminating ecological association. In Healthnuts, challenge-confirmed peanut allergy was 3 times more common in infants with parents born in East Asia compared with those with parents born in Australia.⁵⁰ Similar effects were seen for other food sensitizations and food allergies and for eczema. The increased risk of allergic disease in Australian-born infants of Asian-born parents appears to have occurred in a single generation, with the prevalence of reported allergic disease similar or even lower in Asian-born parents themselves compared with Australian-born parents. Furthermore, the increased risk of peanut allergy appeared to be specific to infants of Asian parents and was not seen among infants of parents born in the UK or Europe. We have confirmed this finding in a separate cohort in Victoria and additionally found that children born in Asia who subsequently migrate to Australia in early life are protected against food allergy (Panjari et al 2015, manuscript submitted). Migration is likely to be associated with changes to all of the factors described above, which in the context of a particular genetic background may contribute to the high risk of food allergy in the Asian population born in Australia. Earlier observations from the UK of an overrepresentation of non-Caucasian children in pediatric allergy clinics suggest that this migration effect may also be present among children of Asian parents migrating to other developed countries.^{51,52} In the National Health and Nutrition Examination Survey in the USA, children born in the USA to immigrant parents had the highest risk of food sensitization, compared with both children born in the USA to US-born parents and children born outside the USA.⁵² Similar risk factors might apply in all of these cases.

Migration to more developed countries may be associated with changes to a number of potentially interrelated factors, including humidity (with an impact on skin barrier function), microbial exposure (hygiene hypothesis), dietary changes, and changes in

latitude (vitamin D).⁵³ These factors could act through a number of mechanisms to increase the risk of food allergy. Genetic polymorphisms more prevalent in the Asian population because of selective pressures of the Asian environment might increase the risk of allergy when these environmental factors are removed after migration. Alternatively, transgenerational effects might be involved, perhaps acting through epigenetic modifications. Maternal environmental exposures in a less developed country could affect the epigenetic signature of the offspring such that the child growing up in a more developed country and lacking these same exposures is at increased risk.

WHAT CAN WE TELL OUR FAMILIES?

- (1) Emerging evidence suggests that optimization of early life skin barrier function through a decrease in drying soaps and detergents and an increase in the use of nonallergenic moisturizers is a reasonable clinical recommendation.
- (2) Current allergy recommendations are that infants should be introduced to solids around the age of 4 to 6 months irrespective of family history risk and that allergenic solids do not need to be avoided by infants when solids are introduced or by mothers when breastfeeding or lactating^{30,54} (www.allergy.org.au—Australasian Society of Clinical Immunology and Allergy infant feeding guidelines).
- (3) It is universally agreed that human milk should be the first and most important source of nutrition for the infant as it contains a vast array of bioactive factors including hormones, growth factors, neuropeptides, anti-inflammatory, and immunomodulatory agents that influence many physiological systems and promote normal gut colonization. Its role in protection against food allergy risk remains unclear.
- (4) The data suggest that recommendation of modified formula as a prevention measure for allergic disease may be premature, with the results of an updated Cochrane review expected to further inform infant feeding guidelines.
- (5) There is insufficient data that probiotics or prebiotics protect against food allergy.
- (6) At this point in time, there is insufficient evidence to support the use of vitamin D either as a prevention or treatment for food allergy.

REFERENCES

1. Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011;22:155-60.
2. 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.
3. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy* 2015;45:255-64.
4. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;127:661-7.
5. Tan HT, Ellis JA, Koplin JJ, Matheson MC, Gurrin LC, Lowe AJ, et al. Filaggrin loss-of-function mutations do not predict food allergy over and above the risk of food sensitization among infants. *J Allergy Clin Immunol* 2012;130:1211-1213.e3.
6. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012;129:1187-97.
7. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin Exp Allergy* 2005;35:757-66.
8. 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;134:867-875.e1.
9. Brough HA, Liu AH, Sicherer S, Makinson K, Douiri A, Brown SJ, et al. Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. *J Allergy Clin Immunol* 2015;135:164-70.
10. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;134:818-23.
11. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;134:824-830.e6.
12. 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.
13. 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;132:387-392.e1.
14. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. *J Allergy Clin Immunol* 2015;136:258-61.
15. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-13.
16. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126:77-82.e1.
17. Poole JA, Barriga K, Leung DY, Hoffman M, Eisenbarth GS, Rewers M, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006;117:2175-82.
18. Koplin JJ, Allen KJ. Optimal timing for solids introduction—why are the guidelines always changing? *Clin Exp Allergy* 2013;43:826-34.
19. Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuit J, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. *J Allergy Clin Immunol* 2014;133:1056-64.
20. Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN, et al. Diet and food allergy development during infancy: birth cohort study findings using prospective food diary data. *J Allergy Clin Immunol* 2014;133:511-9.
21. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 2014;40:833-42.
22. Grimshaw KE, Allen K, Edwards CA, Beyer K, Boulay A, van der Aa LB, et al. Infant feeding and allergy prevention: a review of current knowledge and recommendations. *A EuroPrevall state of the art paper. Allergy* 2009;64:1407-16.
23. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15:291-307.
24. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. *Adv Exp Med Biol* 2004;554:63-77.
25. de Silva D, Geromi M, Halken S, et al. Primary prevention of food allergy in children and adults: systematic review. *Allergy* 2014;69:581-9.
26. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol* 1999;104(Pt 1):457-61.
27. Wetzig H, Schulz R, Diez U, Viehweg B, Borte M, et al. Associations between duration of breast-feeding, sensitization to hens' eggs and eczema infantum in one and two year old children at high risk of atopy. *Int J Hygiene Environ Health* 2000;203:17-21.
28. Lodge CJ, Tan DJ, Lau M, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* 2015;104:38-53.
29. 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;46:99-110.
30. Greer FR, Sicherer SH, Burks AW. American Academy of Pediatrics Committee on N, American Academy of Pediatrics Section on A, 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;121:183-91.
31. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;(4):CD003664.

32. Lowe AJ, Dharmage SC, Allen KJ, Tang ML, Hill DJ. The role of partially hydrolyzed whey formula for the prevention of allergic disease: evidence and gaps. *Expert Rev Clin Immunol* 2013;9:31-41.
33. Allen KJ, Lowe AJ, Dharmage SC. The role of hydrolysates for atopy prevention—con. *Pediatr Allergy Immunol* 2013;24:724-6.
34. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2011;128:360-5.e4.
35. von Berg A, Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013;131:1565-73.
36. von Berg A, Koletzko S, Filipiak-Pittroff B, Heinrich J, Bauer CP, Kramer U, et al. The German Infant Nutritional Intervention (GINI) study and formulation issues. Reply. *J Allergy Clin Immunol* 2013;132:770-1.
37. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
38. Marrs T, Bruce KD, Logan K, Rivett DW, Perkin MR, Lack G, et al. Is there an association between microbial exposure and food allergy? A systematic review. *Pediatr Allergy Immunol* 2013;24:311-20.e8.
39. Koplin JJ, Dharmage SC, Ponsonby AL, Tang ML, Lowe AJ, Gurrin LC, et al. Environmental and demographic risk factors for egg allergy in a population-based study of infants. *Allergy* 2012;67:1415-22.
40. Hesselmar B, Sjöberg F, Saalman R, Adlerberth I, Wold AE. Pacifier cleaning practices and risk of allergy development. *Pediatrics* 2013;131:e1829-37.
41. Mullins R, Clark S, Camargo CJ. Regional variation in EpiPen prescriptions in Australia: More evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol* 2009;103:488-95.
42. Camargo CA, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007;120:131-6.
43. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol* 2010;21(Pt 2):e413-20.
44. Rudders SA, Espinola JA, Camargo CA Jr. North-south differences in US emergency department visits for acute allergic reactions. *Ann Allergy Asthma Immunol* 2010;104:413-6.
45. Vassallo MF, Banerji A, Rudders SA, Clark S, Camargo CA Jr. Season of birth and food-induced anaphylaxis in Boston. *Allergy* 2010;65:1492-3.
46. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA Jr. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 2011;22:583-9.
47. Osborne NJ, Ukoumunne OC, Wake M, Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. *J Allergy Clin Immunol* 2012;129:865-7.
48. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *J Allergy Clin Immunol* 2013;131:1109-16.
49. Koplin JJ, Suaini NH, Vuillermin P, Ellis JA, Panjari M, Ponsonby AL, et al. Polymorphisms affecting vitamin D-binding protein modify the relationship between serum vitamin D (25[OH]D) and food allergy. *J Allergy Clin Immunol* 2015 [Epub ahead of print].
50. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML, et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014;69:1639-47.
51. Dias RP, Summerfield A, Khakoo GA. Food hypersensitivity among Caucasian and non-Caucasian children. *Pediatr Allergy Immunol* 2008;19:86-9.
52. Keet CA, Wood RA, Matsui EC. Personal and parental nativity as risk factors for food sensitization. *J Allergy Clin Immunol* 2012;129:169-75.e1-5.
53. Allen KJ, Koplin JJ. Why does Australia appear to have the highest rates of food allergy? [e-pub ahead of print]. *Pediatr Clin North Am* 2015;62:1441-51.
54. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;69:590-601.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.