



Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic?

Jennifer J. Koplin^{a,b}, E.N. Clare Mills^c, and Katrina J. Allen^{a,c}

Purpose of review

Food-induced anaphylaxis continues to be an important cause of hospital admissions, particularly in children. This review outlines recent advances in understanding the epidemiology of IgE-mediated food allergy and potential mechanisms for its rise in prevalence.

Recent findings

The rise in food allergy prevalence in Western countries has happened more quickly than changes to the genome can occur; thus, environmental changes are likely to be important. Recent studies, however, suggest that genetic risk determines responses to environmental risk factors. Environmental peanut exposure has been associated with increased peanut allergy risk in individuals with filaggrin null mutations, consistently with sensitization occurring through a damaged skin barrier. Reduced microbial and vitamin D exposure is also leading candidates for risk factors for food allergy in the context of genetic susceptibility. In addition, HLA-DR and HLA-DQ gene region variants appear to play a role in peanut allergy, although no studies have yet assessed their susceptibility to environmental cues. Finally, findings from observational cohorts and the first large-scale intervention trials for food allergy prevention support early oral allergen exposure to reduce the prevalence of specific food allergies, which is informing changes in public health guidelines at the population level. Further research will be required to assess the impact of these guideline changes on the population prevalence of food allergy.

Summary

New studies are providing important insights into the prevalence, causes, and mechanisms of food allergy. Recent findings are informing changes to population health guidelines in developed countries, which have the potential to halt or reverse the increase in food allergy prevalence. By contrast, food allergy in the developing world remains understudied.

Keywords

epidemiology, food allergy, gene–environment interactions, genetics, prevalence, risk factors

INTRODUCTION

IgE-mediated food allergy continues to be an important cause of anaphylaxis hospital admissions in the developed world, particularly in children and young adults. By contrast food allergy in the developing world remains understudied. Despite an increasing awareness of food allergy as an important public health issue in the Western world, the epidemiology has been poorly understood. New studies are, however, starting to provide insights into the prevalence, causes and mechanisms of this condition. Recent findings are informing changes to population health guidelines in developed countries, which have the potential to halt or reverse the increase in food allergy prevalence. In

this review, we outline recent advances in characterizing the epidemiology of IgE-mediated food allergy.

^aMurdoch Childrens Research Institute, University of Melbourne Department of Paediatrics and Royal Children's Hospital, ^bSchool of Population and Global Health, University of Melbourne, Parkville, VIC, Australia and ^cUniversity of Manchester, Institute of Inflammation and Repair and Manchester Institute of Biotechnology, Manchester, UK

Correspondence to Dr Jennifer J. Koplin, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, VIC 3052, Australia. Tel: +61 3 8341 6236; e-mail: jennifer.koplin@mcri.edu.au

Curr Opin Allergy Clin Immunol 2015, 15:409–416

DOI:10.1097/ACI.0000000000000196

KEY POINTS

- The rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by population-based changes in genetic sequence, supporting a key role for environmental factors.
- There is increasing evidence that the effect of environmental factors on risk of food allergy depends on genetic predisposition.
- Evolving evidence points to differential risk factors (both genetic and environmental) for different phenotypes of allergic disease, such as differences in risk factors for IgE-mediated peanut vs. egg allergy.
- Findings from the first large-scale intervention trial for prevention of peanut allergy provide support for current infant feeding guidelines which recommend introduction of potentially allergenic foods including peanut around 4–6 months of age.

FOOD ALLERGY PREVALENCE IN WESTERN AND NON-WESTERNIZED COUNTRIES

Traditionally, the prevalence of allergic disease was thought to be lower in non-Westernized countries, although allergy has generally been less studied in these countries. Global studies using uniform validated methodology such as the International Study of Asthma and Allergies in Childhood [1] found a lower prevalence of childhood eczema in developing countries. Recent evidence, however, suggests there has been a rise in eczema in low-income countries in Africa and East Asia [2]. If true, we might also expect a rise in food allergy prevalence in these countries as early onset eczema (or atopic dermatitis) is strongly associated with an increased risk of food allergy in infants [3[¶]].

Studies of challenge-confirmed food allergy prevalence using standardized methodology between countries are essential to further our understanding of both the burden of food allergy and differential risk factors (both genetic and environmental) between countries and their impact on risk of food allergy development. These data are being collected throughout Europe and several partner countries as part of the EuroPrevall project [4] through studies in unselected populations, with a birth cohort collecting data in infants and young children [5] and community surveys in school age children and adults [6]. The study centres spanned the different climatic regions of Europe and were complimented by an outpatient clinic study [7] which provided a large cohort of well characterized food allergic individuals for other investigations, including low-dose threshold studies.

The birth cohort recruited a total of 12 049 babies and their families, with 9336 children being followed up to the age of 24 months [8]. Although the overall adjusted incidence of challenge-proven cow's milk allergy in the cohort was 0.74% (95% confidence interval 0.56–0.97), rates of allergy varied widely across Europe [9[¶]]. Thus, the incidence was highest (~1.3%) in Lithuania and the UK, whereas in Greece no individuals were identified with a challenge-proven cow's milk allergy. Overall, around one in every five children with cow's milk allergy had no serum-specific IgE to cow's milk, although again rates varied across Europe, with around half of all confirmed adverse reactions to cow's milk in the UK not involving IgE. All of the children with non IgE-mediated cow's milk allergy became tolerant during the year following their original diagnosis, as did 57% of the children with IgE-mediated allergy. These differences in prevalence across Europe, as well as differences in prevalence compared with other cohort studies outside Europe conducted in the same age group [10], suggest regional variations in environmental and lifestyle factors will be important to dissect.

There is international variation in food allergens most commonly associated with reactions in both children and adults although it can be difficult to compare results between studies as methods vary. In infants and young children, cow's milk and egg allergy are the most commonly reported food allergies, with egg allergy predominating in Australia and Asia and milk allergy in the Americas and the Middle East. In older children and adults, seafood (fish and shellfish) are commonly reported allergens in Asia, whereas peanut and other nuts are commonly reported allergens in Australia, Western Europe and the United States [11]. In some areas of Europe, IgE-mediated sensitization to plant components related to pollen allergens (associated with oral allergy syndrome) is common in adults and correlates with prevalence of sensitization to birch-pollen-associated allergens [12]. A molecular analysis of patterns of sensitization to hazelnut in 423 patients from the EuroPrevall outpatient clinic study [13[¶]] further emphasized that birch-pollen-driven sensitization to the hazelnut PR10 homologue, Cor a 18 dominated in most European centres apart from those in the south of Europe (Sofia, Athens and Madrid) and Reykjavik where reporting of hazelnut allergy was also less frequent. Instead sensitization to the lipid transfer protein from hazelnut dominated in Athens and Madrid, while storage proteins (Cor a 9, 11) and oleosin (Cor a 12) were relatively minor allergens. For peanut the dominant allergen in all centres was the 2S albumin allergen Ara h 2 with allergen specific IgE at least 1.0 kUA/l

conferring a 97% probability for a systemic reaction ($P=0.0002$) [14[¶]]. Sensitization to Ara h 1 and 2 was exclusively observed in early onset peanut allergy. As for hazelnut, geographic differences in sensitization were observed, with the PR10 homologue Ara h 8 being an important sensitizer in central/western Europe and the lipid transfer protein allergen, Ara h 9 being important in southern Europe. Individuals sensitized to Ara h 8 or 9 and not to storage proteins (Ara h 1, 2, 3) were, however, peanut tolerant.

Confirmation of allergy in all the EuroPrevall cohort studies was undertaken using a harmonized low-dose threshold study protocol, which allowed examination of eliciting doses for different foods (the lowest dose at which a reaction occurred in allergic individuals). These data were pooled and dose distributions modelled using interval censoring survival analysis with three parametric approaches for five allergenic foods, peanut, hazelnut, celery, fish and shrimp [15[¶]]. The plant-based foods (peanut, hazelnut and celeriac) gave similar dose distributions with estimated doses eliciting reactions in 10% of the allergic population (ED10) ranging from 1.6 to 10.1 mg protein with overlapping 95% confidence intervals. Fish gave a slightly higher ED10 value of 27.3 mg protein, although the confidence intervals were wide and overlapping between fish and the plant foods. Shrimp gave radically different dose distributions with an ED10 of 2.5 g protein, almost 100-fold greater than the other foods, despite anecdotal reports of traces of shrimp causing allergic reactions.

IS THERE AN INCREASING PREVALENCE OF FOOD ALLERGY AND FOOD-INDUCED ANAPHYLAXIS?

Increasing recognition of the importance of food allergy in the population is illustrated by an increasing number of prevalence studies internationally. Unfortunately, characterizing long-term trends in prevalence is difficult as there are no earlier population-based prevalence studies from before about 20 years ago with which these new figures can be compared. More recently, several repeated cross-sectional studies within the same population provide some evidence of an increase in food allergy over a 10-year period. In a UK study, Venter *et al.* [16] found in three sequential early childhood cohorts from the same geographic area that peanut sensitization and allergy increased from 1993–1994 (1.3% and 0.5%, respectively) to 1997–1999 (3.3% and 1.4%). There was no further increase in 2004–2005 (2.0% and 1.2%). Between three US-wide phone surveys conducted in 1997, 2002 and 2007,

the prevalence of self-reported peanut and/or tree nut allergy increased from 0.6% to 1.2% to 2.1% among children, whereas no change was observed for adults [17].

In the absence of previous studies with challenge-proven outcomes, time trends of food allergy prevalence can be estimated through proxy measures, such as hospital admissions for food-induced anaphylaxis – the most severe expression of food allergy. Over an 11-year period (from 1994–1995 to 2004–2005), Liew *et al.* [18] found hospital admissions for food-induced anaphylaxis, a potentially fatal condition, increased 350%. Similar increases were observed in the United States [19] and the United Kingdom [20]. Intriguingly, the highest rates predominated in the children under 5 years of age, highlighting the need to understand early life risk factors for childhood food allergy. Following on from their previous publication, Mullins *et al.* examined hospital admissions for food-induced anaphylaxis for the years 2004–2014 and found an ongoing overall increase in admission rates, with an acceleration of rates in the 5–14-year-old age group in which admissions rose 3.3-fold between 2004/2005 to 2011/2012 compared with a 1.8-fold increase for the overall population [21]. These findings forecast an increasing burden of disease amongst older children, who carry the highest risk for fatal anaphylaxis.

A study [22[¶]] published this year in the United Kingdom also reported a 106% increase in admissions for food-induced anaphylaxis between 1998 and 2012, with the greatest increase in the 0–14-year age group. Although hospital admissions were most frequent in children under 5 years of age, fatalities were most common in the teenage and young adult age group (10–29 years). There was no evidence of an increase in the rate of fatal food-induced anaphylaxis over the study period, possibly suggesting increasing awareness of food allergy diagnosis contributed to this increase, or alternatively that a true increase in prevalence was balanced by improvements in treatment leading to improved outcomes.

Less is known about food allergy prevalence and changes in prevalence in non-Western countries, although a study [23] in China reported an increase in food allergy between two cross-sectional studies 10 years apart, with the latest survey conducted in 2009. A recent study [24[¶]] in 11 473 school aged children (7–12 years) in China reported a prevalence of food allergy (defined by clinical history and positive skin prick test) of 4% in the urban centre of Guangzhou and a similar prevalence in the regional centre of Shaoguan (3.5%).

NATURAL HISTORY AND PHENOTYPES OF FOOD ALLERGY

Until recently, data on the resolution of food allergies have been undermined by the potential bias of natural history cohort studies conducted only in clinic populations. Because those with persistently elevated skin prick test (SPT) or serum-specific IgE to foods are not routinely offered the opportunity to undergo challenge to determine tolerance, results from retrospective clinic cohorts could have been biased to demonstrating low prevalence of tolerance development. In order to address this gap in the literature, Peters *et al.* [25[¶]] systematically undertook oral food challenges on all infants with detectable IgE antibody (irrespective of wheal size) at both age 1 and age 4 years. Remarkably, this large population-based study [26] found almost identical rates of peanut-allergy resolution (20%) as previously published clinical cohorts. Furthermore, they provided confirmatory evidence that the best predictor of allergy resolution remains the level of peanut-specific IgE antibody detectable by blood or skin prick test.

There is now emerging evidence to support the concept that there is variation in phenotypes of IgE-mediated food allergy. In the HealthNuts study [27[¶]] 80% of egg-allergic infants at age 1 year passed a food challenge to egg in baked goods. At the age 2-year follow-up those who were tolerant to baked egg were three times more likely to outgrow raw egg allergy than those who could not tolerate egg in baked goods at age 1. The CoFAR consortium found similar results in a clinical cohort [28[¶]] and both studies found that the best predictor of egg-allergy tolerance was SPT or sIgE levels at baseline with those with the highest antibody levels least likely to develop tolerance with age. These findings are not only clinically important for prognostic predictions but also because it suggests that novel treatments under investigation (including egg oral immunotherapy) should phenotype for baked egg at baseline to ensure balanced recruitment across control and active arms and potentially to target those groups more likely to have persistent egg allergy without treatment.

Recent findings also suggest that subphenotypes of allergy clusters might be important when attempting to understand the mechanism of disease, as well as to predict allergy resolution. Peters *et al.* [29[¶]] recently undertook latent class analysis of infants at age 1 and found that egg-allergy predominant clusters appear to differ from peanut-allergy-predominant clusters with regards to risk factors. Follow-up of this cohort is likely to provide insights into drivers of differential rate of allergy resolution amongst the subphenotypes of allergic disease and

help understand whether food allergy is part of the atopic march and its impact on risk of other allergic disease such as asthma.

RELATIONSHIP BETWEEN FOOD ALLERGY AND ECZEMA – POTENTIAL MECHANISMS AND IMPLICATIONS

An association between eczema and food allergy has long been recognized; however, the magnitude of this association was only recently formally characterized at the population level using oral food challenges to diagnose food allergy. At 1 year of age, one in five infants with a history of eczema in the first year of life was allergic to peanut, egg white or sesame compared with one in 25 infants without eczema. This was even higher in infants with earlier onset eczema and more severe eczema (requiring topical corticosteroid treatment). More than half of the infants with moderately severe early onset eczema (defined as onset before age 3 months and requiring treatment with topical corticosteroids) had challenge-proven food allergy by age 1 year [3[¶]].

Ecema and food allergy might share common genetic or environmental risk factors, leading to immune dysregulation and an atopic predisposition to both eczema and food allergy, and potentially asthma and allergic rhinitis in later life [30]. An alternative hypothesis postulates that the presence of a damaged skin barrier in individuals with eczema might allow absorption of food allergens through the skin, leading to the development of an immune response to these allergens and subsequently to IgE-mediated food allergy [31]. If eczema and food allergy are causally related through increased allergen exposure secondary to a damaged skin barrier, prevention of eczema in infancy may have the additional benefit of also reducing the risk of developing food allergy.

Two recently published studies undertook an intervention trial (randomized controlled trial) of daily moisturising from birth in an attempt to reduce infantile eczema and associated effects. Both demonstrated an impressive reduction in eczema of up to 50% [32[¶],33[¶]]. One of these studies also examined egg sensitization as a secondary outcome; however, there was no evidence of a reduction in sensitization to egg white in this relatively small study of 118 infants. Larger studies are required and are currently underway to determine whether prevention of infantile eczema can also reduce the risk of food sensitization and allergy. Alternative strategies to prevent eczema and food allergy through promoting healthy immune development are also being explored.

The relationship between eczema and food allergy also has implications for identifying populations at high risk of developing food allergy in infancy. Traditionally, 'high risk' was defined based on the presence of an immediate family member with allergy (asthma, eczema, allergic rhinitis or food allergy), but this is now extremely common in the general population (up to 70% of population-recruited infants have a family member with allergy) and poses only a moderate increase in food allergy risk for the infant [34]. Intervention trials have more recently begun recruiting infants with eczema as a truly high risk group for food allergy development [35], although this can only be undertaken for trials of postnatal interventions.

TIMING OF ORAL ALLERGEN EXPOSURE IN INFANTS AND THE DEVELOPMENT OF FOOD ALLERGY

In the early 1990s, concern about food allergy led to recommendations to delay introduction of allergenic foods to infants, particularly those believed to be at high risk of developing food allergy. In one of the more extreme cases, delaying introduction of peanut until after 3 years of age was recommended in the United Kingdom for infants with a family history of allergy. A series of ecological and observational cohort studies subsequently found no evidence of a beneficial effect of delaying the introduction of allergenic foods, and in fact seemed to support the hypothesis that introduction earlier in infancy might promote the development of tolerance. Infant feeding guidelines were consequently revised, starting around 2008, and recommendations to delay introduction of allergenic foods were largely removed [36].

Results of the first intervention study [37^{***}] in this area have now been published, demonstrating that earlier introduction of peanut to infants with early signs of atopic disease can reduce the likelihood of developing peanut allergy in childhood. The Learning Early About Peanut Allergy study involved 640 infants with severe eczema and/or egg allergy. Infants were recruited at ages 4–11 months and, after skin prick test screening to remove those likely to be allergic at baseline (peanut skin prick test >4 mm), were randomized to either regular peanut consumption or avoidance until 5 years of age. Infants with a negative SPT (0 mm) at baseline had high rates of new onset peanut allergy on oral food challenge at age 5 years in the context of peanut avoidance (13.7%); this was significantly reduced by peanut consumption (1.9%). Infants with a 1–4 mm wheal to peanut at baseline were randomized separately, and consumption was potentially less effective

in this group, although still associated with a reduction in the rate of positive peanut challenge at age 5 years (35.3% vs. 10.6%). It is currently not clear whether protection against peanut allergy in the consumption group can be maintained even after cessation of peanut consumption. A follow-up study is in progress investigating whether tolerance to peanut persists in these individuals.

The relevance of these findings to other food allergies is currently unclear. Although observational studies also suggest a potential protective effect of introduction of egg at 4–6 months of age for egg allergy [38], this was only partially supported by findings of a randomized controlled trial. The Starting Time for Allergy Reduction trial, which randomized infants with eczema to egg avoidance or early regular egg consumption from age 4 months, found a somewhat lower prevalence of egg allergy by 12 months in the intervention group (33% vs. 51%, $P=0.11$), but results also indicate that egg sensitization and allergy (at least in infants with eczema) may already be present as early as 4 months of age [39]. Similarly, the Learning Early About Peanut Allergy study [37^{***}] excluded 9% of potentially eligible infants because of a high peanut skin prick test at baseline. Collectively, these results suggest that although earlier introduction of allergenic foods at the population level may reduce the prevalence of at least some types of food allergy, additional strategies are likely to be required. In addition, although recently updated guidelines have already had some effect in promoting earlier introduction of allergenic foods, uptake has been greater among those without a family history of allergy and with a higher socioeconomic index, posing challenges for implementation of these guidelines in groups potentially most at risk [40[■]].

GENETIC RISK FACTORS FOR FOOD ALLERGY AND MODIFICATION OF GENETIC RISK BY ENVIRONMENTAL EXPOSURES

Recent studies highlight the importance of individual genetic and environmental factors, and their interaction, in food allergy. Familial aggregation studies and heritability estimates support a role for genetic factors in food allergy, but there has been limited evidence to identify the specific genetic factors involved, and the rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by population-based changes in genetic sequence, supporting a key role for environmental factors. Environmental factors might, however, act differently to affect risk of food allergy according to genetic predisposition. This is well

illustrated in the recent finding that the prevalence of childhood food allergy is three to four times higher in Asian infants born in Australia compared with Caucasian infants born in Australia, whereas paradoxically childhood food allergies in Asia are still relatively low [41[¶]]. This finding suggests that removal of protective environmental factors present in the Asian environment, or conversely exposure to environmental risk factors in the Australian environment, uncovers a genetically determined risk of food allergy in children of Asian descent. The specific genetic and environmental factors involved have yet to be determined, and studying this population further has the potential to provide new insights into the etiology of food allergy.

The first genome-wide association study [42^{¶¶}] for food allergy in US children was recently published, identifying genetic variants in the HLA-DR and HLA-DQ gene region variants as a risk factor for peanut allergy, but not egg or milk allergy, in children of European ancestry. This supports findings from some earlier candidate gene studies [43]. No studies have yet assessed the susceptibility of these variants to environmental cues; however, other specific examples of interactions between individual genes and environmental factors have been described. Recently, higher levels of peanut protein in the household environment were associated with an increased risk of peanut sensitization, but only in the presence of filaggrin loss-of-function mutation [44[¶]]. Filaggrin loss-of-function mutations result in reduced production of filaggrin, a protein involved in maintaining integrity of the stratum corneum, which leads to increased permeability of the skin. An association between increased levels of environmental peanut proteins and an increase in risk of peanut sensitization only in those with filaggrin loss-of-function mutations provides support for the hypothesis [31] that sensitization to peanut can occur through the skin, and that this requires both a reduced skin barrier and presence of peanut allergen in the environment.

Gene by environment interactions have also been explored for microbial exposure and allergic disease, although these have not yet been investigated for food allergy outcomes. In one of the best studied examples, the influence of the CD14/-260 C>T promoter polymorphism on allergy risk appears to depend on microbial stimulation from the environment [45]. Children carrying the TT genotype had consistently lower IgE levels with pet exposure, whereas pet exposure showed no effect in children with CC or CT genotype. Finally, genetic factors may also modify the association between vitamin D and allergic disease [46,47], potentially by influencing

utilization and bioavailability of serum vitamin D [48].

CONCLUSION

Studies of challenge-confirmed food allergy using standardized methodology are revealing large disparities in prevalence between countries in the Western world. Reasons for these disparities are not yet clear. Food allergy may also be increasing in non-Westernized countries although food allergy remains understudied in many of these regions. Findings from observational cohorts and the first large-scale intervention trials for food allergy prevention support early oral allergen exposure to reduce the prevalence of specific food allergies, which is informing changes in public health guidelines at the population level. Further research will be required to assess the impact of these guideline changes on the population prevalence of food allergy. Evolving evidence points to differential risk factors for different phenotypes of allergic disease, including different types of food allergy, and our understanding of the interplay between eczema and food allergy is increasing. Additional research to more clearly characterize environmental factors leading to immune dysregulation and allergic predisposition, and how these interact with genetic factors to determine presence or absence of allergic disease in early life, may lead to novel intervention strategies.

Acknowledgements

None.

Financial support and sponsorship

J.J.K and K.J.A. are supported by fellowships from the National Health and Medical Research Council (NHMRC) of Australia. KJA has received funding from the NHMRC and Australian Egg Corporation and has received speakers fees from Abbott, Danone, Wyeth and Pfizer, Nutricia, and Alphafarm.

E.N.C.M. has received research support from the European Union (FOOD-CT-2005-514000), the Biological and Biotechnological Sciences Research Council (BBS/E/F/00041800, BBS/E/F/00042204), the UK Food Standards Agency (T07062), the European Food Safety Authority, the UK Technology Strategy Board (grant no. 101130), DBV Technology, and Novartis; is a board member for Novartis, the UK Food Standards Agency, PepsiCo International, the UK Biological and Biotechnological Sciences Research Council, and Reacta Biotech Ltd; is employed by the University of Manchester and the Institute of Food Research; has stock/stock options in Standard Life and Reacta Biotech; has received travel support from ILSI, EAACI, the University of Bologna, Europa Bio, the British High Commission, the Iceland

Allergy Society, Fresenius, EuroFood Tox 2013, and the IUNS Annual Meeting (Granada, Spain September 2013); and was paid as a lecturer and supervisor of masters students at Imperial College and as an external examiner at the University of Birmingham.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Asher MI, Montefort S, Björkstén B, *et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–743.
2. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014; 69:3–16.
3. 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; 45:255–264.

This population-based study examines the prevalence of challenge-confirmed food allergy at 12 months of age according to severity and age of onset of eczema in the first year of life.

4. Mills EN, Mackie AR, Burney P, *et al.* The prevalence, cost and basis of food allergy across Europe. *Allergy* 2007; 62:717–722.
5. Keil T, McBride D, Grimshaw K, *et al.* The multinational birth cohort of EuroPrevall: background, aims and methods. *Allergy* 2010; 65:482–490.
6. Kummeling I, Mills EN, Clausen M, *et al.* The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. *Allergy* 2009; 64:1493–1497.
7. Fernandez-Rivas M, Barreales L, Mackie AR, *et al.* The EuroPrevall outpatient clinic study on food allergy: background and methodology. *Allergy* 2015; 70:576–584.
8. McBride D, Keil T, Grabenhenrich L, *et al.* The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol* 2012; 23:230–239.
9. 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. [Epub ahead of print]

These are the first data on challenge-confirmed food allergy prevalence in infants and young children using standardized methods across multiple countries as part of the EuroPrevall project.

10. Osborne NJ, Koplin JJ, Martin PE, *et al.* The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allergy* 2010; 40:1516–1522.
11. Prescott SL, Pawankar R, Allen KJ, *et al.* A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013; 6:21.
12. Burney PG, Potts J, Kummeling I, *et al.* The prevalence and distribution of food sensitization in European adults. *Allergy* 2014; 69:365–371.
13. Datema MR, Zuidmeer-Jongejan L, Asero R, *et al.* Hazelnut allergy across Europe dissected molecularly: a EuroPrevall outpatient clinic survey. *J Allergy Clin Immunol* 2015. [Epub ahead of print]

A molecular analysis of patterns of sensitization to hazelnut and differences between countries in patients from the EuroPrevall outpatient clinic study.

14. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, *et al.* IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015; 70:391–407.

A multicountry analysis of molecular sensitization patterns to peanut in the EuroPrevall outpatient clinic study and their association with clinical reactions to peanut.

15. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, *et al.* How much is too much? Threshold dose distributions for 5 food allergens. *J Allergy Clin Immunol* 2015; 135:964–971.

This study modelled the distributions of the minimum dose of peanut, hazelnut, celery, fish and shrimp required to elicit reactions in a population of food allergic individuals.

16. Venter C, Hasan Arshad S, Grundy J, *et al.* Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 2010; 65:103–108.

17. Sicherer SH, Munoz-Furlong A, Godbold JH, *et al.* US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010; 125:1322–1326.
18. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol* 2009; 123:434–442.
19. Lin RY, Anderson AS, Shah SN, *et al.* Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006 annals of allergy, asthma and immunology: official publication of the American College of Allergy. *Asthma Immunol* 2008; 101:387–393.
20. Gupta R, Sheikh A, Strachan DP, *et al.* Time trends in allergic disorders in the UK. *Thorax* 2007; 62:91–96.
21. Mullins R, Dear K, Tang M. Time trends in Australian hospital anaphylaxis admissions in 1998–1999 to 2011–2012. *J Allergy Clin Immunol* 2015. (In Press).
22. 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. *J Allergy Clin Immunol* 2015; 135:956–963.

Reports UK prevalence data for hospital admissions and fatalities because of anaphylaxis, including food-induced anaphylaxis, between 1998 and 2012.

23. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing versus. *Pediatr Int* 2010; 52:820–824.
24. Yang Z, Zheng W, Yung E, *et al.* Frequency of food group consumption and risk of allergic disease and sensitization in school children in urban and rural China. *Clin Exp Allergy* 2015. [Epub ahead of print]

Reports the prevalence of food allergy (defined by clinical history and positive skin prick test) in a population-based sample of school children recruited from urban (Guangzhou) and regional (Shaoguan) centres in China.

25. Peters RL, Allen KJ, Dharmage SC, *et al.* Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol* 2015; 135:1257–1266.

Reports the prevalence and predictors (including skin prick test and peanut-specific IgE levels) of peanut-allergy resolution between 1 and 4 years of age in a population-based cohort.

26. Ho MH, Wong WH, Heine RG, *et al.* Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008; 121:731–736.
27. Peters RL, Dharmage SC, Gurrin LC, *et al.* The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. *J Allergy Clin Immunol* 2014; 133:485–491.

Reports the prevalence of baked egg allergy in a population-based cohort of raw egg-allergic 1-year-old infants, and the relationship between ability to tolerate egg in baked goods and resolution of raw egg allergy by 2 years of age.

28. Sicherer SH, Wood RA, Vickery BP, *et al.* The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014; 133:492–499.

Reports the prevalence of baked egg allergy in a clinical cohort of egg-allergic patients and examines predictors of egg-allergy resolution, including ability to tolerate baked egg.

29. 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; 45:953–963.

Uses a latent class analysis approach to identify phenotypes of infantile food allergy and assess differential and shared risk factors across food allergy classes.

30. Allen KJ, Dharmage SC. The role of food allergy in the atopic march. *Clin Exp Allergy* 2010; 40:1439–1441.
31. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012; 129:1187–1197.
32. 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; 134:818–823.

Randomized controlled trial to prevent atopic dermatitis in infants using daily moisturising from birth.

33. Horimukai K, Morita K, Narita M, *et al.* Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014; 134:824–830.

Randomized controlled trial to prevent atopic dermatitis in infants using daily moisturising from birth.

34. Koplin JJ, Allen KJ, Gurrin LC, *et al.* The impact of family history of allergy on risk of food allergy: a population-based study of infants. *Int J Environ Res Public Health* 2013; 10:5364–5377.
35. Du Toit G, Roberts G, Sayre PH, *et al.* Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. *J Allergy Clin Immunol* 2013; 131:135–143.
36. Koplin JJ, Allen KJ. Optimal timing for solids introduction: why are the guidelines always changing? *Clin Exp Allergy* 2013; 43:826–834.
37. 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; 372:803–813.

Presents the results of the first large-scale intervention study for peanut-allergy prevention. This study randomized infants with severe eczema and/or egg allergy (high risk infants) to either early introduction of peanut (between 4 and 11 months of age) or peanut avoidance and examined the effect of this intervention on peanut allergy at 5 years of age.

38. 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; 126:807–813.

39. 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; 132:387–392.
40. Tey D, Allen KJ, Peters RL, *et al.* Population response to change in infant feeding guidelines for allergy prevention. *J Allergy Clin Immunol* 2014; 133:476–484.
Examines the effect of recent changes to infant feeding guidelines, with removal of advice to delay introduction of allergenic foods, on infant feeding practices at the population level.
41. Koplin JJ, Peters RL, Ponsonby AL, *et al.* Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014; 69:1639–1647.
A population-based study of challenge-confirmed peanut allergy in Melbourne, Australia, which compares the prevalence of peanut allergy among Australian-born infants of East Asian migrants to the prevalence in Australian-born Caucasian infants.
42. Hong X, Hao K, Ladd-Acosta C, *et al.* Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. *Nat Commun* 2015; 6:6304.
Results of the first genome-wide association study for food allergy.
43. Madore AM, Vaillancourt VT, Asai Y, *et al.* HLA-DQB1*02 and DQB1*06:03P are associated with peanut allergy. *Eur J Hum Genet* 2013; 21:1181–1184.
44. Brough HA, Simpson A, Makinson K, *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.
Describes the interaction between levels of peanut protein in the household environment, filaggrin loss-of-function mutations (associated with increased skin permeability) and peanut allergy in children.
45. Lau MY, Dharmage SC, Burgess JA, *et al.* CD14 polymorphisms, microbial exposure and allergic diseases: a systematic review of gene-environment interactions. *Allergy* 2014; 69:1440–1453.
46. Vimalaswaran KS, Cavadino A, Hypponen E. Evidence for a genetic interaction in allergy-related responsiveness to vitamin D deficiency. *Allergy* 2012; 67:1033–1040.
47. Liu X, Wang G, Hong X, *et al.* Gene-vitamin D interactions on food sensitization: a prospective birth cohort study. *Allergy* 2011; 66:1442–1448.
48. Koplin J, Suaini N, Vuillermin P, *et al.* Polymorphisms affecting vitamin D-binding protein modify the relationship between serum vitamin D (25[OH]D3) and food allergy. *J Allergy Clin Immunol* 2015; In Press.