

The Epidemiology of IgE-Mediated Food Allergy and Anaphylaxis

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KEYWORDS

• Epidemiology • Food allergy • Prevalence • Risk factors

The prevalence of IgE-mediated food allergy and anaphylaxis seems to have risen rapidly in developed countries^{1,2} and is an evolving public health problem with emerging evidence that countries with rapid industrialization may follow suit.³ Despite an increasing number of studies mounted to investigate the rise of allergic disease in general and food allergy in particular, the cause of the current epidemic of food allergy remains elusive.

It is estimated that about a quarter of the population will have an adverse reaction to food (of which food allergy is just one type) during their lifetime,⁴ most of which occur during infancy and early childhood. An estimated 10% to 15% of children report symptoms of food allergy, although the prevalence of IgE-mediated food allergies (ie, symptoms of food allergy in the presence of food-specific IgE) is reported to be lower, at approximately 6% to 8% in children younger than 3 years and 3% to 4% of the adult population.⁵ By contrast not much is known about the prevalence of non-IgE-mediated food allergies, although both eosinophilic esophagitis and celiac disease have been documented to be on the rise.^{6,7}

More than 90% of IgE-mediated food allergies in children are caused by just eight food items: (1) cow's milk, (2) soy, (3) hen's egg, (4) peanuts, (5) tree nuts, (6) wheat, (7) fish, and (8) shellfish. Most children with cow's milk and egg allergy develop tolerance by late childhood, whereas allergies to peanut, sesame seeds, and tree nuts

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are more persistent, with less than 20% developing tolerance.⁸ As a result, cow's milk and egg allergies are uncommon in adults and allergies to peanuts, tree nuts, fish, and shellfish predominate.⁹ Much less is known about the natural history or population prevalence of non-IgE-mediated food allergy,¹⁰ which is outside the scope of this article.

METHODOLOGIES FOR MEASURING FOOD ALLERGY PREVALENCE

Studies have shown that self-reported food allergy is an inaccurate measure of true food allergy.⁹ There are multiple reasons why food allergy may be overreported by individuals, including inability to distinguish between food intolerance and allergy and incorrectly attributing symptoms to allergic reactions to food even where there is no evidence to support such contentions. It is also not possible to determine allergic status based on parent-report to foods that have not yet been introduced into an infant's diet. As such, any study on the prevalence of food allergy needs to be contextualized by the outcome used to define the condition.

The gold standard for the diagnosis of IgE-mediated food allergy is double-blind placebo-controlled food challenges. However, even this gold standard is limited by methodologic differences between studies in choice of food for challenges (eg, cooked vs raw eggs, which have different allergenicity) and criteria for defining a positive challenge because until recently criteria for the definition of a positive oral food challenge (OFC) have never been formalized.¹¹ Although most protocols state that a positive challenge is demonstrated by evidence of an immediate reaction consistent with IgE-mediated food allergy, such as urticaria, angioedema, or anaphylaxis, interpretation of more subjective symptoms, such as abdominal pain or nausea, or the more ubiquitous and less clearly defined sign of an eczema flare remains difficult. Differences in criteria for the definition of a positive OFC across different studies and different centers hinders the ability to compare food allergy prevalence estimates between studies and to identify risk factors for the development of food allergy (because phenotypes might vary across different study cohorts), and to assess the success of various treatment strategies (including oral immunotherapy).

A further limitation of even the small number of studies that have conducted formal graded food challenges is that most studies have not addressed the question of whether study participants are representative of the population from which they were sampled. The generalizability of their results to the general population may therefore be poor, particularly if families at high risk of allergic disease are overrepresented among participants. The extent to which this type of selection bias may affect results is rarely formally assessed, although recent cohort studies of food allergy have begun to address this using short questionnaires to assess prevalence of risk factors for allergy among those who do not wish to undergo testing for food allergy.¹²

Performing large-scale studies of challenge-proved food allergy is not always possible because of issues with compliance, risk to participants, and cost. As such, many population-based prevalence studies have relied on the detection of food-specific IgE antibodies as an indirect marker of food allergy, either alone or in conjunction with reported symptoms on ingestion of the food. The presence of IgE specific to food allergens can be detected using skin prick testing or in vitro measurement using the cap-fluoroenzyme immunoassay or radioallergosorbent test. Individuals are said to be "sensitized" to the food being studied if the size of the wheal (skin prick testing) or measured IgE level (cap-fluoroenzyme immunoassay or radioallergosorbent test) exceeds a prespecified threshold but confirmation of food allergy requires symptomatic ingestion of the food. Larger skin prick testing wheal sizes or higher measured IgE

levels are associated with an increased likelihood that individuals are truly food allergic,^{13,14} however this increase in specificity occurs with a corresponding loss of sensitivity.

THE MOST RECENT PREVALENCE ESTIMATES OF IGE-MEDIATED FOOD ALLERGY

Existing studies of food allergy incidence, prevalence, and natural history are difficult to compare because of inconsistencies and deficiencies in study design and variations in the definition of food allergy.¹⁵ Rona and colleagues⁹ assessed data from 51 publications and provided separate analyses for the prevalence of food allergy for five common foods (cow's milk, hen's egg, peanut, fish, and shellfish), stratified by whether the studies were in adults or children. The investigators report a pooled overall prevalence of self-reported food allergy for adults and children of 13% and 12%, respectively, to any of these five foods. However, pooled results are far lower (~3%) when food allergy is defined as either sensitization alone; sensitization with symptoms; or positive double-blind, placebo-controlled food challenge.

The prevalence of common food allergies as measured in recent population-based studies is illustrated in **Fig. 1**. Two recent cohort studies from the United Kingdom and Denmark reported that the foods most often responsible for symptoms of food allergy in infants and young children were egg, cow's milk, and peanuts. In the Danish study, the prevalence of egg and milk allergy reached a peak around 18 months of age, at 2.4% and 1% for egg and milk, respectively; with around 20% becoming tolerant to egg by 3 years; and 100% becoming tolerant to milk by 6 years of age.¹⁶ Oral food challenges to peanut were not performed until the children reached 3 years of age; however, at 3 years of age the United Kingdom study reported a peanut allergy prevalence of 1.2%.¹⁷

Population data using challenge-proved outcomes is likely to represent the best quality data for prevalence estimates. Such data have been collected in the HealthNuts study, which reports a prevalence of challenge-proved peanut allergy of 3% (95% confidence interval [CI], 2.4–3.8); egg allergy of 8.9% (95% CI, 7.8–10); and sesame allergy of 0.8% (95% CI, 0.5–1.1) in 1-year-old infants in Melbourne, Australia.¹⁸ These figures were weighted to account for participation bias and represent the highest prevalence figures published to date. They reflect previous observations of a generally high prevalence of other allergic diseases in Australia and suggest that factors in Australia are primed for an evolving epidemic of allergic disease. The design strengths of the HealthNuts study include the use of a formal sampling frame to attain a representative population base, assessment of the degree of participation bias using short questionnaires administered to all nonparticipants, and use of oral food challenges to assess food allergy outcomes. In addition, oral food challenges were undertaken on all sensitized children irrespective of wheal size or previous history of ingestion reaction unless occurring in the previous 1 month for egg or 2 months for peanut and sesame.

Prevalence figures and the spectrum of food allergens seem to vary considerably between geographic regions,⁹ and have been thought to predominantly reflect variations in diet among different cultures. Alternatively, some of the differences in food allergy prevalence between regions may be explained by either genetic variation across populations or variations in exposure to environmental factors, such as sunlight (ie, related to vitamin D levels) or factors related to the hygiene hypothesis (discussed later). Recent prevalence data from Chongqing, China, demonstrated a higher than expected rate of IgE-mediated food allergy,³ with 2.5% reporting egg allergy and 1.3% cow's milk allergic, suggesting that increased urbanization might play a role in rising rates in countries undergoing rapid development.¹⁹

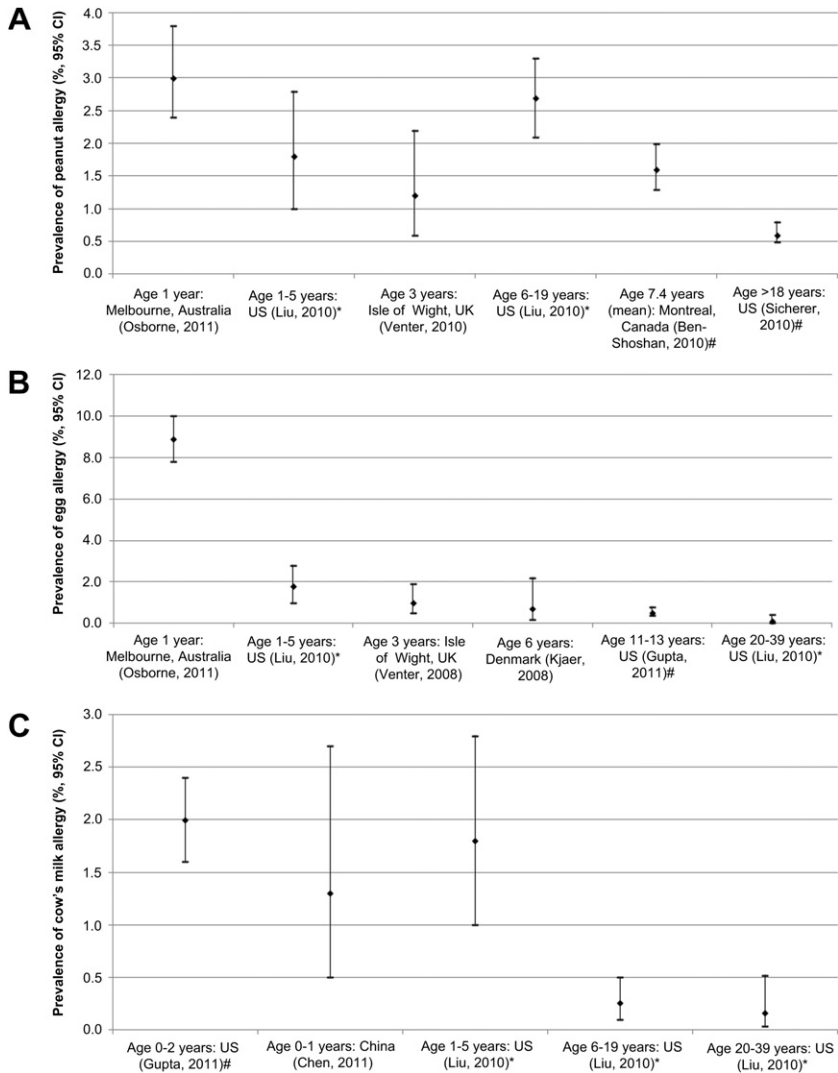


Fig. 1. Prevalence of common food allergies in different age groups in recent population-based studies: (A) peanut, (B) egg, (C) milk, (D) sesame, and (E) shellfish. Preference was given to those using oral food challenges to diagnose food allergy where available. * Based on specific IgE levels. # Self- or parent-reported food allergy. †Prevalence of SPT ≥ 3 mm. Note: Egg allergy in the Healthnuts study reflects raw egg challenge data - the most immunogenic form of egg.

FOOD-INDUCED ANAPHYLAXIS

Attempting to determine the population prevalence of anaphylaxis is made more difficult because of varying opinions on what constitutes anaphylaxis. Several classification systems have been used; however, a recent consensus document has defined anaphylaxis as a “serious allergic reaction that is rapid in onset and may cause death,” and proposed diagnostic criteria for use in clinical care.²⁰ By these criteria, a diagnosis of anaphylaxis can be made if there is involvement of the respiratory or cardiovascular

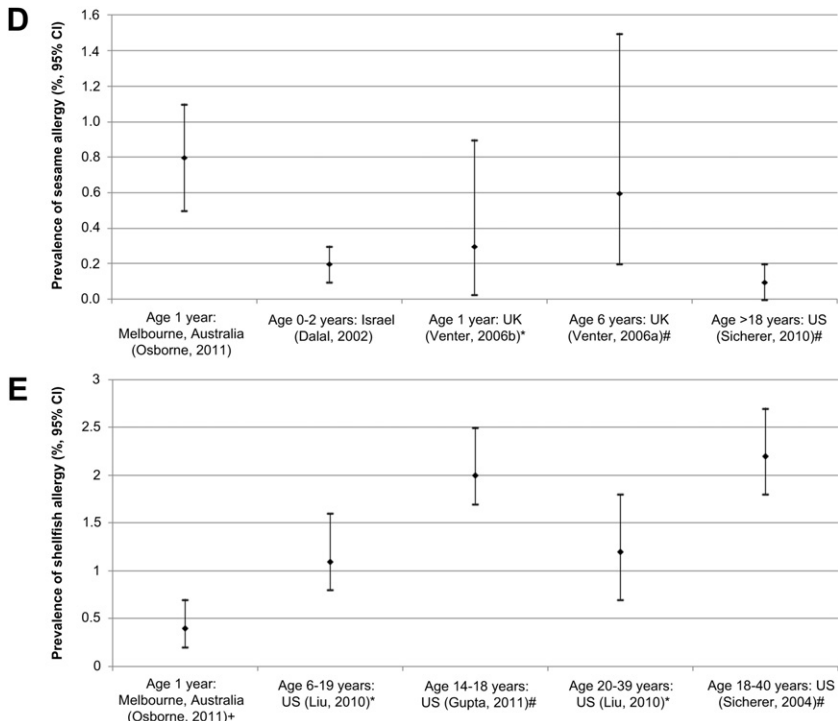


Fig. 1. (continued)

systems during an allergic reaction, or if a less severe reaction occurs in the setting of previously diagnosed allergy and likely exposure to the relevant allergen. In addition to the lack of consensus on the definition of anaphylaxis, the population prevalence of anaphylaxis has been difficult to accurately quantify because of analysis of different sample populations (eg, emergency department presentations, hospital admissions, general practitioner presentations, specialist allergist presentations), and the use of varying methodologies for data collection.²¹

Recent reports have found that the incidence of anaphylaxis is rising in Australia, the United Kingdom, and the United States.^{2,22,23} In a recent study, Liew and colleagues² confirmed previous reports of an increasing world-wide incidence of hospital admissions for food-induced anaphylaxis, with an incidence in the Australian population of around 6 per 100,000 population reported in 2004 and 2005, an overall rise of 350% above the previous 11 years. Children younger than the age of 5 years had the highest rates of hospital admissions for food-induced anaphylaxis (9.4 per 100,000 population) and the rate of increase in hospital admissions over time was also greatest for this age group.

The spectrum of foods commonly responsible for causing allergic reactions including anaphylaxis varies between countries, although peanuts, tree nuts, and sea-food were commonly implicated in hospitalizations and deaths from food-induced anaphylaxis in Australia, the United States, and the United Kingdom.^{2,24,25} However, there are now increasing reports of anaphylaxis occurring to a wide range of foods including fruits and other foods not previously commonly associated with anaphylaxis, such as lupin.^{26,27}

Attention has turned recently to identification of factors that may increase the risk of episodes of food-related anaphylaxis including clinical risk factors and modifiable lifestyle factors.²⁸ Recent studies confirm that individuals with asthma are at increased risk of anaphylaxis, including food-induced anaphylaxis, and that those with severe asthma are at the highest risk.^{29,30} One of the most interesting recent lifestyle factors to be investigated is the relationship between vitamin D insufficiency and increased risk of food-induced anaphylaxis. There is now an emerging base of evidence demonstrating the relationship between latitude and anaphylaxis to support this contention.^{31–34}

EPIDEMIOLOGY OF FATAL ANAPHYLAXIS

Data from national mortality reporting systems in the United Kingdom and Australia estimate the prevalence of anaphylaxis fatalities from all causes (including food, medication, insect sting, and idiopathic) to be 0.33 deaths per year per million population in the United Kingdom,³⁵ with Australia reporting the highest rate of 0.64 deaths per year per million population.² For as yet undetermined reasons in Australia only 6% of anaphylaxis deaths are ascribed to food-induced anaphylaxis compared with 31% in the United Kingdom.

Risk factors for a poor outcome from an episode of food-related anaphylaxis include age (risk is highest in adolescence and young adults); peanut or tree nut allergy; coexistent and poorly controlled asthma; posture (failure to be kept in the supine position); lack of access to self-injectable adrenaline; and failure to administer adrenaline in a timely manner. Although never formally investigated, hypothetical reasons for poorer outcomes in the adolescent and young adult age group include increased risk-taking behavior, issues of transition from parental locus of control, failure to adequately educate young people about the risks of anaphylaxis at the time that they are taking increased responsibility for their own health, and an increased prevalence of asthma and poorly managed asthma in these age-groups compared with those younger than 5 years of age.

WHAT IS THE EVIDENCE FOR A RISE IN INCIDENCE OF FOOD ALLERGY?

Food allergy is widely believed in the lay and scientific communities to be becoming increasingly common. Unfortunately, reports of an increasing prevalence of food allergy are difficult to substantiate because studies documenting the population prevalence of food allergy before the 1980s are not available to provide baseline data.

Recent studies have attempted to confirm anecdotal evidence of an increased incidence of peanut allergy. In a United Kingdom study, Venter and colleagues³⁶ found that peanut sensitization varied from 1.3%, to 3.3% to 2% in three sequential early childhood cohorts from the same geographic area, each surveyed 6 years apart, whereas reported peanut allergy increased from 0.5% to 1.4% then 1.2%. Although there was evidence that both peanut sensitization and allergy were significantly more common in the second cohort (born in 1994–1996) compared with the initial cohort (born in 1989), there was no evidence of a further increase in prevalence in the third cohort (born in 2001–2002).

Between three United States-wide telephone surveys conducted in 1997, 2002, and 2007, the prevalence of self-reported peanut or tree nut allergy increased from 0.6%, to 1.2% to 2.1% among children, although no change was observed for adults.³⁷ However, this increase in reported allergy was paralleled by a decreasing response rate across surveys (42% response rate in 2007), raising questions about whether these prevalence figures can be generalized to the wider population.

Further surveillance of allergy prevalence within populations using standardized methods is required to measure any future rise in allergy prevalence.

FACTORS ASSOCIATED WITH THE PRESUME RISE IN PREVALENCE

The cause of the presumed rise in food allergy and anaphylaxis prevalence is not known, but the short period over which the increase has occurred suggests that genetic factors alone cannot be causative because changes to the genome occur at an evolutionary pace. Environmental factors must therefore be central to the increase in prevalence, although these may be mediated through epigenetic modification (discussed later). Because food allergy is more common in developed than developing countries, and migrants seem to acquire the incident risk of allergy of their adopted country, it seems likely that the cause of the rise is linked to the “modern lifestyle.” Although environmental factors including those associated with the hygiene hypothesis and dietary factors have been found to be associated with the development of eczema and atopy, there has been little investigation into whether they may also play a role in the development of food allergy. In addition to factors previously linked to allergic disease in general there may well be some factors that are specific to food allergy. These might include changing methods of food manufacturing and preparation, the advent of widespread use of antacids and proton pump inhibitors, use of medicinal creams containing food allergens, or later introduction of allergenic foods into the diet of infants.

THE ROLE OF GENETICS IN PREDISPOSITION TO FOOD ALLERGY

Although the rise in food allergy prevalence cannot be explained by genetic factors alone, there is strong evidence that susceptibility to food allergy is at least partly determined by genetics. Twin studies have shown that the concordance rate for peanut allergy was much higher among monozygotic (64.3%) than dizygotic (6.8%; $P < .0001$) twin pairs.³⁸ However, a recent study of familial aggregation observed the heritability of common food allergies (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp, and cod fish) to be between 0.15 and 0.35³⁹ suggesting genetic factors are not as important as other factors, such as environmental exposures, in the development of food allergies.

Eczema and food allergy seem to be closely linked, with eczematous infants having a greatly increased risk of food allergy.⁴⁰ There is increasing interest in the role of loss of function mutations in the filaggrin (FLG) gene, which lead to defects in skin barrier permeability, in the pathogenesis of eczema. Null mutations (R501X and 2282del4) in FLG are associated with an increased susceptibility to eczema.⁴¹ Individuals with two null alleles in FLG have been shown to be four to seven times more likely to have eczema than those without.⁴² One recent case-control study investigated whether FLG mutations were also associated with peanut allergy, reporting that those with peanut allergy were around five times more likely to have FLG loss-of-function mutations.⁴³ This result along with previous studies suggesting that peanut sensitization may occur through damaged skin^{44–46} indicates that epithelial barrier dysfunction may play a role in the pathogenesis of peanut allergy.

ROLE OF RACE AND GENDER IN FOOD ALLERGY PREDISPOSITION

Gender disparities in the prevalence of some allergic disorders including allergic asthma have been well-described; however, the relationship between gender and food allergy is less clear.⁴⁷ Although asthma is more common in young boys, a gender switch occurs around the time of puberty with asthma being more common and more

severe in women.^{48,49} The reasons for this have yet to be elucidated but may relate to hormonal changes occurring during puberty.⁴⁸ Although this gender switch is also evident in clinical presentations with food allergy, this has not been formally explored at the population level.

Similarly, racial and ethnic differences in asthma prevalence have also been well described, whereas there have been few studies investigating the influence of ethnicity on the likelihood of developing food allergy. One United Kingdom study found that nonwhite infants were overrepresented in a pediatric food allergy clinic compared with general pediatric clinics.⁵⁰ In the United States, the 2007 National Health Interview Survey found that non-Hispanic children had higher rates of reported food allergy compared with Hispanic children.⁵¹ Recently, the authors have found a higher rate of food-sensitized eczema among children of Asian descent in the HealthNuts cohort.⁵² Interestingly, on examination of risk factors for eczema development (a closely associated infantile allergic disease) the authors found that Asian children were not only more likely to have eczema than their non-Asian counterparts but that their parents were less likely to have allergic disease than non-Asian parents. This was particularly so for Asian parents who had migrated to Australia less than 5 years previously, suggesting a strong gene–environment interaction even over and above that of a migrational generational effect (P. Martin, unpublished data, 2011).

MODIFIABLE ENVIRONMENTAL RISK FACTORS FOR FOOD ALLERGY DEVELOPMENT

Because the rise in food allergy has occurred more rapidly than changes to the genome would allow there has been more emphasis placed on what putative environmental factors might be associated with food allergy. Those that have changed most dramatically in the last half of the twentieth century and early part of the twenty-first century are under the most intense investigation. There are several hypotheses relating to modifiable environmental factors for an increased predisposition for food allergy. These include the “hygiene hypothesis,” microbial diversity of the gastrointestinal tract, the “old friends” hypothesis, factors related to infant feeding, and the vitamin D hypothesis (Fig. 2).

There is now emerging evidence that at least some environmental exposures may exert their influence by “epigenetic” mechanisms of gene alteration. Animal models have demonstrated that environmental changes at critical times during development can alter the phenotype of genetically identical animals through epigenetic modification.⁵³ These include activating or silencing genes by altering DNA and histone methylation, histone acetylation, and chromatin structure. These epigenetic modifications determine the degree of DNA compaction and accessibility for gene transcription. The potential role of epigenetic variation in the cause of food allergy has recently been reviewed.⁵⁴

The “Hygiene” Hypothesis

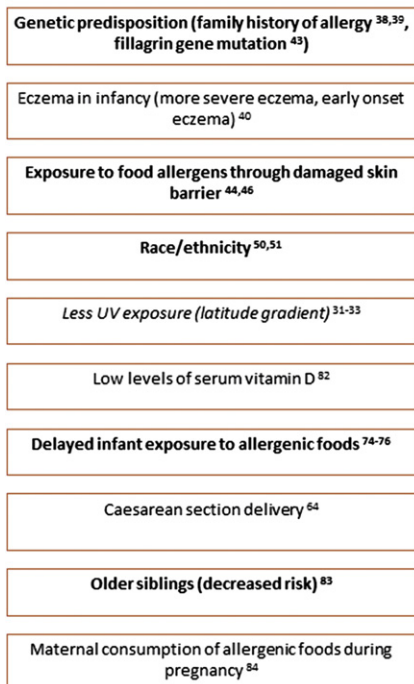
Microbial stimulation in early life plays a vital role in the development of the immune system⁵⁵ and the role of microbial exposures in allergic disease has been the subject of intense research since the development of the hygiene hypothesis in 1989.⁵⁶ Exposure to siblings and to other children through childcare, contact with pets, and delivery by caesarean section, all of which can occur in the early postnatal period before the introduction of food and expression of food allergy, have all been reported to affect the type or quantity of microbes (or their products) to which a child is exposed.^{57–63} Further research is required to elucidate whether these factors play a role in the development of food allergy.

Evidence for an association with food sensitization or allergy

***Bold** = study shows an association with food allergy*

Not bold = association with food sensitization only

Italics = indirect evidence for an association



**Risk of food
allergy**

**Evidence for an association with atopy/other
allergic diseases (may also play a role in food
allergy)**

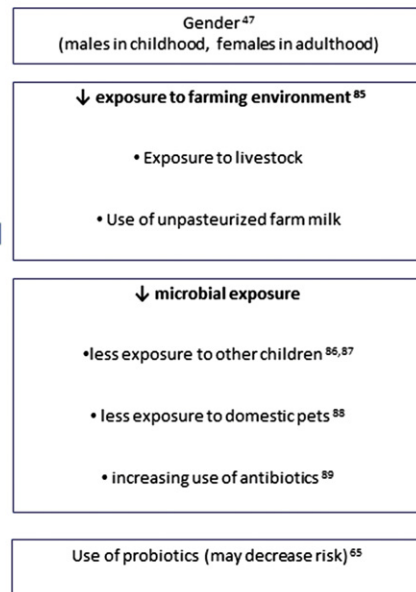


Fig. 2. Factors that may increase the risk of IgE-mediated food allergy.

The Impact of Gastrointestinal Flora Composition

The composition of the gastrointestinal flora in infancy is affected by various factors, but because the fetal intestine is sterile the initial colonizing events in the infant are likely to be highly important in governing the type of commensal bacteria present in the first few days of life and possibly longer. The initial colonizing event is likely to be influenced by mode of delivery, with infants delivered by caesarean section having less contact with maternal flora, which acts a source of intestinal bacteria for the newborn. It has been hypothesized that differences in colonization might lead to an increased risk of allergy among infants born by caesarean section.⁶⁴ It is possible that commensal bacteria in the gastrointestinal tract may exert an immunomodulatory effect that leads to tolerance to both the commensal bacteria themselves and also to ingested food allergens.

The demonstrated importance of gastrointestinal flora in the development of the gut immune system has led to multiple studies of the impact of probiotics on the prevention and treatment of allergic disease. A recent review of these studies concluded that there is currently no evidence that probiotics are effective in the treatment of eczema, despite early studies in small numbers of infants and children showing promising results.^{65,66} Few studies have investigated whether probiotic supplementation aids in the development of tolerance among food allergic individuals. Those that do exist have not shown any protective effect. In preventing allergic disease, there is some evidence that probiotic supplementation may reduce the risk of eczema in those with a family history of allergic disease. Again, food allergy was less often studied and there is currently little evidence for a protective effect of probiotic supplementation in the prevention of food allergy.

The "Old Friends" Hypothesis

After the initial colonizing events at birth, the infant immune system continues to be exposed to stimulus not only from the commensal bacteria in the infant gastrointestinal tract but also from external sources. The "old friends" hypothesis states that the immune system evolved at a time of constant exposure to certain organisms in the environment, such as helminths and environmental saprophytes, found in food and water.⁶⁷ These organisms needed to be tolerated, either because they were harmless and ubiquitous (environmental saprophytes, such as some species of mycobacteria) or because mounting an immune response would damage the host (some helminths). It is thought that continued exposure to these organisms might have caused down-regulation of the immune response not only to these organisms but also to self-antigens (autoimmunity) and food allergens (food allergy), possibly through the induction of regulatory T cells. Reduced exposure to these groups of organisms in the modern environment could therefore potentially explain the rise in allergic diseases and autoimmunity.

Other factors associated with a "modern lifestyle" include a myriad of changes to the level of public health including improved sanitation; secure water supplies (with associated decreased prevalence of *Helicobacter pylori* infection); widespread use of antibiotics and increasing rates of immunization; decreased helminthic infestation; improved food quality (and presumably less microbial load in the food chain); and generally improved nutrition and associated obesity. These factors might work individually or in concert to affect a failure in the development of oral immune tolerance in the first year of life when development of IgE-mediated food allergy is most likely to occur.

Evidence for Change in the Timing of Introduction of Solids and the Impact on Food Allergy Prevalence

Along with changes in food quality and a likely decrease in the microbial content of foods, there have also been significant changes in the age at which foods are introduced to infants. The age at which infants were typically introduced to solids has varied from extremely delayed introduction (after 1 year) before the 1920s to introduction in the first 3 months of life in the 1950s.⁶⁸ This was followed by recommendations in the 1980s to delay solids until 4 to 6 months of age.⁶⁹ By the late 1990s, expert bodies began to recommend delaying solids until after 6 months of age, with further delay in the introduction of allergenic foods, such as egg and nuts, until at least 2 years of age recommended for infants with a family history of allergy.⁷⁰ Recently revised guidelines from Europe, the United States, and Australia now state that there are no data to support the delay of introduction of allergenic solids in an infant's diet for the prevention of allergic disease.⁷¹

Recent attempts to study the relationship between timing of introduction of foods and food allergy have led to the suggestion that delayed introduction of allergenic foods may actually prevent the normal development of tolerance that occurs when foods are introduced during a "window of opportunity" in early infancy.⁷² This was initially based on the observation that Israeli infants are introduced to peanut at a young age yet Israeli schoolchildren experience a low prevalence of peanut allergy, whereas the opposite is observed in the United Kingdom.⁷³ Early studies examining this issue were unable to rule out confounding factors as an explanation for the increased risk of food sensitization and allergy among infants with delayed introduction of foods.⁷⁴ As such these studies could be biased by "reverse causation," such that introduction of allergenic foods is preferentially delayed in infants who are already at increased risk of food allergy, either because of signs of allergy, such as eczema in the child, or because of a family history of allergy.

Recently, the relationship between timing of introduction of egg and risk of egg allergy was explored in the HealthNuts population-based study of infants. Those introduced to egg after 10 months of age were more likely to be egg allergic at 1 year compared with those introduced to egg at 4 to 6 months, even after controlling for family and personal history of allergy.⁷⁵ Consumption of cooked egg seemed to be more protective than consumption of egg in baked goods. This may suggest that dose and timing of introduction is important in the development of tolerance, an area that requires further investigation. The relationship between timing of introduction of cow's milk formula and risk of milk allergy has also been recently studied. In a study of 13,234 newborn infants in Israel, those introduced to cow's milk formula in the first 14 days of life were significantly less likely to develop symptoms of cow's milk allergy compared with infants first exposed to cow's milk formula between 15 and 194 days. However, the authors were unable to control for important potential confounding factors, such as socioeconomic status and atopic background.⁷⁶ Randomized controlled trials of early introduction of allergenic foods are currently underway exploring the relationship between timing of exposure and allergy.

Vitamin D Status

Recently, data have emerged demonstrating a latitude gradient in prevalence of food allergy, with those countries furthest from the equator recording the highest admissions to hospital for food allergy-related events,³³ prescriptions for adrenaline autoinjectors for the treatment of anaphylaxis,^{31,32} and prescription of hypoallergenic infant formula.⁷⁷ These findings seem to be independent of longitude, physician density, or

socioeconomic status. The authors have recently confirmed that Melbourne, the most southern major city in Australia, has the highest reported prevalence of infantile food allergy in the world with more than 10% of 1-year-old infants recruited from the general population having challenge-proved IgE-mediated food allergy.¹⁸

Because regions most distant from the equator are exposed to less ultraviolet radiation, one postulated explanation for the link between latitude and risk of food allergy is that low vitamin D levels in early life may be causing food allergy.⁷⁸ Further evidence to support this contention is the recent finding that children attending emergency departments in Boston with a food-related acute allergic reaction were more likely to be born in autumn and winter, when vitamin D levels reach their nadir, than in spring and summer.⁷⁹ This relationship between season of birth and food allergy has recently been confirmed in the Southern hemisphere.⁸⁰ Furthermore, the authors have recently demonstrated that the delayed introduction of egg, one of the richest sources of vitamin D in the infant diet,⁸¹ in the first year of life increases the risk of developing egg allergy by at least fivefold independent of potential confounders.⁷⁵ One study has also reported that serum vitamin D deficiency is more common among children with peanut sensitization.⁸²

SUMMARY

The last few years has seen an increased focus on better defining the prevalence of food allergy and studies are now emerging that attempt to understand the drivers of the rise in prevalence. As for other allergic diseases, the cause of the rise in food allergy is likely to be multifactorial. Improved precision about measurement of food allergy outcomes and epidemiologic exposures and the advent of improved epigenetic methodology is likely to accelerate the uncovering of putative causative factors.

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