

Epidemiology and Risk Factors for the Development of Food Allergy

CME EDUCATIONAL OBJECTIVES

1. Discuss the factors that result in different estimates of the prevalence of diagnosed food allergy in children.
2. List food allergies known to have a favorable history.
3. Determine the role of food exposures in utero, via lactation, and in early life in the development of food allergy.

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Approximately 5.3% of Americans report a physician diagnosis of food allergy on national surveys.¹ Even based on conservative estimates using the National Electronic Injury Surveillance System, food allergy leads to an estimated 20,821 emergency department visits every 2 months nationwide.² Furthermore, food allergy significantly impairs the quality of life of affected families.³⁻⁵

PREVALENCE OF FOOD ALLERGY IN THE GENERAL POPULATION

Although reviews have previously estimated the prevalence of food allergy in American children as being approximately 6%,⁶ prevalence estimates are dependent on the methods used to diagnose food allergy, the age of the cohort studied, and the presence of any disease-modifying environmental exposures. The prevalence of food allergy has been variably reported to be as high as 35% by self report to as low as 1% by studies using only double-blind placebo-controlled food challenges (DBPCFC).⁷ Even within studies grouped by the same method of food allergy diagnosis there remains significant heterogeneity between reports.^{7,8} Food allergy diagnoses may vary within the

same subject when one compares open challenges to DBPCFC.⁹ However, because a DBPCFC remains the gold standard for diagnosis in studies here, we focus on those studies, which used this methodology for the most accurate prevalence estimates.

Rona et al carried out a meta-analysis (stratified by age group) on all food allergy studies between 1990 and 2005, finding a range of 1% to 10.8% prevalence for food allergy diagnosed by DBPCFC.⁷ For specific foods, preva-

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lence based on challenges ranged from 0% to 3% for milk and 0% to 1.7% for egg. Because studies of peanut allergy typically included as positive those with a clear history of immediate symptoms and a positive skin prick test but not DBPCFC, these were not analyzed. However, two studies of peanut allergy

used a population-based approach and found peanut allergy present in 1.5% to 1.6% of children.^{10,11}

Before taking the results of meta-analyses at face value, there are a number of factors to consider. First, a population-based study will give a more representative determination of prevalence with less selection bias. Second, the age group under study may result in different prevalence estimates because of the natural history of food allergies such as egg and milk which are common in early childhood. Studies of the Isle of Wight, a population-based cohort in which food allergy was diagnosed by DBPCFC. In these studies, the prevalence at age 1 year was 3.2%,¹² the prevalence at 3 years of age was 2.9%, and the cumulative incidence of food allergy at age 3 was 5%.¹³ In an earlier cross-sectional study by the same authors, skin testing and open food challenges (corroborated with DBPCFC in those with positive open food challenges) at age 6 years revealed an even lower prevalence of food allergy of 1.6%.¹⁴ Although this last study was less optimal because of a low participation rate, together these studies reveal the importance of the age of study participants.

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A third factor in evaluating which prevalence studies most accurately represent the entire patient population is evaluation of the population studied. A Danish population-based, birth cohort study also used food challenges to diagnose food allergy. Subjects underwent DBPCFC in this cohort. Only those who refused were diagnosed on the basis of open food challenge. In the Danish cohort, the estimates were similar to the Isle of Wight study. Danish children at < 3 years of age had a prevalence of 2.3%,¹⁵ which decreased to 1.2% by age 6 years.¹⁶ Studies also suggest that the prevalence of food allergies in less industrialized nations may be lower than that of westernized countries.^{17,18}

There are no population-based estimates with diagnosis by DBPCFC from the United States. Population-based estimates of prevalence have been based on random digit dial studies of a general population (not specifically children), with likely diagnosis based on physician diagnosis or timing and type of symptoms.^{19,20} One birth cohort of children from a single pediatric practice suggested a rate of 8% of children, with food allergy confirmed by challenges.²¹ However, this was a medically-selected cohort, challenges were both open and double-blinded, and allergy testing was not universally performed. These factors limit the generalizability of the study findings. It is possible that U.S. estimates would be in the range of those reported by rigorous European population-based studies, which have used DBPCFC as a diagnostic criteria (around 3% in the first 3 years and declining to about half that by 6 years). However, given the limitations in the literature, this is not definitely established.

AGE OF ONSET OF FOOD ALLERGY AND NATURAL HISTORY

As noted in the population-based studies (Isle of Wight Study¹²⁻¹⁴ and the Danish cohort^{15,16}), the rates of food al-



The evidence for the genetic influences on food allergy includes studies of the development of food allergy in family members.

lergy are higher in the first few years of life and then decrease by almost half by middle childhood. This development of tolerance is also noted in medically-selected cohorts followed over time and challenged with foods on a regular basis.^{21,22} Although this general pattern is the rule, the rates of "outgrowing" food allergy are also dependent on the food.²² The majority of food allergy in the first few years of life is to milk and egg.²³⁻²⁵ Similarly, peanut allergy is also common in early life, with .5% of one general population birth cohort allergic to peanut at 4 years of age.²⁶ However, these food allergies have dramatically different natural history and prognoses.

Most studies suggest that milk allergy is outgrown in childhood. The rate at which this happens is a matter of debate. In a review of six studies of the natural history of IgE-mediated milk allergy, the rate of tolerance ranged from 22% to 76% after follow up to 5 years.²⁷ A population-based birth cohort with challenge-based evaluation of tolerance revealed a 75% rate of tolerance in chil-

dren with IgE-mediated milk allergy by age 3.²³ Further follow-up of this cohort found that only 14% of subjects with IgE-mediated cow milk allergy were still allergic to milk at 10 years of age.²⁸ Other studies in which subjects were medically recruited revealed different results. One study evaluated IgE-mediated milk allergy in children who had immediate symptoms on challenge, revealing only a 22% rate of tolerance after 2 years of follow-up.²⁹ Another study of children with both atopic dermatitis and food allergy also evaluated tolerance on the basis of DBPCFC and found that only 38% of the children had developed tolerance by 7 years.³⁰ In the most recent cohort recruited in allergists' clinics, only 42% had outgrown allergy by 8 years of age and 79% by 16 years of age.³¹ These differences compared with the population-based cohort may be due to the population studied. It may be that subjects who present to specialist clinics may be more severe or at least more atopic, being prone to other diseases, such as asthma, which may be markers of poor prognosis.^{31,32} However, even in the medically-selected cohorts, milk allergy was outgrown in the majority of subjects by mid- to late adolescence.

In contrast to this, individuals with peanut allergy are much less likely to have outgrown their food allergy than those who are milk allergic. A British study³³ carried out open food challenges in subjects with a prior diagnosis of peanut allergy if they had a history of reaction and their current skin test was negative, or if they were reported by parents to be tolerating peanut despite a positive skin prick test. Children with a clinical non-life threatening reaction more than 3 years prior who had a persistently positive skin test were also challenged at parents' request. This protocol resulted in 9.8% of all of the aforementioned subjects being described as tolerant. However, it is not clear whether all of

those originally diagnosed as peanut allergic were clinically allergic, since at least 8 of the 15 children were called allergic on the basis of a history alone with a negative skin prick test, making this study less optimal.

Another retrospective review³⁴ that used open non-blinded challenges revealed that at least 14 out of 293 patients had outgrown peanut allergy. However, only 33 children with a convincing history and positive skin tests were challenged. Skolnick et al³⁵ also challenged individuals with a diagnosis of peanut allergy. In this study, individuals were identified as peanut allergic on the basis of either history of acute reaction to peanut with a positive skin prick test or RAST, or a prior positive open challenge. However, some cases of peanut allergy were also identified on the basis of a specific IgE level for peanut > 20 kU_A/L. The cases identified with this protocol underwent DBPCFC, yielding a 21.5% resolution rate. Although there are problems with this study, because 33% of the subjects were termed peanut allergic on the basis of specific IgE, 20 kU_A/L is a level at which the majority of subjects included based on this criteria would truly be allergic and be expected to have positive food challenges.³⁶ Overall peanut-allergic subjects are much less likely to outgrow their food allergy. Similar findings have been shown for tree nut allergy.³⁷

The natural history of different food allergies needs to be evaluated simultaneously in a longitudinal cohort with good documentation of allergic status and regular challenges to compare rates of resolution and tolerance.

IS FOOD ALLERGY STILL ON THE RISE?

Prevalence estimates are dependent on method of diagnosis, population studied, and age of subjects. As such, comparisons of cross-sectional prevalence studies are not necessarily accu-

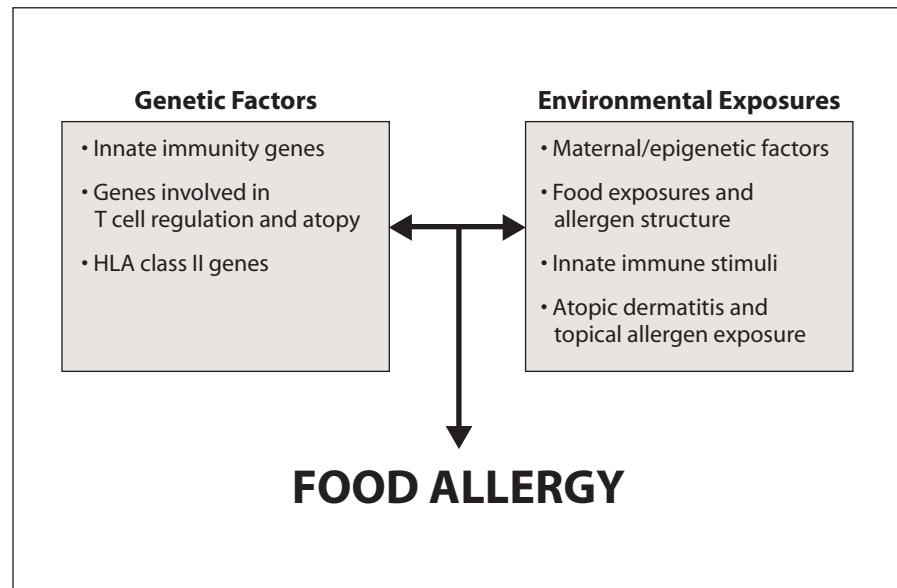


Figure. Genetic influences cannot explain the rapid emergence of food allergies, but environmental factors are more likely to modify predisposition to disease in genetically-susceptible individuals.

rate estimates of changes in prevalence. Random digit dial studies in the United States suggest that the prevalence of peanut allergy doubled throughout a 5-year period of follow-up.²⁰ Similarly, repeated prevalence estimates using challenges in the Isle of Wight cohort were carried out 6 years apart and revealed a three-fold increase in prevalence.¹¹

RISK FACTORS FOR FOOD ALLERGY: GENES AND ENVIRONMENT

Food allergy, like other complex diseases, is likely to be a product of gene–environment interactions. Although genetic influences cannot explain the rapid emergence of food allergies, environmental factors are more likely to modify predisposition to disease in genetically-susceptible individuals. This concept is illustrated in the Figure.

Genetic Factors

The evidence for the genetic influences on food allergy includes studies of the development of food allergy in family members. If a first-degree family member has peanut allergy, the risk of peanut allergy increases seven-fold.³⁸ Similarly, in a high-risk cohort with a family his-

tory of atopy in a parent, 25% of the children developed food allergy before 7 years of age.³⁹ Furthermore, monozygotic twins have a 64% concordance rate for food allergy in comparison to a rate of 6.8% for dizygotic twins.⁴⁰ Thus there is a clear genetic predisposition and the few studies of candidate genes have identified targets which are involved in the atopic pathway.^{41–43}

Environmental Factors

Since food allergy is prevalent in the first few years of life, early life factors including immunological stimuli, infant and maternal diet, medications, and the presence of comorbid eczema have been identified as potential risk factors.

The Hygiene Hypothesis

In terms of immunological stimuli, factors that play a role in the development or prevention of other allergic diseases are likely to play a role in the development of food allergy as well. The “hygiene hypothesis” holds that early life immunological stimuli interact with the innate immune system, including toll-like receptors to promote induction of a tolerant phenotype,

possibly through T regulatory cells.⁴⁴ However, relatively few studies have directly investigated the association of food allergy with epidemiologic markers of early life microbial and innate immune exposures. One such marker is cesarean section delivery, which results in altered timing of colonization⁴⁵ by bacteria, and which has been associated with higher rates of atopic diseases in offspring.⁴⁶ In one study, cesarean section was associated with a four-fold increased risk of egg allergy.⁴⁷ Similarly, dog ownership, an exposure associated with high endotoxin levels, has been associated with a decreased chance of developing food allergy.⁴⁸ This goes along with the fact that a polymorphism in CD14, the co-receptor for endotoxin, is one of the candidate genes identified for food allergy.⁴¹ Although hygiene hypothesis factors are well established for other allergic disorders, there are fewer studies that relate specifically to food allergy.

Food Allergen Exposures in Pregnancy, Lactation, and Early Life

Although food allergen exposure is necessary to develop sensitization to a food, it remains unclear whether early ingestion is a risk factor and whether dietary modification is beneficial. The American Academy of Pediatrics (AAP) recently issued a statement on the role of food exposures in the development of allergic diseases.⁴⁹ This statement is the result of careful review of the literature on food avoidance and states that there is insufficient evidence that avoidance diets in pregnancy prevent atopic disease, with the possible exception of early childhood atopic dermatitis. This was based on the fact that although two earlier studies had suggested a protective effect on eczema,^{50,51} others did not show this effect⁵²⁻⁵⁴ in keeping with systematic reviews.^{55,56} Similarly, the statement notes that exclusive breastfeeding may have no clear long-term effects in terms of de-

velopment of allergic diseases based on two cohort studies with longer duration of follow-up.^{39,57} According to the AAP statement, there is insufficient evidence that allergen exposure via maternal diet during pregnancy and lactation are risk factors for the development of allergic disease, including food allergy.

Similarly, it remains unclear whether the risk of food allergy is increased (or potentially even decreased) by exposure

Cesarean section was associated with a fourfold increased risk of egg allergy.

to food allergens in the first year of life after age 4 months. One study found that, compared with cow milk formula, extensively hydrolyzed casein formula may decrease the rates of atopic dermatitis and atopic diseases combined (including food allergy).⁵⁸ Another study showed that introduction of solid foods before 4 months may be associated with an increase in rate of atopic dermatitis, but no protective effect was noted with delaying introduction of solid foods until after 6 months.⁵⁹ These two studies taken in the context of the conflicting literature led to guarded recommendations by the AAP. However, taken together, these two studies suggest that early oral exposures in the first few months of life may have some bearing on the development of food allergy, and that exclusive breastfeeding for at least 4 months may also be protective. Following this early period, it is a matter of debate whether ingestion of various foods promotes tolerance or allergy.

Atopic Dermatitis

Food allergy is more common in children with atopic dermatitis.⁶⁰ Onset of eczema in the first 6 months of life

also increases the risk of food allergy compared with onset of eczema in the second 6 months of life.⁶¹ One study found an increased risk of peanut allergy in individuals who were topically exposed to peanut-based oils in the perinatal period.⁶² Experts in this area have hypothesized that in atopic dermatitis, cutaneous exposure to food allergens may increase the chance of sensitization, whereas low-grade oral exposures may promote tolerance.⁶³ This remains an area of controversy and ongoing investigation.

Other Risk Factors

A few other studies have found associations with food allergy. One study suggested that micronutrients such as vitamin D may be associated with food allergy.⁶⁴ Similarly, another study suggested that administration of water-soluble forms of vitamins A and D were associated with increased risk of food allergy.⁶⁵ Finally, other exposures including tobacco smoke⁶⁶ and antacid use⁶⁷ have been associated with food allergen sensitization. The roles of these factors in the development of food allergy need to be confirmed in large, prospectively followed, longitudinal birth cohorts.

CONCLUSION

Food allergy is a prevalent condition of childhood, with at least 3% of children younger than 3 years having challenge-proven food allergy in the general population. Unfortunately, the prevalence of food allergy continues to increase rapidly, with studies of populations such as in the Isle of Wight suggesting a doubling of prevalence over the span of 6 years. While the majority of children outgrow certain food allergies, such as eggs and milk, by mid-adolescence, other foods such as peanut and tree nut are less commonly outgrown. Food allergy is a complex disease which is the result of gene-environment interactions.

However, aside from the introduction of foods very early in life, the relative importance of identified environmental and dietary risk factors is still in need of further investigation.

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