

Mechanisms of allergic diseases

Series editors: Joshua A. Boyce, MD, Fred Finkelman MD, William T. Shearer, MD, PhD, and Donata Vercelli, MD

Update on risk factors for food allergy

Gideon Lack, MD *London, United Kingdom*

Despite efforts to prevent food allergy (FA) in children, IgE-mediated FAs are increasing in westernized countries. Previous preventive strategies, such as prolonged exclusive breast-feeding and delayed weaning onto solid foods, have recently been called into question. The present review considers possible risk factors and theories for the development of FA. An alternative hypothesis is proposed, suggesting that early cutaneous exposure to food protein through a disrupted skin barrier leads to allergic sensitization and that early oral exposure to food allergen induces tolerance. Novel interventional strategies to prevent the development of FA are also discussed. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Food allergy, risk factors, filaggrin, genetics, dual-allergen-exposure hypothesis

Recent epidemiologic studies in the United Kingdom (UK) and North America have shown that prevalence rates of food allergy (FA) in children have increased. FA prevention through allergen avoidance during pregnancy, breast-feeding, and infancy has been seen as an effective public health policy to prevent allergies, although there are little epidemiologic data to support this. Interventional trials on dietary elimination have failed to reduce IgE-mediated FA. On the other hand, there are preclinical and some clinical data suggesting that early oral exposure leads to the induction of *tolerance*. New strategies to prevent FA in infants need to be tested in randomized controlled interventional studies. This article reviews potential risk factors for the development of FA. It provides an update to a review published 2 years ago in the *Journal*¹ and highlights new published findings in the field.

From MRC Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, Guy's and St Thomas' NHS Foundation Trust, Children's Allergies Department, St Thomas' Hospital.

Disclosure of potential conflict of interest: G. Lack has received sponsorship from Sodilac, Novartis, the Spanish Society of Allergy and Clinical Immunology (SEAIC), Danone Nutricia, and Nestlé; has received study support from the Immune Tolerance Network/National Institutes of Health, National Peanut Board, Food Standards Agency, Medical Research Council, Food Allergy Initiative, Action Medical Research, ALK-Abelló, and Guy's and St Thomas' Charity; and has served as an advisor for the Anaphylaxis Campaign, National Peanut Board, and DBV Technologies.

Received for publication January 10, 2012; revised February 20, 2012; accepted for publication February 23, 2012.

Corresponding author: Gideon Lack, MD, Children's Allergies Department, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom. E-mail: gideon.lack@kcl.ac.uk.

0091-6749/\$36.00

© 2012 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2012.02.036

Terms in boldface and italics are defined in the glossary on page ■■■.

Abbreviations used

AD:	Atopic dermatitis
FA:	Food allergy
FLG:	Filaggrin
IL-12Rβ1:	IL-12 receptor β1
OR:	Odds ratio
OVA:	Ovalbumin
PA:	Peanut allergy
PGE ₂ :	Prostaglandin E ₂
RCT:	Randomized controlled trial
SNP:	Single nucleotide polymorphism
SPT:	Skin prick test
UK:	United Kingdom

PREVALENCE AND INCREASE OF FA

It should be noted that knowledge about the epidemiology of FA is limited and inaccurate for a number of reasons. First, most studies documenting the prevalence of peanut, milk, and egg allergies are limited to Western countries; there are no published international surveys defining FA on a broader scale. Knowledge about FA in the developing world is limited and relies mainly on case series.

Second, there are methodological explanations for the differences in prevalence observed in different studies. Double-blind, placebo-controlled food challenges, which represent the gold standard, are only used in a minority of studies. Consequently, other studies use questionnaires (mainly unvalidated), IgE positivity, or skin prick test (SPT) response positivity as markers of FA.

A recent meta-analysis of 51 articles from different countries examined the prevalence of FA using various criteria.² The self-reported prevalence of allergy varied from 1.2% to 17% for milk, 0.2% to 7% for egg, 0% to 2% for peanut and fish, 0% to 10% for shellfish, and 3% to 35% for any food. Challenge-proved FA provided lower estimates: 0% to 3% for milk, up to 1.7% for egg, 0.2% to 1.6% for peanut, and 1% to 10.8% for any food. In a second study of plant FA (wheat, soya, tree nut, fruits, and seeds), the authors found marked heterogeneity between studies.³

A striking example of how a small change in methodology leads to a markedly different prevalence of FA is provided by the Australian Health Nuts study. In an article published in the *Journal*,⁴ 9% of a birth cohort of 2848 one-year-old infants had challenge-proved IgE-mediated egg allergy. The reason for this very high prevalence of egg allergy is most instructive. The authors use raw egg white extract to perform both SPTs and raw egg challenges. However, they found that only 19.7% of children with raw egg white allergy reacted during a baked egg challenge. This results in a baked egg prevalence of 2.2%, which

corresponds to other epidemiologic surveys considering the prevalence of baked egg allergy. These previous studies have all used commercial egg white extract for SPTs and baked egg for the challenges. The Australian study highlights how it is possible to underestimate the prevalence of FA depending on the form of extract used to conduct SPTs and food challenges. Indeed, phenotypic analyses of children with egg allergy in select clinic populations have shown that there are children with egg allergy who tolerate egg in baked goods as opposed to children who are completely intolerant to all forms of egg. The former show more rapid resolution of their egg allergy and might be more amenable to oral immunotherapy. Although speculative, it is likely that numerous legume, fruit, and vegetable allergies (usually caused by oral allergy syndrome) and even allergies to beef and other meats would be more prevalent if SPTs and challenges were conducted with raw food products.

Despite such methodological problems, it appears that since the late 1950s, the incidence of allergy in developed countries has increased progressively. In the United States the prevalence of reported FA increased 18% from 1997 through 2007 in children less than 18 years of age ($P < .01$). Ambulatory care visits caused by FA tripled between 1993 and 2006 ($P < .01$). In 2007, 3.9% of US children less than 18 years of age had reported FAs.⁵

In the UK food hypersensitivity prevalence based on food challenges and appropriate clinical history is 5% to 6% by the age of 3 years.⁶ Trends in hospital admissions show that admissions for FA in children increased nearly 7-fold from 16 to 107 per million for the time period 1990-1991 to 2003-2004.⁷ A recent UK

study including 1072 mothers and their children showed that the prevalence of peanut sensitization is 2.8% and the prevalence of peanut allergy (PA) is 1.8% among British children at school entry.⁸

A recent large US study by Sicherer et al⁹ looked at changes in the prevalence of PA and tree nut allergy. The researchers compared 3 large telephone surveys enquiring about PA and tree nut allergy in 5300 households. These cross-sectional surveys were conducted in 1997, 2002, and 2008. They showed a significant increase in PA and tree nut allergy, particularly in children less than 18 years of age. The prevalence of PA increased from 0.4% in 1997 to 0.8% in 2002 and 1.4% in 2008 ($P < .0008$). Although these studies rely on self-report rather than objective testing, the same methodology was used for all 3 surveys. The increase reported is similar to that seen in other studies using objective measures, such as skin testing.

GEOGRAPHY OF FA

Despite limitations in epidemiologic studies and variations in methodologies, it is noteworthy that there are certain geographic associations with FA. For example, bird's nest soup allergy is reported to be common in Singapore,¹⁰ royal jelly allergy in Hong Kong,¹¹ and mustard seed allergy in France.¹² More recently, in their validated questionnaire-based survey Du Toit et al¹³ showed that the prevalence of PA was increased 10-fold in Jewish children in the UK compared with that seen in Jewish children in Israel.

GLOSSARY

ANCESTRY INFORMATIVE MARKERS (AIMs): Ancestry informative markers (AIM) are a set of polymorphisms that have distinct frequencies dependent on the geographic origin of the person. Using AIMs allows an assessment of what proportion of the genome in a person is derived from ancestors from a given geographic location.

CD14: CD14 is the membrane-bound and soluble LPS receptor that mediates Toll-like receptor 4 signaling. Gene-environment interactions in the *CD14* gene include the association of combined dog ownership and *CD14* polymorphisms that are protective for allergic sensitization and atopic dermatitis.

EPITHELIAL BARRIER DYSFUNCTION: Epithelial barrier dysfunction is the concept that the loss of epithelial integrity caused by injury, inflammation, or genetic predisposition leads to increased antigen exposure and the onset of aberrant immune responses.

FLAGGRIN (FLG): FLG is essential for epithelial barrier function. Loss of FLG causes ichthyosis vulgaris, predisposes to eczema and asthma, and allows increased epithelial permeability to passive transfer of protein antigens. Profilaggrin/FLG functions include modulation of skin pH, moisturization, and potentially even antimicrobial activity.

IL-10: IL-10 is generally associated with a dampened immune response to antigen, allergen, or both. IL-10 production increases from CD25⁺ regulatory T cells after successful immunotherapy and is also increased during viral infections. IL-10 suppresses eosinophilia by inhibiting IL-5 and GM-CSF, suppresses IFN- γ and IL-2 production from T_H1 cells, and decreases IL-4 and IL-5 production from T_H2 cells. IL-10 family members include IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29.

IL-12R β 1: IL-12 signals through the IL-12 receptor to cause the release of IFN- γ as activation, proliferation, and cytokine production from natural killer and T cells. Genetic mutations in the IL-12R β 1 chain are associated with severe mycobacterial and *Salmonella* species infections.

IL-13: IL-13 is a T_H2 cell-derived interleukin that is likely a master regulator of allergy. Overexpression of IL-13 causes pulmonary, esophageal, and cutaneous fibrosis, as well as angiogenesis. IL-4 and IL-13 use a common α chain on their receptors and thus can have overlapping effects.

PROSTAGLANDIN E₂ (PGE₂): PGE₂ has anti-inflammatory effects, especially in the airway, and uses 4 distinct receptors after being produced from PGH₂. PGE₂ inhalation decreases bronchospasm in response to allergen, exercise, and aspirin. Increased PGE₂ levels are associated with lower sputum eosinophilia. PGE₂ receptors are expressed on T, B, dendritic, smooth muscle, and epithelial cells, including the airway epithelium.

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 6 (STAT6): The STAT family of transcription factors are phosphorylated during signaling through the Janus-activated kinase (JAK) pathways. STATs dimerize and bind to palindromic DNA elements to activate gene transcription. STAT6 is important for T_H2 gene transcription, such as the signals from IL-4 and IL-13, which activate *GATA3* gene expression.

TOLERANCE: The immunologic state defined by a lack of reactivity to an antigen/allergen. In contrast to desensitization, tolerance refers to a permanent immunologic state in which infrequent and repeated antigen exposures do not result in an allergic reaction. Tolerance can be induced, for example, by immunotherapy and is associated with increased regulatory T cell numbers and increased IL-10 production. Whether oral desensitization to foods is associated with long-term tolerance to a food antigen remains to be elucidated.

THYMIC STROMAL LYMPHOPOIETIN (TSLP): TSLP is expressed on activated epithelium inclusive of the airway and esophagus and promotes antigen presentation by dendritic cells by inducing the expression of costimulatory molecules, such as OX40, CD40, and CD80.

The Editors wish to acknowledge Seema S. Aceves, MD, PhD, for preparing this glossary.

Another recent study reported important clinical and immunologic differences among patients with PA originating from the United States, Sweden, and Spain.¹⁴ American patients often had a high frequency and higher levels of IgE antibodies to Ara h 1, Ara h 2, and Ara h 3 (56.7% to 90%, respectively) and tended to present with more severe symptoms. Patients from Madrid recognized these 3 recombinant peanut allergens less frequently (16% to 42%, respectively) but had higher sensitization rates to the lipid transfer protein Ara h 9 (60%). Swedish patients had the highest sensitization rate to the Bet v 1 homolog Ara h 8 (65.7%).

It therefore appears that geography can affect both the prevalence of certain FA and the pattern of immunologic reactivity to individual allergenic components within the food, thus affecting the clinical expression of FA. These geographic differences could be due to environmental differences in levels of allergen exposure or different preparations and processing of the allergen but could also result from genetic differences in geographically diverse groups with different ancestral origins. The study by Du Toit et al¹³ suggests that differences in PA between the UK and Israel are due to geography and environment rather than ancestry.

HEREDITARY, GENETIC, AND MOLECULAR RISK FACTORS

Family history

Some research suggests a strong genetic component to PA. A child has a 7-fold increase in the risk of PA if he or she has a parent or sibling with PA.¹⁵ Regarding monozygotic twins, a child has a 64% likelihood of PA if his or her twin sibling has PA.¹⁶ Although it is unlikely that genetic risk factors could account for the recent increase in FA, it is nevertheless likely that there are genetic predisposing factors for their development. The contribution of the HLA background and the development of individual FA in the increase of FA remain to be seen.

Sex

It is noteworthy that several studies report that sex could be related to FA, particularly PA and tree nut allergy. In a study by Sicherer et al,¹⁷ the male/female ratio of children with PA is almost 5, whereas for adults, the male/female ratio is less than 1. A similar pattern was seen for tree nut allergies. This is similar to the study reported by Emmett et al.¹⁸ In their cross-sectional study reporting PA by questionnaire in more than 16,000 subjects, the prevalence of PA was significantly higher in young male subjects less than 4 years of age than in female subjects. However, by the teenage years, the male/female ratio was equal, and during adulthood, there were almost twice as many female subjects with PA than male subjects. Thus a number of studies suggest a reversal in the male/female ratio for FA after adolescence. This same change has been observed in asthmatic patients. The change in relative frequency of FA between childhood, adolescence, and adulthood suggests that sex might affect the expression of allergy, possibly through endocrine influences.

In the large National Health and Nutrition Examination Survey study of all ages combined, Liu et al¹⁹ showed an odds ratio (OR) of 1.87 (95% CI, 1.32-2.66) for male sex on the development of FA.

Ethnicity

In the same National Health and Nutrition Examination Survey study (2005-2006), Liu et al¹⁹ showed that the risk of possible and

likely FA was increased in non-Hispanic black subjects (OR, 3.06; 95% CI, 2.14-4.36) compared with that seen in white subjects. This study used specific IgE data from a large survey. Although clinical data were not available, the authors chose a cutoff value of greater than 5 kU/L of food-specific IgE as indicating likely FA. For example, the prevalence of likely FA to shrimp in non-Hispanic black subjects was 2.3% compared with 0.3% in non-Hispanic white subjects. It should be noted that these high cutoff IgE values only reflect high values of IgE sensitization and not clinically proved allergy. However, the authors do argue that these high levels are more likely to correlate with the presence of true clinical FA.

A more recent study by Kumar et al²⁰ showed that black children were more likely to be sensitized to multiple foods compared with white children. Using genetic *ancestry informative markers* as a measure of ancestry, African ancestry was a notable risk factor for increased risk of peanut sensitization at levels associated with clinical reactivity. Because clinical reactivity or challenge results were not known, likely clinical allergy was defined by specific IgE values of greater than 5 kU/L.

Both these studies suggest that FA might be an underrecognized problem in nonwhite ethnic minorities. This could result from a lack of recognition and diagnosis of symptoms or from differential access to health care. A study by Branum and Lukacs⁵ provides thought-provoking data on the link between ethnicity and FA. This study analyzed trends of FA in the United States between 1997 and 2007 and found that FA increased most significantly among Hispanic children despite black non-Hispanic children having the highest rates of detectable IgE antibodies to food. FA levels appeared to be highest in the non-Hispanic white population, despite that population having the lowest prevalence of detectable IgE antibodies to foods. It is possible again to explain the discrepancy between rates of reported clinical FA (hospitalization codes and ambulatory visits) and rates of sensitization to foods as a result of differential health care access in different communities. However, an alternative explanation is that increased IgE levels to food are not necessarily indicative of FA but only indicate sensitization. Thus the increased propensity of IgE that is found in certain ethnic groups might not reflect true FA but might only be indicative of sensitization. This is a topic of great interest on which there are few data. Community-based studies in well-defined different ethnic populations conducted with oral food challenges are needed to further the understanding of the relationship among IgE levels, clinical reactivity, and ethnicity.

Genetic polymorphisms

A *signal transducer and activator of transcription 6* (STAT6) polymorphism has been shown to be associated with nut allergies in one study.²¹ Recently, an *IL10* gene polymorphism has been associated with FA in a Japanese population,²² and an *IL13* polymorphism has been identified in association with FA in another study.²³ These studies will need to be replicated in different populations.

Recently, 2 single nucleotide polymorphisms (SNPs) in the *CD14* gene region have been studied because of association with atopic disease. Dreskin et al²⁴ studied a population of 53 patients with PA and 64 peanut-tolerant siblings. They showed that variations in the 2 important SNPs of *CD14* (rs2569190 and rs2569193) are associated with the presence of PA and increased

levels of total IgE and the frequency of eczema in patients with PA. This is the first report that rs2569190 might be an important risk factor for PA.

More recent studies suggest important gene-environment interactions in the development of food sensitization. In a prospective birth cohort study of 970 children, Hong et al²⁵ showed that children who were ever breast-fed (including exclusively breast-fed children) were at 1.5 times higher risk of food sensitization than never breast-fed children. However, they found that the association was modified by rs425648 in the gene encoding IL-12 receptor β 1 (*IL-12R β 1*). Paradoxically, breast-feeding increased the risk of food sensitization in children carrying the GG genotype but significantly decreased the risk of food sensitization in breast-fed infants carrying the GT/TT genotype. Similar paradoxical interactions were observed for SNPs in the thymic stromal lymphopoietin (*TSLP*) gene and the Toll-like receptor 9 (*TLR9*) gene. In this study the possibility of reverse causality was taken into account. Other studies have also suggested an association between IL-12R β 1 and IL-12R β 2 with atopic dermatitis (AD).²⁶

Filaggrin loss-of-function mutations

In the past 6 years, numerous studies have confirmed that loss-of-function mutations within the *filaggrin* (*FLG*) gene are associated with the development of AD and other atopic diseases. *FLG* was recently studied as a candidate gene in the cause of PA.²⁷ This was a case-control study of 71 English, Dutch, and Irish patients with challenge-proved PA. Thirty-five children with PA were included from a longitudinal birth cohort study (Avon Longitudinal Study of Parents and Children). The most prevalent 6 *FLG* mutations were studied in these European groups and replicated in a group of Canadian patients with PA. Loss-of-function mutations showed a significant association with PA in patients with PA (OR, 5.3; 95% CI, 2.8-10.2). This association was closely replicated in the Canadian study. Importantly, the association of *FLG* mutation with PA was highly significant ($P = .0008$), even after controlling for coexistent AD. This study indicates a role for *epithelial barrier dysfunction* in the pathogenesis of PA (see below).

CHANGES IN DIET

In the past 3 decades, marked changes in diet have caused researchers to suggest that differences in macronutrient and micronutrient dietary content could explain the increase in allergies. There are 4 hypotheses that deserve discussion.

Vitamin D

There are epidemiologic and immunologic data that suggest that either excessive vitamin D or, conversely, vitamin D deficiency results in increased allergies. The first observations were derived from farming communities in Germany in which less vitamin D supplementation was used in foods and a lower prevalence of allergies in children was found. Allergies increased, coinciding with vitamin D supplementation intervention programs to prevent rickets in childhood.²⁸ Likewise, 2 independent cohort studies by Milner et al²⁹ and Hypponen et al³⁰ showed that infants who had vitamin D supplementation were at increased risk of FA.

Conversely, the vitamin D deficiency hypothesis argues that inadequate vitamin D (predominantly caused by inadequate sunlight associated with more time indoors) is responsible for the increase in asthma and allergies. The study by Camargo et al³¹ found a strong north-south gradient for EpiPen (Dey, Napa, Calif) prescriptions in the United States. Northernmost states were prescribing 8 to 12 EpiPen self-injectors per 1000 population, whereas the southern states were prescribing 3 per 1000 population. This gradient persisted despite a multivariate analysis. There was an inverse association between EpiPen prescription and the incidence of melanoma in the population, suggesting that this north-south effect was due to sunlight exposure.

Recent findings by Vassallo et al³² show that season of birth is a risk factor for FA and that infants born during the winter had a higher risk of FA.

Another study by Nwaru et al³³ shows that maternal intake of vitamin D during pregnancy was associated with a decreased risk of food sensitization.

Dietary fat

There are data arguing that reduction in consumption of animal fats and a corresponding increase in the use of margarine and vegetable oils has led to the increase in allergies. Proponents of this hypothesis argue that there has been an increase in the consumption of ω -6 polyunsaturated fatty acids, such as linoleic acid, and through reduced consumption of oily fish, there has been a reduction in ω -3 polyunsaturated fatty acids, such as eicosapentaenoic acid.^{34,35} ω -6 Fatty acids lead to the production of *prostaglandin E₂* (PGE₂), whereas ω -3 fatty acids inhibit synthesis of PGE₂. PGE₂ reduces IFN- γ production by T lymphocytes, thus resulting in increased IgE production by B lymphocytes.

A systematic review identified 10 reports satisfying the inclusion criteria for a meta-analysis on the influence of ω -3 and ω -6 oils on allergic sensitization.³⁶ The study concludes that "supplementation with Omega 3 and Omega 6 oils is unlikely to play an important role in the strategy for the primary prevention of sensitisation or allergic disease."

Antioxidants

The antioxidant hypothesis suggests that the decrease in consumption of fresh fruit and vegetables (containing antioxidants, such as vitamin C, vitamin E, β -carotene, selenium, and zinc) in the UK might account for allergies. However, dietary trends are conflicting; although the intake of some antioxidants has increased, the intake of others has decreased. However, there is epidemiologic, animal, molecular, and immunologic evidence suggesting associations between antioxidants and asthma and a reduced number of studies on AD and allergic rhinitis.³⁷ However, no such data are currently available for FA.

Obesity

The coinciding trend in increasing atopy with increasing childhood obesity has been well studied, especially in the context of asthma. Obesity induces an inflammatory state associated with an increased risk of atopy and theoretically could lead to an increased risk of FA. A recent study by Visness et al³⁸ demonstrated that atopy (as defined by any positive specific IgE measurement) was increased in obese children compared with

normal-weight children. This association was driven primarily by allergic sensitization to foods (OR for food sensitization, 1.59; 95% CI, 1.28-1.98). Increased C-reactive protein levels as a measure of inflammation were associated with total IgE levels, atopy, and food sensitization.

HYGIENE HYPOTHESIS

In general, allergies are associated with a Western lifestyle. The hygiene hypothesis proposes that the lack of early childhood exposure to infectious agents, gut flora, and parasites increases susceptibility to allergic diseases by modulating immune system development, although limited data for the hygiene hypothesis exist with respect to FA.

A Norwegian birth cohort study found that birth by means of cesarean section was associated with a 7-fold increased risk of parental perceived reactions to eggs, fish, or nuts.³⁹ A recent meta-analysis found 6 studies that showed a mild effect of cesarean delivery, increasing the risk of FA or food atopy (OR, 1.32; 95% CI, 1.12-0.55).⁴⁰ However, it should be noted that in a large recent study evaluating 503 infants, the mode of delivery at birth bore no relationship to sensitization or FA, as determined by specific IgE levels in young infants.⁴¹

It has been hypothesized that early colonization of the infant by colonic microflora protects against the development of allergic disease. Such observations have led to strategies to alter commensal gut flora, either directly through the administration of probiotics or indirectly through the administration of prebiotics. Although some studies using probiotics reported some protective effect against the development of eczema, no reduction in allergen sensitization was shown.⁴²

EXPOSURE TO FOOD ALLERGENS

Important questions remain about exposure to food allergens in the maternal and infant diet. Until recently, the American Academy of Pediatrics recommended that infants whose family history placed them at increased risk of atopy should avoid peanuts during the first 3 birthdays and common food allergens until the first (milk), second (egg), or third (tree nuts and fish) birthdays.⁴³ According to these recommendations, mothers should avoid peanuts during pregnancy and breast-feeding and additional allergens during lactation. In the UK similar recommendations were in place with respect to peanut avoidance.⁴⁴ However, more recently, these recommendations were withdrawn by the American Academy of Pediatrics.⁴⁵ The more recent position is that "current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation.... There is also little evidence that delaying timing of the introduction of complementary foods beyond 4-6 months of age prevents the occurrence of atopic disease." Similarly, the UK recommendations on dietary exclusion were rescinded in 2008.⁴⁶

There is a lack of evidence on which to base advice for weaning infants. Little evidence-based guidance exists about the quantities and frequencies with which these foods should be introduced. The World Health Organization strategy to prevent allergy is to promote exclusive breast-feeding during the first 6 months of the infant's life, delaying weaning onto solids and milk formulas.⁴⁷ However, there is no convincing evidence that exclusive breast-feeding beyond 4 months of age has any effect on reducing atopic disease. Indeed, observational cohort studies show that

breast-feeding⁴⁸ and prolonged breast-feeding⁴⁹ are associated with an increased risk of asthma and eczema. Although such studies do not eliminate the possibility of reverse causality (high-risk infants with eczema are deliberately breast-fed longer), they raise the question as to whether exposure to solids in infancy might help prevent allergic disease.

FOOD ALLERGEN EXPOSURE REVISITED

Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to reduce long-term IgE-mediated FA in children.⁵⁰ Four possible explanations exist for this failure.

First, exposure to allergens is irrelevant for the development of FA. This explanation is implausible because FA is an antigen-specific immunologic disease, and antigen exposure is necessary for T-cell maturation, affinity maturation, and isotype switching.

Second, allergen reduction measures have not been sufficient in previous studies, and dietary elimination was not sufficiently stringent. This is more plausible, but it seems unlikely that "complete" allergen avoidance could successfully prevent FA as a public health measure, given that, despite rigorous dietary supervision, careful elimination studies have failed to achieve a reduction in FA.^{50,51}

Third, sensitization to food allergens does not occur as a result of consumption but through other routes of exposure. This is supported by a number of murine studies showing that allergic sensitization to antigen occurs after cutaneous exposure and has also been suggested in recent clinical studies.

Finally, the paradigm of allergen avoidance is flawed. Animal data and some observational clinical data support early oral exposure as a means of preventing the development of allergy.

DUAL-ALLERGEN EXPOSURE HYPOTHESIS

The prevailing view that allergic sensitization to food occurs through oral exposure and prevention of FA is best accomplished through elimination diets has been challenged. It is proposed instead that allergic sensitization to food can occur through low-dose cutaneous sensitization and that early consumption of food protein induces oral tolerance.⁵² The timing and balance of cutaneous and oral exposure determine whether a child has allergy or tolerance (Fig 1).¹

Data suggesting cutaneous sensitization

Current knowledge suggests that AD results from a combination of altered skin barrier function, abnormal immune reactivity, and environmental factors, such as allergens and microbes. There is indeed a molecular basis for the increased skin permeability seen in patients with eczema: the loss-of-function or missense mutations in the gene encoding FLG. This protein is important for epidermal differentiation, desquamation, and barrier function and has been recognized as the strongest genetic contributor to eczema.⁵³⁻⁵⁶ FLG deficiency is also associated with increased transepidermal water loss, and this measurable functional impairment of the skin barrier precedes the development of eczema.⁵⁷

In the positive studies 14% to 56% of cases of eczema carry 1 or more FLG null mutations and the presence of an FLG null allele represents a 1.2- to 13-fold increased risk of AD.⁵⁸ Furthermore, T_H2 inflammation in the skin of patients with eczema reduces

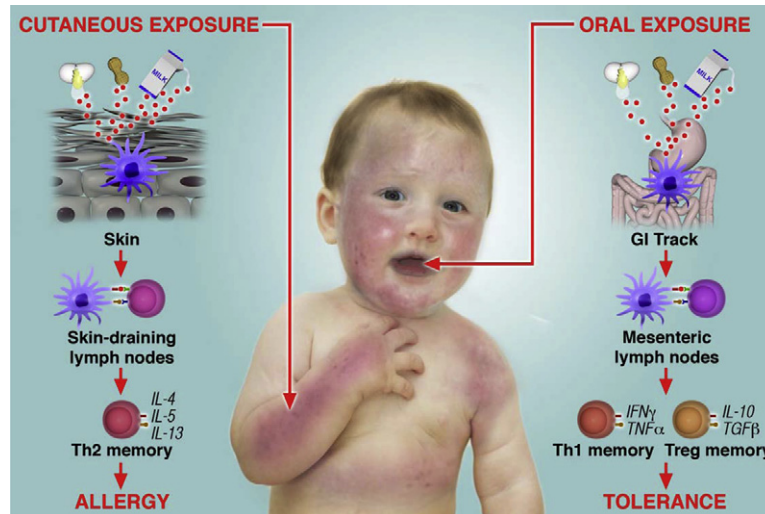


FIG 1. Dual-allergen exposure hypothesis for the pathogenesis of FA. Allergic sensitization results from cutaneous exposure, and tolerance occurs as a result of oral exposure to food. *GI*, Gastrointestinal. Reprinted with permission from Lack.¹

FLG gene expression.⁵⁹ It has been suggested that low-dose exposure to environmental food proteins on tabletops, hands, and dust can occur.⁶⁰ Such food proteins can penetrate the disrupted skin barrier and are taken up by Langerhans cells. This leads to Th2 responses and IgE production by B cells.⁵³ This hypothesis can explain the association between the presence of early severe eczema in infancy and the subsequent development of FA. Furthermore, this hypothesis can explain different rates of FA in different parts of the world and changes in FA over time. Thus in societies in which a food is not consumed, there is no environmental exposure, and therefore allergy to that food will not occur. Allergy to kiwi was not a problem in the UK before it was introduced into the market in the 1970s through 1980s. In countries in which peanut consumption is high and peanut is therefore present in the environment but infants avoid peanuts, one would expect to see allergic sensitization (the UK, US, Canada, and Australia). In countries in which consumption and consequently environmental exposure are high but infants are eating peanut regularly, one would not expect to see PA (southern/western Africa/Asia).¹ If a food is consumed in any given society or location, this results in both environmental and oral exposure.

In animal models exposure of mice to ovalbumin (OVA) or peanut on abraded skin led to significant specific IgE responses.^{61,62}

FA to OVA has recently been demonstrated in a murine model for loss-of-function mutations in the *FLG* gene.⁶³ In this study the authors report a 1-bp deletion mutation (5303delA), which is analogous to common human *FLG* mutations. The authors demonstrate that topical application of allergen in these flaky-tailed mice using OVA as an allergen resulted in cutaneous inflammatory infiltrates and enhanced allergen priming, as measured based on levels of systemic specific IgE to OVA. Wild-type mice did not have increased levels of total serum IgE, nor did they generate a specific IgE or IgG response to OVA in contrast to the mutated mice. This model stands in sharp contrast to the other models of murine cutaneous exposure with normal *FLG* expression. In flaky-tailed mice spontaneous application of allergen to the skin results in an allergen-specific IgE response without any pre-existing cutaneous inflammation or abrasion. This provides

compelling evidence that *FLG* deficiency and consequent skin barrier dysfunction is sufficient to allow cutaneous penetration of allergen and the development of a systemic allergic response.

In human subjects food allergen-specific T cells have been isolated from lesional skin in patients with eczema.⁶⁴ In a prospective birth cohort study it was found that low-dose exposure to peanut in the form of arachis oil applied to inflamed skin of infants was associated with an increased risk of PA at age 5 years.⁶⁵ Thirty-two percent of children using creams containing oat had oat-positive patch test results compared with 0% of children who did not use these creams.⁶⁶ In a recent cross-sectional study⁶⁷ the relevant route of peanut exposure in the development of allergy was evaluated. Maternal peanut consumption during pregnancy, breast-feeding, and the first year of life was captured by using a questionnaire; additionally, peanut consumption among all household members was quantified. The median weekly household peanut consumption in the patients with PA was significantly increased (18.8 g, $n = 133$) compared with that seen in control subjects without allergy (6.9 g, $n = 150$) and high-risk control subjects (1.9 g, $n = 160$, $P < .0001$). A dose-response relationship was observed between environmental (nonoral) peanut exposure and the development of PA. These findings suggest that high levels of environmental exposure to peanut during infancy can promote sensitization, whereas low levels appear protective in atopic children. Early oral exposure to peanut in infants with high environmental peanut exposure might have had a protective effect against the development of PA. This supports the hypothesis that peanut sensitization occurs as a result of environmental exposure (Fig 2).⁶⁷

This contrasts with a study by Sicherer et al⁴¹ based on the National Institutes of Health Consortium Food Allergy Research study that enrolled 503 high-risk atopic infants. In this study frequent peanut consumption in pregnancy was associated with specific IgE levels to peanut of greater than 5 kU/L (OR, 2.9; 95% CI, 1.7-4.9). Although this study reports that peanut present in the home at the time of assessment did not influence sensitization to peanut, the presence of peanut was recorded as a dichotomous variable, and thus detailed household consumption and environmental exposure were not quantifiable.

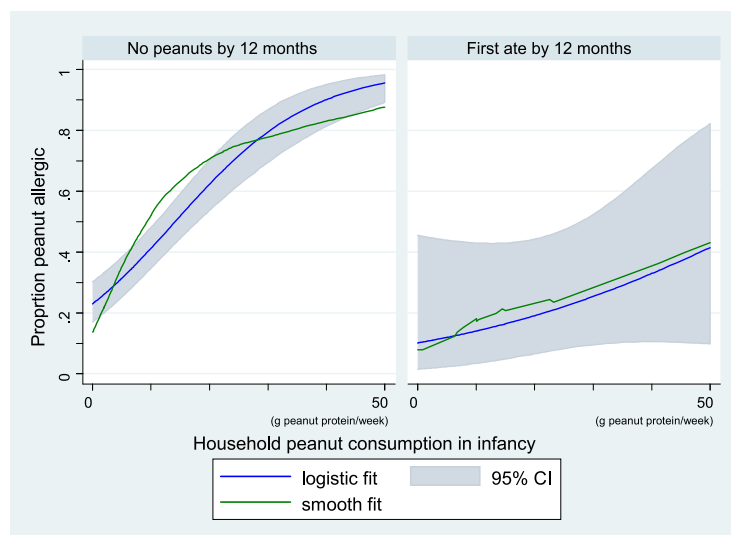


FIG 2. PA among children with FA ($n = 293$) as a function of environmental exposure depending on whether child first ate peanuts by 12 months of age. Reprinted with permission from Fox et al.⁶⁷

Fox et al⁶⁷ also found that increased maternal consumption of peanut during pregnancy and lactation was significantly associated with PA. However, maternal consumption of peanut correlated with household consumption. Once the latter was taken into account, the effect of maternal consumption on PA was no longer significant.

Thus the association between maternal consumption of peanut during pregnancy and the development of PA reported in studies might be explained by the association between maternal and household consumption of peanut. Although there is no strong clinical evidence that low levels of exposure to allergens present in breast milk leads to allergy, it has more recently been argued that allergen-immunoglobulin immune complexes in breast milk might protect against the development of allergies in the neonate. An interesting murine model by Mosconi et al⁶⁸ showed that milk from antigen-exposed sensitized mothers transferred antigen-IgG immune complexes to the newborn and led to the induction of antigen-specific forkhead box protein 3-positive CD25⁺ regulatory T cells and showed that breast-feeding conferred long-term tolerance in the offspring.

Data suggesting oral tolerance

Oral tolerance is well recognized in murine models. Numerous studies have demonstrated that early high-dose oral exposure confers both immunologic and clinical tolerance to food allergens. A single oral dose of allergen (β -lactoglobulin, OVA, or peanut) is sufficient to achieve tolerance and prevent subsequent allergic sensitization.⁶⁹⁻⁷¹ In a murine model a single high dose of peanut flour (100 mg) promoted oral tolerance and prevented subsequent IgE sensitization and T-cell proliferation.⁷¹

In human subjects cutaneous exposure to nickel during childhood leads to sensitization and nickel allergy, but oral exposure to nickel through orthodontic braces before ear piercing protects against nickel allergy.^{72,73} Similarly, subjects exposed to pancreatic extract by means of inhalation or contact have IgE-mediated allergic reactions, whereas subjects exposed orally do not.⁷⁴

Regular fish consumption before age 1 year appeared to be associated with a reduced risk of allergic disease (OR, 0.76; 95%

CI, 0.61-0.94) and sensitization to food and inhalant allergens (OR, 0.76; 95% CI, 0.58-1.0) during the first 4 years of life in a cohort of 4089 newborn infants.⁷⁵ Conversely, delaying initial exposure to cereal grain after 6 months of life was associated with an increased risk of IgE-mediated FA.⁷⁶

In Western industrialized societies in which peanuts are avoided in pregnancy and infancy, the rate of PA is higher.⁷⁷ In regions in which peanut is consumed in high amounts during infancy (the Middle East, Southeast Asia, and Africa), PA is reportedly rare.⁷⁸⁻⁸⁰

In a recent cross-sectional study among Israeli ($n = 5615$) and UK ($n = 5171$) Jewish children, the prevalence of PA was 10-fold higher in the UK (1.85%) than in Israel (0.17%, $P < .001$).¹³ This study also found that peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK (Fig 3).¹³

The median monthly consumption of peanut in Israeli infants aged 8 to 14 months is 7.1 g of peanut protein as opposed to 0 g in the UK ($P < .001$). The median number of times peanut is eaten per month was 8 in Israel and 0 in the UK ($P < .0001$). This difference is not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity. These findings raise the question of whether early introduction of peanut during infancy, rather than avoidance, will prevent the development of PA.

These findings have been improved by 2 recent observational cohort studies demonstrating an association between oral exposure to cow's milk in infants in the first 2 weeks and tolerance to milk⁸¹ and in an Australian cohort study⁸² in which it was shown that introduction of egg before 6 months of age appeared to protect against egg allergy, even after controlling for confounding variables.

No direct clinical data to support the dual-allergen-exposure hypothesis currently exist, and results of randomized controlled trials (RCTs) are awaited. However, there are some human immunologic data consistent with this hypothesis. Chan et al⁸³ showed that the response to peanut in children with PA allergy was seen primarily in the cutaneous lymphocyte antigen, skin-homing, memory T-lymphocyte population and not in the $\alpha 4\beta 7$

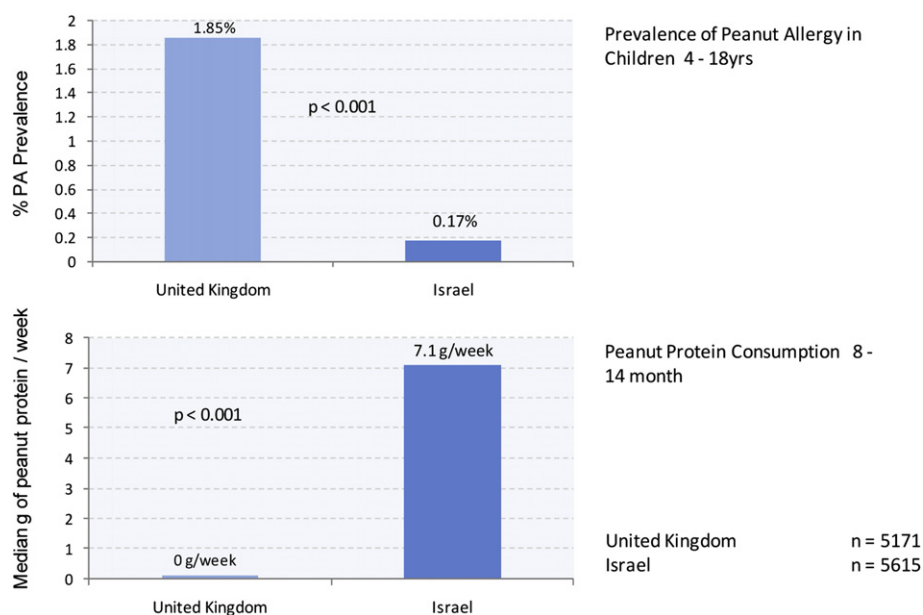


FIG 3. Early consumption of peanuts in infancy is associated with a low prevalence of PA. Adapted from Du Toit et al.¹³

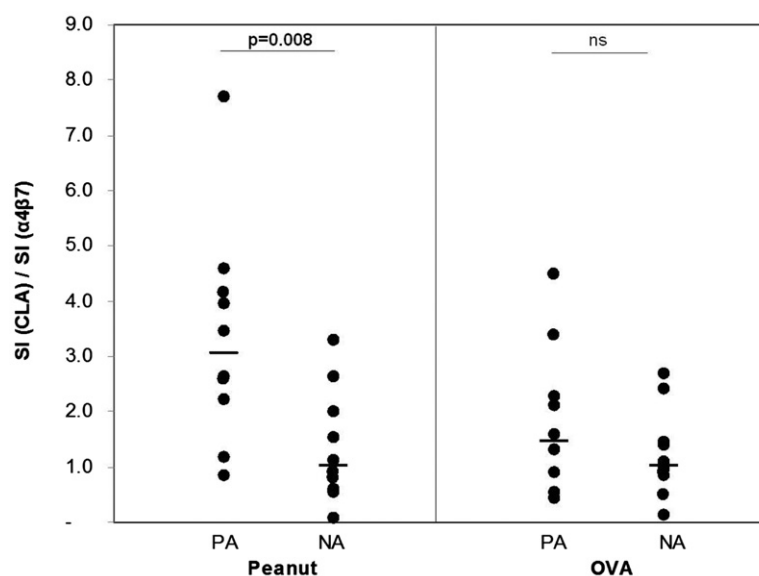


FIG 4. Ratio of stimulation index (SI) in the cutaneous lymphocyte antigen (CLA) subset relative to the SI in the $\alpha 4\beta 7$ subset for patients with PA (n = 10) and nonallergic patients (NA; n = 10) with 400 μ g/mL peanut antigen and OVA. Median values are represented by bars.

gut-homing lymphocytes; conversely, it was shown that peanut-tolerant patients had a mixed cutaneous lymphocyte antigen/ $\alpha 4\beta 7$ response to peanut antigen. The presence of eczema in allergic patients could not explain this difference, and these differences in lymphocyte responses were specific to peanut rather than control antigens (Fig 4).

RCTs USING ORAL TOLERANCE INDUCTION TO PREVENT FOOD ALLERGIES

It has been suggested that early introduction of foods, such as peanut, can lead to tolerance and protect against the

development of FA. These theories are currently being tested in 2 RCTs.

The Learning Early About Peanut Allergy study⁸⁴ involves 640 high-risk children who were enrolled at age 4 to 10 months. Each child was randomly assigned to one of the 2 approaches: avoidance or consumption. Children in the avoidance group completely avoid eating peanut-containing foods; in the consumption group parents are asked to feed their child a peanut snack 3 times per week (equivalent to about 6 g of peanut protein per week). The proportion of each group with PA by 5 years of age will be used to determine which approach, avoidance or consumption, works best for preventing PA. The study will reach completion in 2013.

The Enquiring About Tolerance study⁸⁵ is an RCT investigating the effect of early introduction of complementary foods together with breast-feeding. Infants taking part in the study ($n = 1302$) are being recruited from the general population and randomized to one of 2 groups: one group ($n = 651$) introduces 6 allergenic foods from 3 months of age alongside continued breast-feeding, with screening to check for pre-existing FA (early introduction group). The other group ($n = 651$) follows present UK government weaning advice (ie, aim for exclusive breast-feeding for 6 months [standard weaning group]). The children will be monitored until 3 years of age to determine whether early diet has an effect in reducing the prevalence of FA determined by double-blind, placebo-controlled food challenges.

Interventional studies clearly represent an advantage over observational studies in the determination of the role of early food and micronutrient exposure in the development of allergies. RCTs represent the gold standard of clinical medicine, especially when findings are replicated and shown to be consistent in further meta-analyses. However, we should bear in mind that positive RCT results are easier to interpret than negative studies. The pathogenesis of FA is likely to be multifactorial, and it is also likely that the induction of oral tolerance is dependent on several conditions being met. Thus we need to differentiate between necessary and sufficient causality. Exposure to food proteins in the gastrointestinal tract might require an optimal microenvironment if the necessary conditions for the induction of tolerance are to be met (eg, immune factors, such as cytokines, antibodies, regulatory T cells [the function of which might depend on vitamin D], and bacterial colonization). For example, in animal models oral tolerance induction with a single dose of food protein protects against the development of allergies. However, oral tolerance cannot be induced in germ-free mice; tolerance requires the presence of both intestinal microflora and food antigen.⁸⁶ Each factor is necessary, but neither is sufficient for the development of tolerance. The consequence is that we might intervene with a single factor, which in itself is necessary but might not be sufficient to induce tolerance. For example, if foods or micronutrients are introduced into the diet of young Western infants with reduced microbial exposure, no effect might be seen, but we could be wrong to interpret this lack of effect as evidence of causal irrelevance. A Western urban lifestyle is associated with numerous changes in the way foods are presented to young infants. For example, it might be important that food allergens be presented to the gastrointestinal tract in the context of breast milk, which contains numerous immunomodulatory factors.⁸⁷

SUMMARY

Antigen exposure through a disrupted skin barrier or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. Immune responses to such allergen exposures are likely to be modulated by nonspecific factors, such as gastrointestinal microflora, infectious exposure, other dietary factors, and possibly sunlight exposure. Hopefully, interventional trials in progress and those to be conducted in the next few years will help to determine the relative contribution of these different factors and allow us to reduce the burden caused by FA.

REFERENCES

- Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
- Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638-46.
- Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C, et al. The prevalence of plant food allergies: a systematic review. *J Allergy Clin Immunol* 2008;121:1210-8, e4.
- Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668-76, e1-2.
- Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1549-55.
- Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008;63:354-9.
- Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007;62:91-6.
- Hourihane JO, Aiken R, Briggs R, Gudgeon LA, Grimshaw KEC, DunnGalvin A, et al. The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. *J Allergy Clin Immunol* 2007;119:1197-202.
- Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
- Goh DL, Lau YN, Chew FT, Shek LP, Lee BW. Pattern of food-induced anaphylaxis in children of an Asian community. *Allergy* 1999;54:84-6.
- Leung R, Ho A, Chan J, Choy D, Lai CK. Royal jelly consumption and hypersensitivity in the community. *Clin Exp Allergy* 1997;27:333-6.
- Rance F, Dutau G, Abbal M. Mustard allergy in children. *Allergy* 2000;55:496-500.
- Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984-91.
- Vereda A, van Hage M, Ahlstedt S, Ibanez MD, Cuesta-Herranz J, van Ojik J, et al. Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J Allergy Clin Immunol* 2011;127:603-7.
- Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313:518-21.
- Sicherer SH, Furlong TJ, Maes HH, Desnick RJ, Sampson HA, Gelb BD. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol* 2000;106:53-6.
- Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;112:1203-7.
- Emmett SE, Angus FJ, Fry JS, Lee PN. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999;54:380-5.
- Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2010;126:798-806, e13.
- Kumar R, Tsai HJ, Hong XM, Liu X, Wang GY, Pearson C, et al. Race, ancestry, and development of food-allergen sensitization in early childhood. *Pediatrics* 2011;128:E821-9.
- Amoli MM, Hand S, Hajeer AH, Jones KP, Rolf S, Sting C, et al. Polymorphism in the STAT6 gene encodes risk for nut allergy. *Genes Immun* 2002;3:220-4.
- Campos Alberto EJ, Shimojo N, Suzuki Y, Mashimo Y, Arima T, Matsuura T, et al. IL-10 gene polymorphism, but not TGF-beta 1 gene polymorphisms, is associated with food allergy in a Japanese population. *Pediatr Allergy Immunol* 2008;19:716-21.
- Liu X, Beaty TH, Deindl P, Huang SK, Lau S, Sommerfeld C, et al. Associations between specific serum IgE response and 6 variants within the genes IL4, IL13, and IL4RA in German children: the German Multicenter Atopy Study. *J Allergy Clin Immunol* 2004;113:489-95.
- Dreskin SC, Ayars A, Jin Y, Atkins D, Leo HL, Song B. Association of genetic variants of Cdl4 with peanut allergy and elevated IgE levels in peanut allergic individuals. *Ann Allergy Asthma Immunol* 2011;106:170-2.
- Hong X, Wang G, Liu X, Kumar R, Tsai HJ, Arguella L, et al. Gene polymorphisms, breast-feeding, and development of food sensitization in early childhood. *J Allergy Clin Immunol* 2011;128:374-81, e2.
- Namkung JH, Lee JE, Kim E, Kim S, Kim S, Shin ES, et al. Association of single nucleotide polymorphisms in the IL-12 (IL-12A and B) and IL-12 receptor (IL-12R beta 1 and beta 2) genes and gene-gene interactions with atopic dermatitis in Koreans. *J Dermatol Sci* 2010;57:199-206.

27. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao YW, Liao HH, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;127:661-7.
28. Wjst M. Another explanation for the low allergy rate in the rural Alpine foothills. *Clin Mol Allergy* 2005;3:7.
29. Milner JD, Stein DM, McCarter R, Moon RY. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. *Pediatrics* 2004;114:27-32.
30. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, et al. Infant vitamin D supplementation and allergic conditions in adulthood—Northern Finland Birth Cohort 1966. *Ann N Y Acad Sci* 2004;1037:84-95.
31. Camargo CA, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States. *J Allergy Clin Immunol* 2006;117(suppl):S139.
32. Vassallo MF, Banerji A, Rudders SA, Clark S, Mullins RJ, Camargo CA. Season of birth is associated with risk of food allergy in children. *J Allergy Clin Immunol* 2010;125:AB217.
33. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippila C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr Allergy Immunol* 2010;21:29-37.
34. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;115:1109-17.
35. Black PN, Sharpe S. Dietary fat and asthma: is there a connection? *Eur Respir J* 1997;10:6-12.
36. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009;64:840-8.
37. Allan K, Kelly FJ, Devereux G. Antioxidants and allergic disease: a case of too little or too much? *Clin Exp Allergy* 2010;40:370-80.
38. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, et al. Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2009;123:1163-9.
39. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003;112:420-6.
40. Bager P, Wohlfahrt J, Westergaard T. Cesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy* 2008;38:634-42.
41. Sicherer SH, Wood RA, Stablein D, Lindblad R, Burks AW, Liu AH, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. *J Allergy Clin Immunol* 2010;126:1191-7.
42. Dotterud CK, Storro O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol* 2010;163:616-23.
43. Baker SS, Cochran WJ, Greer FR, Heyman MB, Jacobson MS, Jakscic T, et al. Hypoallergenic infant formulas. *Pediatrics* 2000;106:346-9.
44. Committee on Toxicity of Chemicals in Food CPatELDoH. Peanut allergy. 1998.
45. Greer FR, Sicherer SH, Burks AW. American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183-91.
46. Available at: <http://cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf>. Accessed March 22, 2012.
47. Fifty-Fourth World Health Assembly. Provisional agenda item 13.1.1. Global strategy for infant and young child feeding: the optimal duration of exclusive breast feeding. Geneva: World Health Organization; 2001.
48. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002;360:901-7.
49. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002;32:205-9.
50. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children—follow-up at age 7 years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-90.
51. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307-13.
52. Fox DE, Lack G. Letter: peanut allergy. *Lancet* 1998;352:741.
53. Dubrac S, Schmuth M, Ebner S. Atopic dermatitis: the role of Langerhans cells in disease pathogenesis. *Immunol Cell Biol* 2010;88:400-9.
54. Smith FJD, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao YW, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006;38:337-42.
55. Brown SJ, McLean WHI. Eczema genetics: current state of knowledge and future goals. *J Invest Dermatol* 2009;129:543-52.
56. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao YW, Liao HH, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
57. Flohr C, England K, Radulovic S, Campbell L, McLean WHI, Barker J, Perkin M, Lack G. Filaggrin loss-of-function mutations are associated with early onset eczema, eczema severity, and transepidermal water loss at three months of age. *Br J Dermatol* 2010;163:1333-6.
58. Brown SJ, Irvine AD. Atopic eczema and the filaggrin story. *Semin Cutan Med Surg* 2008;27:128-37.
59. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120:150-5.
60. Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA. Distribution of peanut allergy in the environment. *J Allergy Clin Immunol* 2004;113:973-6.
61. Saloga J, Renz H, Larsen GL, Gelfand EW. Increased airways responsiveness in mice depends on local challenge with antigen. *Am J Respir Crit Care Med* 1994;149:65-70.
62. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. *Eur J Immunol* 2004;34:2100-9.
63. Fallon PG, Sasaki T, Sandilands A, Campbell LE, Saunders SP, Mangan NE, et al. A homozygous frameshift mutation in the mouse Flg gene facilitates enhanced percutaneous allergen priming. *Nat Genet* 2009;41:602-8.
64. van Reijssen FC, Feliuss A, Wauters EAK, Bruijnzeel-Koomen CAFM, Koppelman SJ. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998;101:207-9.
65. Lack G, Fox D, Northstone K, Golding J. Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348:977-85.
66. Boussault P, Leaute-Labreze C, Saubusse E, Maurice-Tison S, Perromat M, Roul S, et al. Oat sensitization in children with atopic dermatitis: prevalence, risks and associated factors. *Allergy* 2007;62:1251-6.
67. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417-23.
68. Mosconi E, Rekima A, Seitz-Polski B, Kanda A, Fleury S, Tissandie E, et al. Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development. *Mucosal Immunol* 2010;3:461-74.
69. Frossard CP, Hauser C, Eigenmann PA. Antigen-specific secretory IgA antibodies in the gut are decreased in a mouse model of food allergy. *J Allergy Clin Immunol* 2004;114:377-82.
70. Marth T, Strober W, Kelsall BL. High dose oral tolerance in ovalbumin TCR-transgenic mice—systemic neutralization of IL-12 augments TGF-beta secretion and T cell apoptosis. *J Immunol* 1996;157:2348-57.
71. Strid J, Thomson M, Hourihane J, Kimber I, Strobel S. A novel model of sensitization and oral tolerance to peanut protein. *Immunology* 2004;113:293-303.
72. Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, HenstenPettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop* 1996;109:148-54.
73. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). *Acta Derm Venereol* 2002;82:359-64.
74. Twarog FJ, Weinstein SF, Khaw KT, Strieder DJ, Colten HR. Hypersensitivity to pancreatic extracts in parents of patients with cystic-fibrosis. *J Allergy Clin Immunol* 1977;59:35-40.
75. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009-15.
76. Poole JA, Barriga K, Leung DYM, Hoffman M, Eisenbarth GS, Rewers M, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006;117:2175-82.
77. Lack G. The concept of oral tolerance induction to foods. Nestle Nutr Workshop Ser Pediatr Program 2007;59:63-72.
78. Green R, Luyt D. Clinical characteristics of childhood asthmatics in Johannesburg. *S Afr Med J* 1997;87:878-82.
79. Hill DJ, Hosking CS, Heine RG. Clinical spectrum of food allergy in children in Australia and South-East Asia: identification and targets for treatment. *Ann Med* 1999;31:272-81.
80. Lee BW, Shek LP-C, Gerez IFA, Soh SE, Van Bever HP. Food allergy—lessons from Asia. *World Allergy Org J* 2008;1:129-33.

81. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;126:77-82.
82. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol* 2010;126:807-13.
83. Chan SM, Turcanu V, Stephens AC, Fox AT, Grieve AP, Lack G. Cutaneous lymphocyte antigen and $\alpha 4\beta 7$ T-lymphocyte responses are associated with peanut allergy and tolerance in children. *Allergy* 2012;67:336-42.
84. LEAP: learning early about peanut allergy. Available at: www.leapstudy.co.uk. Accessed March 22, 2012.
85. EAT: enquiring about tolerance. Available at: www.eatstudy.co.uk. Accessed March 22, 2012.
86. Sudo N, Sawamura SA, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997;159:1739-45.
87. Field CJ. The immunological components of human milk and their effect of immune development in infants. *J Nutr* 2005;135:1-4.