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Pediatric Allergic Diseases, Food Allergy, and Oral Tolerance

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Abstract

Pediatric allergic disease is a significant health concern worldwide, and the prevalence of childhood eczema, asthma, allergic rhinitis, and food allergy continues to increase. Evidence to support specific interventions for the prevention of eczema, asthma, and allergic rhinitis is limited, and no consensus on prevention strategies has been reached. Randomized controlled trials investigating the prevention of food allergy via oral tolerance induction and the early introduction of allergenic foods have been successful in reducing peanut and egg allergy prevalence. Infant weaning guidelines in the United States were recently amended to actively encourage the introduction of peanut for prevention of peanut allergy.

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INTRODUCTION

Pediatric allergic disease is a significant health concern worldwide, and the prevalence of allergic diseases in children continues to increase. Worldwide, rates of sensitization to one or more common allergens among school children are currently approaching 40–50% (Gupta et al. 2011). Allergic conditions such as eczema, food allergy, asthma, and allergic rhinitis affect 52% of UK children and together are one of the commonest long-term childhood conditions in the United Kingdom, with 12.5 million associated general practitioner visits per year (Gupta et al. 2003). The first cross-sectional phase of the International Study on Asthma and Allergies in Childhood (ISAAC), which was carried out in the 1990s, reported prevalence rates for eczema, asthma, and rhinoconjunctivitis of 3.6%, 8%, and 7.5%, respectively, while more recent estimations show an increased prevalence of 8% for eczema and 13% for asthma and allergic rhinitis (ISAAC Steering Committee 1998, Pols et al. 2015, Rona et al. 2007). There are geographical variations in prevalence that are hard to define due to an underrepresentation of prevalence studies in developing countries (Wang et al. 2019), but it is thought that typically Western environments, especially urban areas, have the highest prevalence of atopic disease (Botha et al. 2019). There are variations according to different risk profiles, most notably direct family history of atopy, which increases the prevalence of allergic disease in children by up to three times (ISAAC Steering Committee 1998, Lau et al. 2019).

The term atopic (or allergic) march is used to describe the relationship between eczema, food allergy, asthma, and allergic rhinitis and is based on the principle that, of these atopic conditions, eczema usually manifests earliest in life, followed sequentially by the others. However, recent research has highlighted that not all children follow this typical path and that there are variations in progression of allergic sensitization and disease (Howard et al. 2018). In infants with eczema in the first 6 months of life, the risk of progression to food allergy and then asthma and allergic rhinitis in later childhood is significantly increased. Both genetic and environmental factors are responsible for the development of allergic diseases, and the development of a single allergy, e.g., eczema, may predispose children to the development of the other allergic conditions. Indeed, eczema is

strongly associated with other allergic conditions, and therefore the prevention of eczema is an area of significant importance, as the ability to lower the risk of eczema may in turn lower the risk of other atopic diseases. The question remains as to whether the association between eczema and other atopic diseases is causal, i.e., whether preventing eczema prevents the development of other allergies.

ECZEMA: PREVENTION

Strategies for the prevention of eczema in children are limited, and the global prevalence of eczema is currently estimated as 16% to 30% of UK children and 20% of children worldwide (Martin et al. 2015, Zheng et al. 2011). Interventions focus predominantly on diet modification during pregnancy, lactation, and infancy in the form of supplements and direct dietary intake. This focus on dietary interventions is largely due to the ease with which diet can be modified at various stages and the acceptance thereof as an intervention. Recent meta-analyses on fish intake and omega-3 fatty acid intake in pregnancy showed no benefit for eczema risk, but high fish intake during early life did have a protective effect in a meta-analysis of three studies [relative risk (RR) 0.71; 95% confidence interval (CI) 0.61–0.82; $p < 0.001$] (Lloyd-Lavery et al. 2019). Similarly, supplementation with polyunsaturated fatty acids during infancy had no effect on the childhood prevalence of eczema or on the incidence of eczema in children under 2 or between 2 and 5 years of age (Schindler et al. 2016). Prebiotic and probiotic supplementation in pregnancy or infancy has not showed any overall protective effects, despite individual trials suggesting a reduction in eczema incidence (Kukkonen et al. 2007, Lloyd-Lavery et al. 2019, Venter et al. 2017). While the timing of allergenic food intake has been shown to reduce the risk of specific food allergies, a recent systematic review by Ierodiakonou et al. (2016) showed no association between the timing of allergenic food intake and the risk of eczema in 17 interventional trials and 37 observational studies.

In addition to studies on dietary modification, randomized controlled trials (RCTs) are under way to look at emollient use from birth as a prevention strategy following observational evidence of the potential protective effect of treatment before development of eczema. There is a strong association between filaggrin mutations and the development of eczema, and therefore the skin barrier would seem to play a key role in the development of this disease. Flohr et al. (2010) showed that skin barrier dysfunction, which is characterized by dry skin and increased transepidermal water loss, preceded the development of clinical eczema symptoms and that filaggrin mutations were associated with these changes in infants, even before the development of eczema.

While the use of water softeners to decrease the hardness of household water has not been shown to be an effective treatment strategy (Thomas et al. 2011), trials are under way to assess such use as a preventative measure by installing water softeners during pregnancy.

The role of breastfeeding in eczema prevention is limited. Although some studies have found a modest reduction in the incidence of atopic dermatitis in high-risk infants following breastfeeding for the first 4 months of life (Taylor-Robinson et al. 2016), overall there is a lack of evidence for an effect of prolonged exclusive breastfeeding on childhood eczema (Flohr et al. 2011).

ASTHMA: PREVENTION

Asthma is a common chronic respiratory disease in childhood and is associated with a significant clinical burden worldwide (Pearce et al. 2007). While significant advances have been made in the treatment of asthma, effective, globally applicable, evidence-based prevention strategies are lacking (Beasley et al. 2015, Brunwasser & Hartert 2019, Gur et al. 2017).

A double-blind RCT investigated the role of maternal supplementation with *n*-3 long-chain polyunsaturated fatty acids (LCPUFAs) during pregnancy in the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC₂₀₁₀) cohort. Fish oil supplementation in women after 24 weeks of gestation showed an absolute risk of asthma or persistent wheeze of 16.9% compared with 23.7% for the control group (hazard ratio 0.69; CI 0.49–0.97; $p = 0.035$), with a 30.7% RR in the offspring at 3–5 years of age. A subgroup analysis highlighted a greater intervention effect in the children whose mothers had the lowest third of LCPUFA blood levels at enrollment (Bisgaard et al. 2016).

A random effects combined analysis was performed on two placebo-controlled RCTs on maternal supplementation with an additional dose of vitamin D3 of 2,400–4,000 IU per day during pregnancy. The Vitamin D Antenatal Asthma Reduction Trial (VDAART) and COPSAC₂₀₁₀ studies found a 25% reduction in the risk of asthma/recurrent wheeze in children at 3 years of age [adjusted odds ratio (OR) 0.74; CI 0.57–0.96; $p = 0.02$]. Again, the intervention was more effective among children whose mothers had 25-hydroxyvitamin D (25OHD) levels ≥ 30 ng/mL at the beginning of the study (adjusted OR 0.54; CI 0.33–0.88; $p = 0.01$) (Wolsk et al. 2017).

In a pilot study, suplatast tosylate, a lymphocyte Th2 cytokine inhibitor, demonstrated a reduction of asthma incidence relative to ketotifen treatment (20.8% versus 65.6%; $p < 0.01$) after 24 months in infants with food allergies and atopic dermatitis (Yoshihara et al. 2009). However, in the control group, patients were treated with ketotifen, and results from placebo-controlled trials of this drug's effect on asthma prevention are lacking.

The Isle of Wight Study, based on multiple outcome measures, focused on high-risk infants with a family history of atopy and serum IgE > 0.5 kU/L in the cord blood. These infants were randomized to interventions reducing house dust mite (HDM) exposure and dietary interventions based on a multiple allergenic food exclusion diet by mothers during lactation and by the children in the first year of life. Such interventions had a preventive effect on asthma (adjusted OR 0.24; CI 0.09–0.66; $p = 0.005$) in the first 8 years of life (Arshad et al. 2007). Moreover, the lower asthma prevalence in the intervention group persisted until 18 years of age (OR 0.23; CI 0.08–0.70; $p = 0.01$) (Scott et al. 2012).

In contrast, the Manchester Asthma and Allergy Study investigated the role of multiple and intensive measures for HDM avoidance in the prevention of asthma, starting prenatally, and there was no statistically significant difference in respiratory signs and symptoms at 3 years of age (Woodcock et al. 2004).

Results from a Cochrane review showed that multifaceted food and/or inhalant allergen reduction interventions were effective in asthma prevention in high-risk children (< 5 years: OR 0.72; CI 0.54–0.96; > 5 years: OR 0.52; CI 0.32–0.85) with family history of atopy or asthma in at least one close family member relative to standard care. In contrast, singular intervention did not show a significant difference in asthma prevention relative to standard care.

Allergen immunotherapy with standardized extracts has shown evidence of efficacy in short-term asthma prevention in children and adolescents with moderate to severe allergic rhinitis and birch and grass pollen allergy, for up to 2 years after the interruption of the therapy (Halken et al. 2017). This recommendation is supported by the result of a systematic review and meta-analysis (Kristiansen et al. 2017). Additionally, data from a German retrospective nonrandomized real-life study, based on a large national database, showed a lower risk of asthma incidence (risk ratio 0.60; CI 0.42–0.84; $p = 0.003$) in patients with allergic rhinitis who underwent immunotherapy after 5 years from the beginning of the treatment (Schmitt et al. 2015).

One prospective, randomized, double-blind, placebo-controlled study investigated the role of HDM immunotherapy in the prevention of the atopic diseases in high-risk patients younger than 1 year of age with ≥ 2 first-degree allergic relatives. After 1 year of treatment, the results showed

that there was a lower frequency of sensitization to any common allergen (16.0%; CI 1.7–30.4%) in the intervention relative to the placebo group (9.4% versus 25.5%, respectively; $p = 0.03$), but there was no significant effect on HDM sensitization and wheezing (Zolkipli et al. 2015).

ALLERGIC RHINITIS: PREVENTION

Allergic rhinitis is a common chronic airway disease that is associated with significant morbidity and for which effective prevention strategies are not established (Bousquet et al. 2008). Environmental factors that exacerbate rhinitis include sulfur dioxide; carbon monoxide; nitrogen oxide; and other traffic-related pollutants, cigarette smoke, and aeroallergens such as HDM, mold, animal dander, and pollen (Hwang et al. 2006, Saulyte et al. 2014). Dietary factors such as breastfeeding, hydrolyzed formula, and dietary supplements such as probiotics, vitamin D, and polyunsaturated fatty acids (omega-3 and omega-6) have been investigated as preventative interventions.

Among multiple outcome measures, the Isle of Wight Study also investigated whether mattress covers and acaricide to reduce HDM exposure and exclusion of multiple allergenic foods by mothers during lactation and by children in the first year of life had a preventive effect on allergic rhinitis, showing a protective effect (adjusted OR 0.42; CI 0.19–0.92; $p = 0.03$) in the first 8 years of life (Arshad et al. 2007).

To date, there are no interventions demonstrated to reduce allergic rhinitis, and generic advice therefore focuses on a variety of general health recommendations, such as avoiding cigarette smoke and traffic-related pollutants (including during pregnancy) and practicing healthy weight management. As with many chronic allergic conditions, in the case of allergic rhinitis, multiple instead of single preventive measures would likely be necessary, given the complex multifactorial nature of this disease and its genetic and acquired components.

FOOD ALLERGY

Prevalence

As with other atopic diseases, recent data suggest an increase in the prevalence of pediatric food allergy in the last decade (Sicherer 2011). Accurately determining the correct prevalence of food allergy is challenging, with geographical variations significantly impacting global food allergy rates. For example, a validated questionnaire-based survey showed that the prevalence of peanut allergy in Jewish children in the United Kingdom is ten times higher than that of Jewish children in Israel (Du Toit et al. 2008). Geographical variations may be influenced by environmental factors such as food preparation and allergen exposure, by genetic differences, or by a combination of factors. The prevalence of food allergy in children is currently estimated to be approximately 8–9% in the United Kingdom and United States (Gupta et al. 2017, Perkin et al. 2016). In Australia, between 2005 and 2012, there was a fivefold increase in the prevalence of food-induced anaphylaxis in children aged 0–4 years (Mullins et al. 2015).

Genetic factors. Family history plays a large part in children's risk of developing food allergy. For peanut allergy, the risk increases sevenfold if a parent or sibling has a peanut allergy (Hourihane et al. 1996), and a study of monozygotic twins showed that the likelihood of developing peanut allergy was 64% if the twin sibling had a peanut allergy (Sicherer et al. 2000). While genetic risk factors may predispose children to developing disease, they are unlikely to account for recent rises in prevalence.

Gene polymorphisms in interleukin-10 (IL-10) (Alberto et al 2008) and IL-13 (Lui et al 2004) have been identified in association with food allergy, but these studies will need to be replicated

in different populations. Two single-nucleotide polymorphisms (SNPs) in the CD14 gene region were studied in a population of 53 peanut-allergic individuals and 64 peanut-tolerant siblings (Dreskin et al. 2011). Variations in the two important SNPs of CD14 (rs2569190 and rs2569193) were associated with the presence of peanut allergy. Multiple novel loci were identified as risk factors for peanut allergy in a recent study of 1,776 individuals, and C11orf30 was identified as a risk locus for both peanut allergy and food allergy in general (Asai et al. 2018). Gene-environment interactions are important in the development of food sensitization. The risk of food sensitization is 1.5 times higher in breastfed children than in those never breastfed, but this association was altered by rs425648 in the IL-12 receptor β 1 gene (Hong et al. 2011). Breastfeeding increased the risk of food sensitization in children carrying the GG genotype but significantly decreased the risk of food sensitization in breastfed infants carrying the GT/TT genotype. Similar interactions were observed for SNPs in the TSLP gene and the Toll-like receptor 9 gene (Hong et al. 2011).

Ethnicity. Ethnicity plays a significant role in the risk of allergic disease, with nonwhite ethnicity associated with an increase in food allergy risk in UK, US, Australian, and Canadian populations. In the UK population-based EAT (Enquiring About Tolerance) Study, the prevalence of food allergy in white children was 5.3%, in comparison to a prevalence of 9.4% in children of mixed ethnicity and a prevalence of 19.3% in Asian (Indian/Pakistani/Bangladeshi), black, or Chinese children (OR 2.09; 95% CI 1.19–3.66 for nonwhite in comparison to white individuals) (Perkin et al. 2016). Similar differences in peanut allergy prevalence in different ethnic groups were seen in the LEAP (Learning Early About Peanut Allergy) Study (Du Toit et al. 2015). In the United States, Kumar and others (Kumar et al. 2011) found an increase in sensitization to multiple foods in black children relative to white children. African ancestry was also a notable risk factor for increased peanut sensitization at levels indicative of clinical reactivity (Kumar et al. 2011). A recent Australian study showed higher rates of peanut and tree nut allergies among Asian (predominantly Chinese, Filipino, and South Korean) infants relative to non-Asian infants, but this effect was absent in children who had been born in Asia and had migrated to Australia (Panjari et al. 2016).

Gender. In general, allergic disease is more prevalent in male children, although this male-to-female ratio reverses during and after adolescence, possibly due to endocrine changes. For food allergy, this same predominance among male children is seen, especially for peanut allergy, for which the male-to-female ratio is almost 3:1 (Sicherer et al. 2003). However, by adolescence the prevalence is equal, and in adulthood the prevalence is reversed, with double the number of females having peanut allergy relative to males (Emmett et al. 1999).

Hygiene hypothesis. The hygiene hypothesis proposes that one reason for increases in atopic disease is the decreasing exposure to infectious agents, gut flora, and parasites in childhood. That large parts of the world are now living “cleaner” lives may be increasing our susceptibility to allergic diseases by way of modulating the immune system. The extent to which the hygiene hypothesis is relevant to food allergy development is uncertain, as evidence is limited. In a meta-analysis, six studies found that cesarean delivery is associated with an increase in food allergy or food atopy (Bager et al. 2008), but in contrast, no relationship was found between mode of delivery and sensitization or food allergy in a cohort of 503 infants (Sicherer et al. 2010).

Vitamin D. Both excessive vitamin D and vitamin D deficiency have been associated with an increase in allergy prevalence (Hyppönen et al. 2004, Milner et al. 2004). In one study, the prevalence of allergic disease was initially low but increased in communities receiving vitamin D supplementation to prevent childhood rickets (Wjst 2005). In contrast, a body of evidence suggests that too

little vitamin D may be associated with increases in allergy and food sensitization. EpiPen use is higher in northern versus southern areas of the United States (Camargo et al. 2007), and infants born during winter and therefore exposed to less vitamin D in early infancy had a higher risk of developing a food allergy (Vassallo et al 2010).

Routes of Exposure to Food

Prevention strategies have historically focused on delaying the introduction of allergenic foods, and in the 1980s and 1990s, guidelines in support of such a practice recommended exclusive breastfeeding for the first 6 months of life, followed by weaning to relatively nonallergic foods and then the introduction of foods such as milk, eggs, peanut, and fish between 1 and 3 years of age (Grimshaw et al. 2017). Specifically, until 2008, the American Academy of Pediatrics recommended that children with a family history of atopy avoid common allergens such as milk (until their first birthday); egg (until their second birthday); and peanuts, tree nuts, and fish (until their third birthday) (Baker et al. 2000). Additionally, women were advised to avoid peanuts during pregnancy and breastfeeding (Baker et al. 2000). However, further research showed that these strategies offered limited success in preventing food allergies, and likewise, interventions involving avoidance of allergens during pregnancy showed no benefit. As a result, these recommendations were withdrawn in the United States and the United Kingdom in 2008 (COT 2008, Greer et al. 2008).

The World Health Organization continues to promote exclusive breastfeeding during the first 6 months of life and includes allergy prevention in the list of associated health benefits. However, there is no evidence that exclusive breastfeeding for 6 months impacts the prevalence of allergic disease. In fact, observational data show that breastfeeding and prolonged breastfeeding are associated with an increased risk of asthma and eczema (Bergmann et al. 2002, Sears et al. 2002). These studies are open to bias because infants at the highest risk of allergy (e.g., those with eczema) may be deliberately breastfed longer, but ultimately no beneficial effect of prolonged breastfeeding on the development of allergic disease has been found.

Strategies to avoid food allergens during pregnancy, breastfeeding, and infancy have failed to impact the prevalence of IgE-mediated food allergy (Zeiger & Heller 1995). This may be due to errors in the avoidance strategies of studies but may also be because food sensitization occurs via other routes of exposure, and not via consumption.

Evidence Supporting a Cutaneous Route of Sensitization

Loss of function in the gene encoding for filaggrin has been recognized as the strongest genetic contributor to eczema (Brown & McLean 2009, Dubrac et al. 2010, Palmer et al. 2006, Smith et al. 2006). Furthermore, Flohr et al. (2010) showed that skin barrier dysfunction, characterized by dry skin and increased transepidermal water loss, preceded the development of clinical eczema symptoms and that filaggrin mutations were associated with these changes in infants even before the development of eczema. Infants may be exposed to low doses of environmental food proteins on household surfaces, hands, and dust, and such proteins can penetrate the disrupted skin barrier to be taken up by Langerhans cells, leading to a Th2 response and IgE (Dubrac et al. 2010, Perry et al. 2004). This route of cutaneous sensitization may explain the association between early eczema and the development of food allergy later in childhood and may also explain geographical differences in food allergy prevalence. For example, in countries with high levels of peanut consumption but where infants avoid peanuts (e.g., the United Kingdom, United States, Australia, and Canada), we would expect that such practices would lead to higher rates of peanut allergy, whereas one would expect peanut allergy rates to be lower in countries where infants eat peanuts

regularly, even in the context of high environmental exposure (e.g., southern and western Africa and Asia).

Animal models have provided strong evidence that filaggrin loss of function and subsequent skin barrier impairment can allow for cutaneous penetration of allergens and the development of food sensitization. Topical application of the allergen ovalbumin (OVA) in flaky-tailed mice with filaggrin loss-of-function mutations resulted in cutaneous inflammation and sensitization, as measured by specific IgE to OVA (Fallon et al. 2009). Human studies give similar results. An increased risk of peanut allergy at 5 years of age was seen following low-dose exposure to *Arachis* oil applied to the inflamed skin of infants (Lack et al. 2003). In a cross-sectional study evaluating maternal peanut consumption during pregnancy, breastfeeding, and infancy and among household members, a dose-response relationship was observed between increasing environmental peanut exposure and the development of peanut allergy (Fox et al. 2009). Furthermore, increasing eczema severity increases the risk of peanut sensitization from peanut allergens in household dust (Brough et al. 2013). It therefore seems likely that allergic sensitization to food can occur as a result of low-dose cutaneous exposure, but evidence is also growing that early consumption of allergens can induce oral tolerance. The balance of cutaneous and oral exposure then becomes key to determining whether a child will develop allergy or tolerance to a specific food protein (**Figure 1**).

Evidence Supporting Oral Tolerance Induction for Allergy Prevention

It is now recognized that allergen elimination may not be a suitable strategy for allergy prevention, as food sensitization does not occur following consumption but occurs via other routes, such as cutaneous exposure. Studies have shown that clinical and immunological tolerance to food allergens can be achieved using early high-dose oral exposure. In animal models, a single dose of lactoglobulin, OVA, or peanut allergen induces tolerance and prevents later sensitization (Frossard et al. 2004, Marth et al. 1996, Strid et al. 2004), while in humans several studies have shown exposure to nickel via orthodontic braces prior to ear piercing is associated with less nickel allergy (Kerosuo et al. 1996, Mortz et al. 2002). In contrast, delaying introduction of cereal beyond 6 months of age was associated with an increased risk of IgE-mediated food allergy (Poole et al. 2006).

Observational data from Du Toit et al. (2008) confirmed previous evidence that the prevalence of peanut allergy in Western societies where children are avoiding peanut in infancy is higher than in countries where peanut is regularly consumed in high amounts during infancy, e.g., the Middle East, Southeast Asia, and Africa (Green & Luyt 1997, Hill et al. 1999, Lack 2007, Lee et al. 2008). Du Toit and colleagues analyzed data from 5,615 Israeli Jewish children and 5,171 UK Jewish children and found the prevalence of peanut allergy to be 10 times higher in the UK children (1.85% versus 0.17%; $p < 0.001$) (Du Toit et al. 2008). In addition to this finding, this study also found that peanut was introduced at an earlier age and was eaten more frequently and in larger quantities in Israel (Du Toit et al. 2008). Two further observational studies showed an association between early introduction of cow's milk and egg and protection against milk allergy and egg allergy, respectively (Katz et al. 2010, Koplin et al. 2010).

Oral Tolerance Induction for the Prevention of Food Allergies: Results from Clinical Trials

The observational evidence above implies that the early introduction of peanut, egg, and milk could prevent the development of peanut, egg, and milk allergies, respectively, and subsequent RCTs were set up to investigate this hypothesis in a controlled setting. To date, a number of RCTs have been completed worldwide, investigating oral tolerance induction to peanut (the LEAP Study), egg [the BEAT (Beating Egg Allergy Trial), HEAP (Hens' Egg Allergy Prevention), STEP

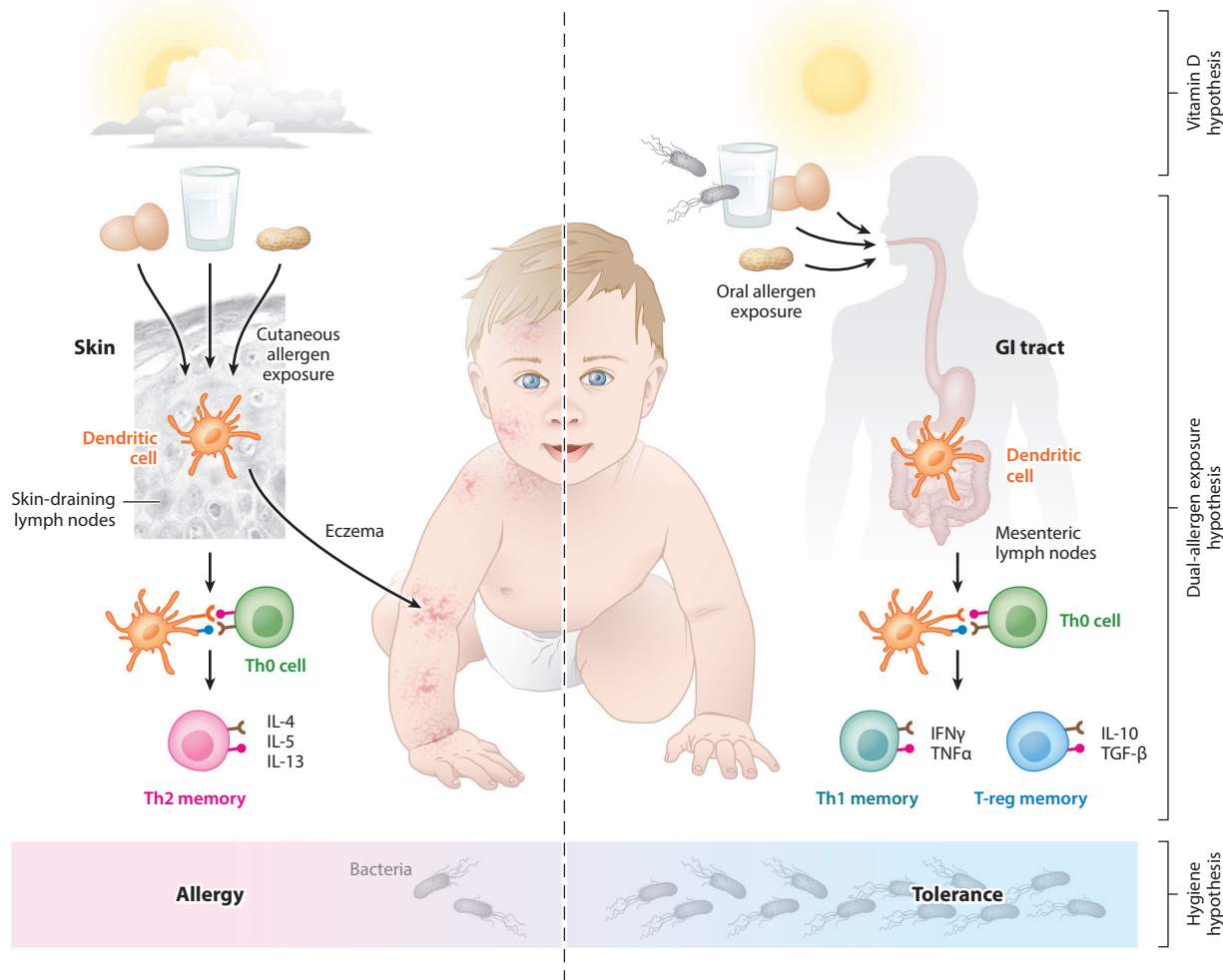


Figure 1

Integration of the vitamin D deficiency, hygiene, and dual-allergen exposure hypotheses. (*Right*) Sufficient levels of vitamin D, a diverse microbiota, and oral allergen exposure support the development of tolerance. (*Left*) Conversely, allergic sensitization is promoted through cutaneous exposure, reduced diversity of the microbiota, and vitamin D deficiency. Diminished microbial diversity and vitamin D deficiency are thought to interrupt the regulatory mechanisms of oral tolerance, with the latter also contributing to decreased epidermal barrier function. Abbreviations: GI, gastrointestinal; IFN γ , interferon gamma; IL, interleukin; T-reg, regulatory T cell; TGF- β , transforming growth factor beta; Th0, naïve helper T cell; TNF α , tumor necrosis factor alpha. Figure redrawn with permission from Du Toit et al. (2018); copyright 2018 Elsevier.

(Starting Time of Egg Protein), STAR (Solids Timing for Allergy Research), and PETIT Studies], and multiple foods such as peanut and egg (the EAT Study) (Bellach et al. 2017; Du Toit et al. 2015; Natsume et al. 2017; Palmer et al. 2013, 2017; Perkin et al. 2016; Tan et al. 2017) (**Table 1**).

Between 2006 and 2009 the LEAP Study enrolled 640 children between the ages of 4 and 11 months who were at high risk of developing a peanut allergy due to eczema and/or egg allergy at enrollment (Du Toit et al. 2013). In this trial, children were randomized either to consume 6 g of peanut protein per week in the form of a peanut snack (the consumption group) or to completely avoid all peanut-containing foods (the avoidance group). The prevalence of peanut allergy

Table 1 Summary of oral tolerance induction RCTs^a

Name of trial	Type and number	Population	Screen failures due to allergy/likely allergy	Intervention group (protein per week)	Control group	Age (in months) at study entry	Outcome assessed (age in months)	Per-protocol adherence rates for I and C	Primary outcome	Outcome in ITT (p value)
LEAP (Learning Early About Peanut Allergy), United Kingdom	RCT, open label (640)	High risk (infants with moderate/severe eczema and/or egg allergy)	76/834 SPT $\geq$ 5 mm	Peanut snack or peanut butter (6 g)	PN avoidance until 60 months	4–11	60	SPT-negative group: I = 96%, C = 93% SPT-positive group: I = 95%, C = 98%	PN allergy (OFC)	AR 11.8% (95% CI 3.4–20.3; $p < 0.0001$)
Enquiring About Tolerance (EAT), United Kingdom	RCT, open label (1,303)	General population	No exclusions required per protocol	Cooked whole HE, peanut butter, cow's milk (yoghurt), fish (white, cooked), sesame (tahini), wheat (wheat-based breakfast cereal) (4 g of each allergen)	Exclusive breastfeeding and avoidance of all six study foods until 6 months of age	3	12–36	I = 31.9% C = 92.9%	Allergy to one or more of the six study foods (OFC)	RR 0.69 (95% CI 0.40–1.18; $p = 0.17$)
Hens' Egg Allergy Prevention (HEAP), Germany	RCT, blinded (298)	General population	23/406 egg white IgE $\geq$ 0.35 KU/AL	Pasteurized raw HE, white powder (7.5 g), HE-free diet	Placebo powder (rice), HE-free diet	4–12	12	I = 86.7% C = 93.5%	HE sensitization (slgE)	RR 2.20 (95% CI 0.68–7.14; $p = 0.24$)
Solids Timing for Allergy Research (STAR), Australia	RCT, blinded (86)	High risk (infants with moderate/severe eczema)	Not required per protocol	Pasteurized raw whole HE powder (6.3 g)	Placebo powder (rice)	0–8	12	I = 94% C = 97%	Raw HE allergy (OFC) and sensitization (SPT)	RR 0.65 (95% CI 0.38–1.11; $p = 0.11$)
Starting Time of Egg Protein (STEP), Australia	RCT, blinded (820)	Moderate risk (atopic mothers)	Not required per protocol	Pasteurized raw whole HE powder (2.8 g)	Placebo powder (rice)	4–10	12	I = 84% C = 85%	Raw HE allergy (OFC) and sensitization (slgE)	Adjusted RR 0.75 (95% CI 0.48–1.17; $p = 0.20$)
Beating Egg Allergy Trial (BEAT), Australia	RCT, blinded (254)	Moderate risk (first degree relative with allergy)	13/332 SPT $\geq$ 2 mm	Pasteurized raw whole HE powder (2.45 g), HE-free diet	Placebo powder (rice), HE-free diet	4–8	12	I = 81% C = 89%	HE sensitization (SPT)	OR 0.46 (95% CI 0.22–0.95; $p = 0.03$)
Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT), Japan	RCT, blinded (121)	Moderate risk (with atopic dermatitis)	Not required per protocol	Heated HE powder (0.175 g for 3 months and then 0.875 g for 3 months)	Placebo powder (squash)	4–12	12	I = 92% C = 93%	HE allergy (OFC)	RR 0.222 (95% CI 0.08–0.61; $p = 0.0012$)

^aTable adapted with permission from Fisher et al. (2018); copyright 2018 Elsevier.

Abbreviations: AR, absolute risk; C, control; CI, confidence interval; HE, hen's egg; ITT, intention to treat; I, intervention; IgE, immunoglobulin E; OFC, oral food challenge; OR, odds ratio; PN, peanut; RCT, randomized controlled trial; RR, relative risk; slgE, specific immunoglobulin E; SPT, skin prick test.

in those avoiding peanuts and with no peanut sensitization at enrollment was 13.7%. Among children consuming peanuts and with no peanut sensitization at enrollment, the prevalence of peanut allergy was 1.9%, demonstrating an 86% reduction in peanut allergy in the consumption group ($p < 0.001$). In children sensitized at enrollment into the LEAP Study, there was also a significant reduction in peanut allergy prevalence, from 35.3% in the avoidance group to 10.6% in the consumption group ($p = 0.004$) (Du Toit et al. 2015).

Following the LEAP Study, the question of whether tolerance could be maintained following a period of avoidance was investigated in the LEAP-On Study, in which children from the LEAP cohort were asked to avoid eating peanuts for 12 months. No increase in the prevalence of peanut allergy was seen, and therefore tolerance was maintained 12 months after ceasing consumption.

While the LEAP Study successfully demonstrated the efficacy of early peanut introduction in preventing peanut allergy, the effects were peanut specific and did not impact the prevalence of other food allergies, including tree nut allergies. To further investigate the effectiveness of oral tolerance induction for food allergy prevention, the EAT Study was set up in 2009 to test this hypothesis in a general population setting (no high-risk inclusion criteria) and with the introduction of multiple food allergens. The EAT Study enrolled 1,303 exclusively breastfed infants who were randomized either to begin consumption of six allergenic foods (peanut, egg, milk, sesame, wheat, and fish) from 4 months of age alongside breastfeeding or to comply with UK infant feeding guidelines of 6 months exclusive breastfeeding. The trial resulted in a nonsignificant reduction in overall food allergy prevalence, with a prevalence of 7.1% in the standard introduction group and a prevalence of 5.6% in the early introduction group (Perkin et al. 2016). Adherence to the intervention in the EAT Study was low, and this was likely the cause of the nonsignificant result. In per-protocol analysis of children complying with the early introduction regimen, a significant (66%) reduction in overall food allergy prevalence was seen, along with food-specific reductions in the prevalences of peanut and egg allergies (Perkin et al. 2016).

A number of other RCTs have investigated the same early introduction hypothesis specifically for egg, milk, and fish allergies. In a recent meta-analysis, Ierodiakonou et al. (2016) concluded that, despite limitations within primary studies, the early introduction of egg and peanut was associated with a lower risk of developing egg allergy and peanut allergy, respectively, with no significant effects noted for milk or fish allergies.

Immunological Mechanisms in Oral Tolerance Induction and Prevention of Peanut Allergy

From the LEAP and LEAP-On Studies, the changes over time in IgE and IgG levels and in IgE:IgG4 ratios have been explored. In the LEAP Study, there was an increase in IgG4 production by 12 months of age after just a few months of consumption and a decline in peanut-specific IgE levels after 2.5 years of age (Turcanu et al. 2017). The relationship between IgG4 and peanut-specific IgE levels in the LEAP Study reflected the children's peanut allergy status. In the avoidance group, children with peanut allergy had low IgG4:IgE ratios, and after 12 months of avoidance in the LEAP-On Study, peanut-specific IgG4 levels and IgG4:IgE ratios were higher in the consumption group than in the avoidance group (Turcanu et al. 2017). Low levels of peanut-specific IgE and high IgG4:IgE ratios were characteristic of children in the peanut consumption groups who tolerated peanut, even after 12 months of subsequent peanut avoidance (Turcanu et al. 2017).

The longitudinal peanut-specific antibody levels resulting from early-life consumption of relatively high amounts of peanut show a sustained IgG- and IgG4-dominated immune response reflecting the establishment of oral tolerance to peanuts. These findings suggest, therefore, that early-life, high-dose peanut consumption closes a temporal window of higher peanut allergy risk.

During this window, infants are at higher risk of undergoing allergic sensitization because they are not protected by a well-established immune tolerance response to peanuts.

A recent observational study (Peters et al. 2019) supports this interpretation. It found that infants' exposure to cow's milk in the first 3 months of life is associated with reductions in risk of both cow's milk sensitization (adjusted odds ratio 0.44; 95% CI 0.23–0.83) and cow's milk allergy (adjusted odds ratio 0.31; 95% CI 0.10–0.91) at 1 year of age.

These findings provide an efficient strategy for food allergy prevention (by early-life consumption) but do not explain the population-wide food allergy increase. This increase in allergy level could conceivably result from (a) a failure of immunological tolerance development, (b) an increase in allergic sensitization, or (c) a combination of both.

Indeed, the immune system may encounter food allergens in both the gut and the skin, as proposed by the dual-allergen exposure hypothesis. The competition between proallergenic and pro-tolerance immune responses may occur at both of these locations.

In the gut, the default response to foods is oral tolerance. Antigens that reach the gut epithelium are delivered via goblet cell-associated antigen passages to CD103⁺CX3CR1[−] lamina propria dendritic cells (DCs) (Tordesillas & Berin 2018). The CD103⁺ DCs that capture food antigens migrate to the gut-draining mesenteric lymph nodes and induce the differentiation of naïve T cells into regulatory T cells (Tregs) in the presence of retinoic acid and transforming growth factor- β (TGF- β) (Tordesillas & Berin 2018). Nevertheless, oral tolerance induction in the gut may be disrupted; for example, retinoic acid-deficient DCs drive naïve T cells toward a pathogenic Th2 phenotype instead of toward Tregs (Yokota-Nakatsuma 2014). Additional elements of the immune response are involved in modulating the induction of oral tolerance, for example, intestinal epithelial cells that can secrete IL-33, TSLP, and IL-25 as well as alarmins that activate type 2 innate lymphoid cells (ILCs) to produce IL-13. Nevertheless, the increased gut permeability that may result from different processes (e.g., in germ-free mice that have altered goblet and mucus cell production associated with defects in barrier function or microbial dysbiosis) is associated with a higher susceptibility to food sensitization (Plunkett & Nagler 2017). Notably, therapy with microbial species impacted by gut dysbiosis (e.g., Clostridiales or Bacteroidales species) that restores the gut barrier suppressed food allergy in mice. This resulted from the MyD88-dependent induction of the transcription factor ROR- γ t in Treg cells (Abdel-Gadir 2019).

In the healthy skin Langerhans cells are precommitted to inducing immune tolerance, as T cells activated by these cells proliferated initially but then failed to differentiate into effector or memory subsets and in the long term did not survive (Shklovskaya 2011). The default gain of tolerance response when the skin barrier is intact is further demonstrated by the induction of gastrointestinal LAP⁺ Tregs, which can prevent food-induced anaphylaxis by epicutaneous immunotherapy in mice (Tordesillas 2017).

Conversely, in atopic dermatitis the immune response is skewed toward Th2 pathways that drive epidermal barrier disruption. This in turn stimulates keratinocytes to express TARC (CCL17), macrophage-derived chemokine (MDC) (CCL22), IL-1 β , IL-33, and TSLP. These mediators then expand and activate skin-resident group 2 ILC2 and enhance Th2 cell-mediated immune responses driven by inflammatory DCs (Weidinger 2018). Notably, a decrease of microbiome diversity and dominant *Staphylococcus* colonization is correlated with both atopic dermatitis severity and the dysregulation of the skin barrier transcriptome (Altunbulakli 2018).

In conclusion, in the absence of a preestablished oral tolerance to foods, cutaneous exposure to food allergens that takes place in an area where the skin barrier is disrupted and there is an on-going Th2-dominated response might explain the induction of allergic sensitization. Recent advances have led to the identification of microbiome dysbiosis that increases both skin and gut permeability and interferes with natural tolerance induction at both sites.

Peanut Immunotherapy

Trials of immunotherapy have shown positive results in inducing tolerance to small quantities of peanut in peanut-allergic children and adults. The recently published PALISADE trial showed that treatment with AR101 peanut immunotherapy resulted in a significant increase in the amount of peanut protein that participants could tolerate relative to children in the placebo group (PALISADE Group Clin. Investig. 2018). In real-world terms, 85% of children completing the trial tolerated a quantity of peanut protein equivalent to 3–4 peanuts, and 50% of participants tolerated 7–8 peanuts. In children receiving AR101, the IgE:IgG4 ratio decreased during the PALISADE trial, but the change over time from baseline to the end of the trial was not significant (PALISADE Group Clin. Investig. 2018). The regulatory and approval costs of AR101 and similar oral immunotherapy programs making use of native food products are yet to be established. A multicenter RCT of peanut epicutaneous immunotherapy via a skin patch demonstrated a modest treatment response after 52 weeks, with the highest responses in younger children. Adherence and retention rates were high, warranting further investigation of this type of immunotherapy (Jones et al. 2017).

National and International Guidelines

Recent RCTs provide direct evidence that the early introduction of peanut and egg into infants' diets provides a successful approach for the prevention of food allergy, and as a result, guidelines are changing. The National Institutes of Health in the United States have revised their recommendations as to allergen consumption in infancy to actively encourage the introduction of peanut for the prevention of peanut allergy (Togias et al. 2017). This includes the introduction of peanut between 4 and 6 months of age for children with moderate to severe eczema. Other countries, including the United Kingdom and Australia, have updated guidelines to recommend that peanut and other allergenic foods be included in the normal weaning process, but they make no recommendations as to the introduction of allergenic foods before 6 months of age. Importantly, studies such as LEAP and EAT have demonstrated that one or more common food allergens can be added to the diet of infants without compromising duration of breastfeeding and with no detrimental effect on growth and nutrition (Du Toit et al. 2015, Perkin et al. 2016). However, preventative effects appear to be antigen specific, and the challenges ahead are to prevent the development of multiple food allergies and to determine the optimal timing and duration of, and adherence to, any public health intervention.

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Errata

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