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## TITLE PAGE

### **The role of dietary interventions in the prevention of IgE-mediated food allergy in children**

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## Abstract Page

# The role of dietary interventions in the prevention of IgE-mediated food allergy in children

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### Abstract:

Over the last 30 years, the prevalence of food allergy has been on the rise and remains a disease that can have a significant impact on the quality of life of children and their families. There are several hypotheses that have been suggested to account for the increasing prevalence but this review will focus on the impact dietary factors have on food allergy development. In the past food allergy prevalence has largely focused on allergen avoidance; however there is increasing evidence from interventional studies that have shown that early introduction to potential food allergens may have a beneficial role in allergy prevention. This review aims to look at the evidence in support of early introduction of allergens into infant diets to prevent against the development of food allergy.

### *Background*

The prevalence of food allergy has been on the rise over the last 30 years with 6-8% of children being affected worldwide with disease burden being higher for infants and preschool children (2-4). Food allergy can be classified as immunoglobulin E (IgE)-

mediated food allergy, non-IgE mediated food allergy or mixed IgE and non-IgE mediated food allergy (5). IgE-mediated food allergies are type 1 immediate hypersensitivity reactions with a quick onset of symptoms usually within minutes to 1-2 hours after exposure to a food antigen compared to non-IgE mediated food allergy where there is a delayed onset of symptoms following exposure to a food (2). Having food allergies has been shown to have a significant impact on the quality of life of the children affected and their families (6-8). Unfortunately, there is no definitive cure for IgE-mediated food allergy and the main treatment remains food avoidance. Specific oral tolerance induction for various allergenic foods have been trialled; however many of these trials have been small, uncontrolled and not without risks thus, further research is required to establish its exact role in allergy prevention (9, 10). Therefore, focus on developing strategies to prevent allergy at an early stage has become the forefront of current allergy research.

#### *History of IgE-mediated food allergy*

In the 1960s, most infants were exposed to solids by 4 months of age (11). However, this changed in the 1970's due to concern that early introduction of gluten was contributing to a rise in coeliac disease; thus new guidelines were introduced which recommended a delay in the introduction of solids until after 4 months (12). The World Health Organisation (WHO) recommended a further delay in the introduction of solid foods in the 1990s to 6 months of age, and advised parents to delay the introduction of allergenic solids such as egg to 10 months and peanut to 3 years. (11, 13) This was followed by the UK Department of Health suggesting that atopic pregnant and lactating women as well as children in the first 3 years of life should avoid the consumption of peanuts (14, 15). These

recommendations were intended to be for 'at risk' families; however, they soon became adopted recommendations for the majority of the population (16, 17). The Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology in 2013 endorsed exclusive breast-feeding for at least 4 and up to 6 months but complementary foods could be introduced between 4 to 6 months of age (18). Subsequent reviews have looked to see if there are any benefits in introducing complementary foods between 4-6 months of age to prevent allergy and without any concrete evidence to suggest it is of benefit, age of introduction of solids has remained at 6 months old in most countries (19). More specifically, a 2006 US consensus document suggested dairy products to be introduced at 12 months, hen's egg at 24 months and at the earliest, peanut, tree nuts, fish and seafood at 36 months of age (20).

Despite these measures to prevent allergy by delayed introduction of allergenic foods, the prevalence of food allergy has continued to rise. For prevention strategies to be effective, we need to understand the causative factors underpinning this rise. Genetic factors are clearly important in the development of FA, but given the dramatic increase in prevalence over a short period of human evolution, it is unlikely that FA arises through germline genetic changes alone. A plausible hypothesis is that one or more environmental exposures, or lack thereof, induce epigenetic changes that result in interruption of the default immunologic state of tolerance.

There are various hypotheses that exist for the rise in food allergy and these include the hygiene hypothesis, vitamin D hypothesis and dual-barrier hypothesis (Figure 1 (21)). The hygiene hypothesis describes the protective influence early-life microbial exposure has on the development of allergies (22). Several studies have shown that there are various factors that can influence the immune defence system and microbiome, which can have an impact on the development of oral tolerance (23, 24). These include the mode of delivery, siblings, pets at home, birth order which can influence the exposure to micro-organisms and therefore, potential development of allergic disease (23, 25-27). The vitamin D hypothesis suggests that low vitamin D may increase the risk of developing food allergy (28). A study in Australia found that vitamin D insufficiency was associated with challenge-proven food allergy in children at 12 months of age (29) and further research looking at the genetic polymorphisms affecting vitamin D metabolism have suggested that serum 25(OH)D<sub>3</sub> bioavailability could affect the development of food allergy (30). Another key hypothesis is the dual-barrier hypothesis which suggests that early allergic sensitization to food and environmental allergens occurs through breakdown of the skin barrier and that a close relationship exists between eczema and food allergy (i.e. eczema, filaggrin (FLG) loss-of-function mutations) (23, 31). A recent study reported that 50% of children with eczema developed food allergy by 1 year old (32). Previous work by Lack *et al*, showed that children who used topical peanut-based emollients exposed them to peanut allergen and was associated with the development of peanut allergy (33). Similarly, an association between eczema and sensitization to egg white in early infancy has also been demonstrated (32). Further research has been conducted looking at the role of FLG in relation to food allergy as it is known to have an important role in epithelial barrier function and therefore

the development of eczema (31, 34). Brough *et al* looked at the effect of environmental peanut exposure in a population-based birth cohort and found that children who carried a FLG mutation had an increased risk of peanut sensitization and allergy associated with early life environmental peanut exposure (35). This has led to research looking at improving the skin barrier in order to prevent the development of food allergy in children. Simpson *et al* has shown that the application of a daily emollient in neonates from birth resulted in a 50% relative risk reduction in the development of eczema at 6 months old (36).

#### *Dietary factors in food allergy*

As the prevalence of food allergy has risen, there has been increasing evidence that has challenged the idea of dietary allergen avoidance in order to prevent the development of food allergy. This has led to research looking at strategies in the prevention of food allergy from maternal diet during pregnancy and lactation to early introduction of allergenic foods.

#### *Maternal factors*

There has been considerable debate whether sensitization to food and inhalant allergens occurs in utero or during the post-natal period. There is a lack of solid evidence to suggest that the manipulation of maternal diet in pregnancy or post-partum during lactation has a preventative role in food allergy (37). With regards to peanut allergy, there is some evidence to show that there is no association between maternal consumption of peanuts during pregnancy and the development of peanut allergy in infancy and childhood (15, 33). Contrastingly, Sicherer *et al* found that maternal ingestion during pregnancy was strongly

associated with high peanut sensitization in infants aged 3-15 months (38). Khakoo and Lack showed that there was no reduction in risk of developing cow's milk or egg allergy in infants of mothers who avoided foods containing these allergens during pregnancy (39). There is also limited evidence of the direct impact breastfeeding has on the development of food allergy. Despite breast milk being a potential factor in influencing food allergy development through its anti-allergic properties or the presence of antibodies that could combine with food antigens to induce tolerance, there is little evidence to suggest a direct influence (21, 39). For example, Lack *et al's* study found that the duration of breastfeeding was not significantly associated with peanut allergy (33).

#### *Food introduction to infants*

The exact timing of the introduction of foods to help induce oral tolerance has been at the forefront of paediatric food allergy research in the last 10 years. Murine models have shown that early and regular introduction to food allergens can induce immunological change and therefore clinical tolerance to allergens (40, 41). Subsequent work in humans has shown that early exposure to food allergens can lead to the development of oral tolerance (42). The focus on introduction has primarily focused on the most common food allergens, which are hen egg, cow's milk and peanut.

#### *Cow's milk allergy*

Cow's milk is the most common infant food allergy, affecting 1.4-3.8% of young children (43). It can be either IgE-mediated in nature in which exposure to milk causes an immediate reaction with symptoms such as urticaria, angioedema and/or anaphylaxis or it

can be non-IgE mediated, often manifesting with delayed skin or gastrointestinal symptoms (44, 45). Snijders *et al* showed that a delay in the introduction of cow's milk products was associated with an increased risk of atopy at 2 years of age (46). Since then, prospective studies have been conducted looking at the effects of early introduction of cow's milk into infant diets. Katz *et al* found that infants who were started on cow's milk protein formulas within the first 14 days of life were significantly less likely to develop IgE-mediated cow's milk allergy in comparison to infants who had cow's milk introduced between 105 and 194 days of life (0.05% vs 1.75%,  $p < 0.001$ ) (47). A more recent study also showed that avoidance of cow's milk by use of an extensively hydrolysed whey formula instead did not have a protective effect in infants in developing atopy (primarily eczema) at 12 months of age (48).

#### *Hen Egg allergy*

Hen egg allergy is the second most common food allergy with a prevalence rate of approximately 2.5% (44, 49). Several large trials have been conducted which look specifically at early introduction of egg. The Australian Healthnuts cohort demonstrated that a delayed introduction of egg until 10-12 months or infants older than 12 months were both associated with a significantly increased risk of egg allergy compared to those who were introduced to egg at 4-6 months of age (50). This has further been supported by results from the Solids Timing for Allergy Reduction (STAR) randomized control trial which looked at infants with moderate to severe eczema who were introduced to egg from 4 months of age in the form of pasteurized raw whole egg powder (intervention group) (41). Although not statistically significant, when this group was compared to the control

group who avoided egg (given rice powder instead), a lower proportion of infants in the intervention group (33%) had a diagnosis of IgE-mediated egg allergy compared to the control group (51%) (41). The Starting Time of Egg Protein (STEP) study was performed on infants aged 4 to 6 months with no eczema symptoms who were randomized and double-blinded to receive daily pasteurized raw whole egg powder or a colour-matched rice powder (51). All the infants followed an egg-free diet until 10 months at which time cooked egg was introduced to both groups. In the intention-to-treat analysis, there was no difference between the two groups with regards to the development of IgE-mediated egg allergy at 12 months of age, 7% egg group versus 10.3% in the control group (95% CI 0.48-1.17,  $p=0.20$ ). However in the per-protocol analysis, a lower percentage of infants in the egg group (3%) had IgE-mediated egg allergy at 12 months of age compared to the control group (9.9%) (95% CI 0.16-0.65,  $p=0.002$ ). Interestingly, 6.1% of the children in the egg group had a confirmed allergic reaction to the study powder and had to stop taking it compared to 1.5% of the control group.

Another recently published study called the Enquiring About Tolerance (EAT) study (52, 53), which was a randomized controlled trial looking at early introduction of six common food allergens at 3 months of age (early introduction group (EIG)) alongside breastfeeding compared to exclusively breast-fed infants (standard introduction group (SIG)), found that the prevalence of egg allergy was significantly lower in the early-introduction group (1.4% vs. 5.5%,  $p=0.009$ ) in the per-protocol analysis. Egg allergy was confirmed in 3.7% of the EIG compared to 5.4% in the SIG (relative reduction 31%,  $p=0.17$ ). The Hen's Egg Allergy Prevention (HEAP) trial (54), looked at the introduction of egg using pasteurized egg white

powder into infants of the general population. These infants received egg or placebo three times a week from 4-6 months of age until 12 months of age. Early results showed that early consumption of pasteurized egg was not effective in preventing egg allergy at 12 months old with the majority of the infants (94%, 16/17) having a positive food challenge. Most recently, the Beating Egg Allergy Trial (BEAT) results have been published. They conducted a randomized controlled trial on infants who had a SPT response to egg white of  $<2\text{mm}$  and a family history of allergic disease. At 4 months of age, they were randomized to receive whole-egg powder or placebo (rice powder) until 8 months of age with all other dietary egg excluded. Their results showed sensitization to egg white at 12 months of age was 20% in the placebo group compared to 11% in the group consuming egg ( $p=0.03$ ) (55).

Another consideration has been the form of egg that is introduced into an infant's diet (i.e. baked, cooked, raw). In the Healthnuts cohort, they found that first exposure to cooked egg (based on parental report) reduced the risk of egg allergy in their early introduction group (i.e. 4-6months of age) compared to first exposure to egg in a baked form (OR, 0.2, 95% CI 0.06-0.71) (50). Another study found that the introduction of baked egg into the diet of those with a history of IgE-mediated egg allergy based on oral food challenge (OFC), who nonetheless tolerated baked egg, accelerated the development of tolerance to unheated egg when compared to those who strictly avoided egg (56). In the EAT Study, egg was introduced as whole hard-boiled egg (53). The per protocol uptake for egg ingestion was lower compared to the ingestion of the other EAT foods, i.e. peanut and milk, but higher than for sesame, fish, and wheat (which was the last food to be introduced on the study). This low uptake of egg may have been affected by various factors including smell, texture,

or logistic demands of preparation of the egg to make it appropriate and safe for infants to eat. In the HEAP trial, two of the children in the intervention group had an immediate reaction to the pasteurized egg white powder on first exposure at home, suggesting that its use could result in more frequent allergic reactions in the community (54). Many of the interventional trials use different forms of egg in their early introduction studies, which could be less translatable to the general population and therefore, must be considered in future research.

### *Peanut allergy*

Given the high risk of life-threatening anaphylaxis and the increasing rise in prevalence, peanut allergy has become of increasing interest amongst the general population and research community (44). An ecological study by Du Toit *et al* looked at the prevalence of peanut allergy in infants in Israel compared with infants in the UK and found that the prevalence was significantly higher in the UK (1.85% vs 0.17%,  $p<0.001$ ) (57). This 10-fold increase in the prevalence of peanut allergy in UK children was even present when factors such as atopy, genetics, social class and peanut allergenicity were accounted for. However, on further analysis, what was different between the two populations was that peanut was being introduced at an earlier age and consumed more frequently and in larger quantities in the Israeli infants compared to the UK infants. Israeli infants were consuming approximately 7.1grams(g) of peanut protein per month compared to 0g of peanut protein in children in the UK ( $p<0.001$ ). From this, the idea of early peanut introduction and regular consumption of peanuts having a preventative role in the development of peanut allergy gave rise to the design of the Learning Early about Peanut Allergy (LEAP) study (58,

59). The LEAP study was a randomized controlled study that aimed to assess oral tolerance induction of peanut in high-risk children aged between 4 to 11 months of age in the UK. Infants were randomized to consuming peanut products at least 3 times a week (average of 6g of peanut protein a week) or completely avoiding any peanut products until 60 months of age.

The results from the study showed that in this cohort of high-risk atopic children, early introduction and regular on-going consumption of peanut resulted in a significant reduction (81% relative reduction, intention to treat analysis) in the number of children with peanut allergy at 60 months of age compared to those who avoided peanut. The intention-to-treat analysis showed that in the peanut avoidance group, 17.2% of the children had challenge-proven peanut allergy at 60 months of age compared to 3.2% in the peanut consumption group.

The nutritional status of the two groups was also assessed in this cohort of children. The majority of the infants were breastfeeding at the beginning of LEAP and this was not affected by the early introduction of peanut into their diets. There were no significant differences found between height, weight or body-mass index between peanut consumers and avoiders (60). This remained true even when the subgroup of children who consumed the greatest amount of peanut protein were compared to those who avoided peanut entirely. Overall, peanut consumers were in fact consuming a weekly average of 7.5grams of peanut protein, which was more than the recommended level of 6 grams of peanut protein per week. They were able to achieve this within the first month of the study and

continued to eat increasing amounts of peanut protein in a variety of foods with increasing age. Both groups had similar total energy intakes from food and comparable protein intakes. However, the peanut consumers, made more favourable food intake choices compared to the peanut avoiders who for example, ate more savoury snacks such as chips. The peanut consumers had higher fat intakes compared to the avoiders who had higher carbohydrate intake, of which the benefits are currently being debated in nutritional literature (60). Also, from a safety point of view, only 7 out of 319 children (2.2%) randomized to the peanut consumption group had a reaction to peanut during their baseline OFC. However, none of the reactions were severe enough to warrant administration of adrenaline and there were no incidences of choking reported.

The LEAP study demonstrated both primary and secondary prevention of the development of peanut allergy by early introduction of peanut. Both participants who were sensitized to peanut and those who were not sensitized to peanut at baseline (based on skin prick test (SPT) and specific-IgE levels) had reduced peanut allergy at 60 months if peanut was introduced early. The reduction in peanut allergy translates to a number needed to treat (NNT) of 8.5 for participants with a negative SPT response to peanut (no measurable wheal) and NNT of 4.0 for the participants who had a baseline low-positive peanut SPT response (wheal of 1-4mm).

Following on from this was an extension study to LEAP known as the LEAP-On study (61), which looked at whether the consumption of peanut remained protective against developing peanut allergy after a period of peanut consumption cessation for 12 months. A

total of 556 participants (88.5% (556/628)) from the original LEAP trial were enrolled in the follow-on study and the rate of adherence to avoidance was high (90.4% in the peanut-avoidance group, 69.3% in the peanut-consumption group). At 72 months, peanut allergy remained significantly higher in the peanut-avoidance group compared to the peanut-consumption group, 18.6% vs 4.8% ( $p<0.001$ ) respectively. These clinical findings were associated with immunological changes suggestive of immune tolerance. Children with a diagnosis of peanut allergy at 72 months had higher levels of Ara h2-specific IgE compared to those who did not have peanut allergy and the mean level of Ara-h2-specific IgE which had declined significantly in the peanut consumption group in the primary trial ( $p<0.001$ ) remained low at 72 months, after 12 months of peanut avoidance. However, the mean levels of Ara-h2-specific IgE in the peanut avoidance group were significantly higher at 60 months and 72 months compared to the peanut consumption group ( $p<0.001$ ). This follow-on study showed that for the children who had been consuming peanut, their non-allergic status remained stable over 12 months of subsequent peanut avoidance. Thus, the key finding of these two LEAP studies is that early introduction and consumption of peanut until 60 months of age causes a reduction in peanut allergy that persists at 72 months of age, even after a 12-month period of avoidance.

Subsequently, NIAID have updated their recommendations on the introduction of peanut into infant diets. They recommend that infants with severe eczema, egg allergy or both should have age-appropriate peanut containing foods introduced as early as 4-6 months of age. Infants with mild-to-moderate eczema should have peanut containing foods

introduced around 6 months and infants without eczema or any food allergy should have peanut introduced freely into their diet with other solid foods (62).

#### *Other food allergens*

Research looking into the early introduction of other food allergens has been conducted but often using surrogate markers other than OFCs for the diagnosis of food allergy. This includes fish allergy in which one study found that regular consumption of fish in the first year of life was associated with a reduced risk of allergic disease (OR, 0.76; 95% CI 0.61-0.94) and sensitization to food and aeroallergens (OR, 0.76; 95% CI 0.58-1.0) at 4 years of age (63). However, the diagnosis of fish allergy was based on positive specific IgE level of  $\geq 0.35$  kUA/l rather than double-blinded OFCs (64). Another study looked at the early introduction of wheat into infant diets after 6 months of age and found that they had an increased risk of developing wheat allergy compared to those children where it was introduced before 6 months (65).

However, it is the EAT study (53) that has been the most recent study that has looked into oral tolerance through early introduction for multiple allergenic foods in children. Over 1000 infants were recruited with the initial criteria prior to randomization being that infants had to have been exclusively breast-fed from birth until enrolment at 3 months of age. The intervention group of the study had six potentially allergenic foods (cow's milk, egg, wheat, sesame, fish, peanut) introduced into their diets by 4 months of age compared to the control group which followed standard UK government advice of exclusively breastfeeding until 6 months of age with no introduction of allergenic foods before 6

months. The randomized sequence of food introductions for the EIG was cow's milk (yogurt) first, followed by peanut, egg, sesame and whitefish in random order with wheat introduced last. The main outcome was a challenge proven diagnosis of allergy to one or more of the six foods at 1 year and 3 years of age. Two types of analysis were performed. First, the intention-to-treat (ITT) analysis showed that 7.1% of the infants in the SIG developed food allergy to one or more of the six potentially allergenic foods compared to 5.6% in the EIG, although not statistically significant ( $p=0.32$ ). The risk of having a positive SPT to any food was 22% lower in the EIG compared to the SIG at 12 months of age ( $p=0.07$ ) and at 36 months of age ( $p=0.47$ ). However, in the per-protocol analysis, the prevalence of any food allergy was significantly lower in the EIG compared to the SIG (2.4% vs 7.3%,  $p=0.01$ ). More specifically, the prevalence's of peanut allergy (0% vs 2.5%,  $p=0.003$ ) and egg allergy (1.4% vs 5.5%,  $p=0.009$ ) were both significantly less in the EIG compared to the SIG. With regards to cutaneous immunological changes, in the per-protocol analysis both at 12 months and 36 months, the EIG had significantly lower rates of positive SPT to any of the allergenic foods compared to the SIG, 42% ( $p=0.01$ ) and 67% ( $p=0.002$ ) respectively.

### *Adherence*

In the STEP study, 16% of the infants in the egg consuming group and also the control group missed more than 4 doses per week of study powder for 2 months or more. However, only 1% of the infants in both groups consumed egg-containing foods on 10 or more occasions despite trying to maintain an egg-free diet until 10 months of age (51).

In the EAT study, the inclusion criteria for all infants were that they had to be exclusively breastfed which was adhered to extremely well throughout the study. More specifically, of the infants who were in the SIG, the criteria was that they had to continue to exclusively breastfeed until at least 5 months of age. With regards to the actual interventions, the rate of adherence in the SIG was high with 92.9% (524/564) of the participants meeting the per protocol criteria compared to adherence in the EIG which was 42.8% (208/486). Further analysis included calculation of the weekly mean consumption of egg and peanut protein, which was divided into quartiles between enrolment and 6 months of age. Using this data, predictive probability plots were generated which showed that higher consumption of peanut and egg was associated with lower sensitization and prevalence of allergy to the specific food.

In the LEAP study, the overall adherence rate of the two assigned interventions was high (92.0%). This was also observed in the LEAP-On study with an overall adherence to the intervention of peanut avoidance in the follow-up group being 80.0%. There are many reasons for the differences in adherence rates between the studies including factors relating to the foods, mother and family (education, cultural and ethnic differences), as well as the amount of support received during the study (LEAP offered significantly more study contact to participants than EAT did).

### *Future plans regarding food allergy*

The results from the LEAP study have led to consensus statements from international paediatric, allergy and dermatology societies encouraging and recommending the early introduction of peanut to infants at risk of developing food allergy (66-69). For example, the Australasian guidelines advise the introduction of allergenic solid foods including peanut butter, cooked egg, dairy and wheat products to all children in the first year of life, including those at high risk of allergy (70).

Despite this introduction of change in practice, there are various questions that remained to be answered. What must remain paramount when considering introduction of potential allergens is not only effectiveness but also safety. The STEP trial showed that in children without eczema symptoms, the introduction of egg (in the form of pasteurized whole egg powder) at age 4 to 6.5 months did not cause any anaphylactic reactions. Also, of the children who had a confirmed reaction to the pasteurized raw egg challenge at 12 months, 90% were able to tolerate baked or cooked egg in their diet (51). Both the LEAP and EAT studies reported no serious adverse effects between the two groups being compared. The EAT study concluded that early introduction at 4 months of age was safe with no cases of anaphylaxis as well as no adverse effects on breastfeeding or growth of the infants. Similarly, the LEAP study showed no adverse effects or changes in rates of hospitalization between the peanut consuming or peanut avoiding groups.

Another key issue is the timing of early dietary interventions for each potential allergenic food. In the LEAP study, 76 of the 194 patients were excluded as they had a SPT greater than 4mm, which was deemed too high-risk for the study. These children went on to have an OFC at 60 months of age and it was found that a SPT>4mm was predictive of peanut allergy at 60 months of age. In the EAT study, 5.1% (33/652) of the EIG had a positive SPT to one of the six allergenic foods being introduced. These 33 children had OFC conducted and 7 of them had a positive challenge to at least one of the foods. These children were assessed for the study at 3 months of age which suggests that sensitization to allergens may occur earlier than 3 months old which would make targeting early introduction of foods more difficult for children at high-risk given it is unlikely they would be able tolerate solids at an earlier age. There are numerous factors to consider in addition to diet including gender, genetics, environmental factors, which could all influence early exposure and sensitization to allergens. It is perhaps in these higher-risk children where further research is required as they are potentially at greater risk of developing food allergy.

### *Conclusions:*

Over the last few years there is an increasing amount of interest and evidence to support the early introduction of potential allergenic foods to aid in the development of oral tolerance. Findings from the LEAP and EAT studies have had a significant influence in clinical management and practice of children with food allergy, especially peanut allergy. There still remains important questions for future research with regards to the exact timing of introduction of allergenic foods, effectiveness of introduction of other common

food allergens apart from peanut and egg but also strategies for those who are at higher-risk or sensitized already to allergens at a very young age (i.e. <4 months old).

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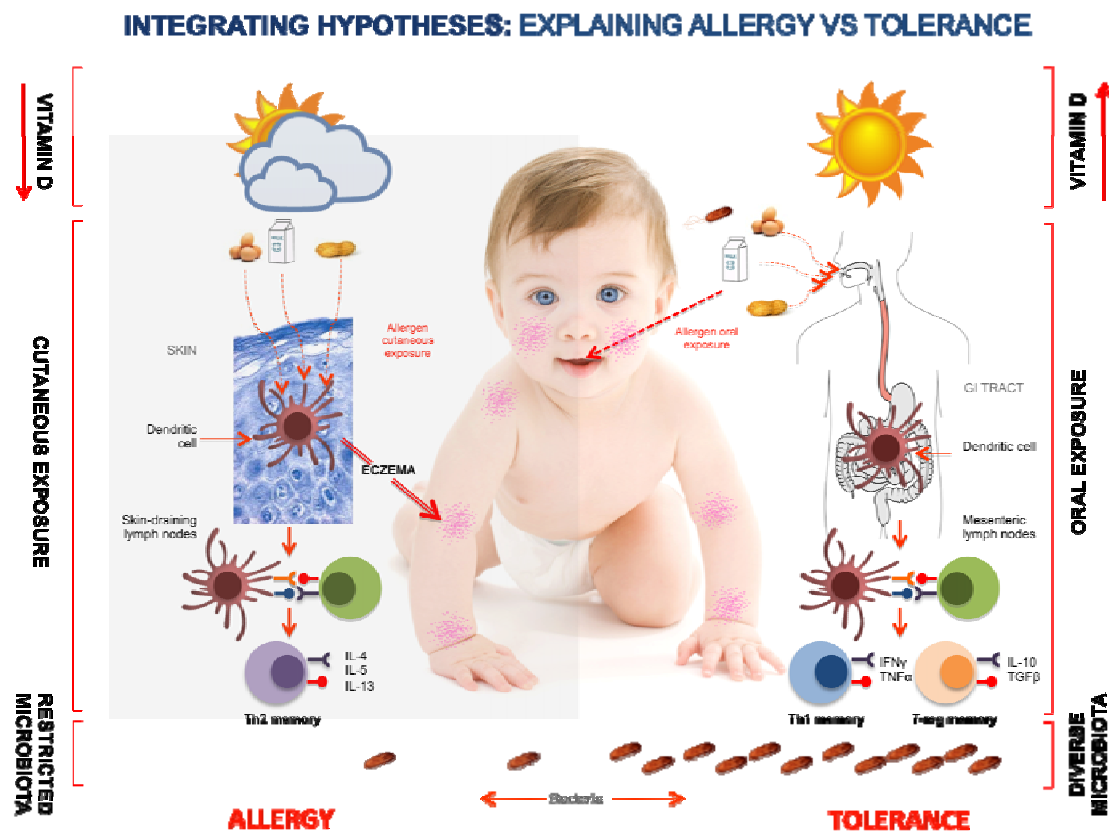
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Figure 1: Explanation of allergy versus tolerance



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