

Article type : Invited Review

Title: The role of environmental exposure to peanut in the development of clinical allergy to peanut

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Keywords: peanut allergy, paediatrics, environment, exposure, sensitization

Abstract:

The presence of peanut allergy has increased over the years and still remains one of the most common causes of food-related anaphylaxis. The way in which peanut sensitization occurs has been explored, such as via maternal consumption in pregnancy, via breast milk and through a disrupted skin barrier. It has previously been shown that environmental exposure to aeroallergens in household dust can be a risk factor for the development of allergic asthma. However, it is likely that the combination of cutaneous sensitisation via a disrupted skin barrier (i.e. children with eczema especially those with filaggrin mutations) and the interaction with

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12992

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environmental peanut exposure influences the development of peanut allergy. This review aims to explore the current evidence of how environmental exposure to peanut affects the development of peanut allergy.

Background:

In Europe, the most common food allergies in children are to hen's egg, cow's milk and peanut [1]. The prevalence of peanut allergy (PA) has been increasing over the years affecting approximately 1-3% of children in Western countries [2]. This has coincided with an overall increase in the prevalence of food allergy over the last 30 years [3, 4], with a recent meta-analysis commissioned by the National Institute of Allergy and Infectious Disease showing a prevalence of between 1-10% across all age groups [4, 5]. In the UK, hospital admissions in relation to food allergies have increased by 500% from 1990 till 2003 [6] and in the same time period, the number of hospitalisations caused by severe allergic reactions increased 7-fold [1]. However, Venter et al compared two large UK birth cohorts and found peanut allergy to be stable over the first 10 years of life and between 1989 and 2001, there were no significant differences in peanut sensitization or clinical peanut allergy [7].

PA and tree nut allergies are the commonest causes of food related anaphylactic deaths in emergency departments around the world [8-10]. More specifically, peanuts, hazelnuts and walnuts cause 50% of all life-threatening allergic reactions in the UK [1]. In Australia, a review of all emergency department attendances between 1998-2003 found that peanut and tree nuts accounted for 36% (37/104) of all food-related anaphylaxis [11]. In the USA, PA has been noted as the leading cause of food allergy related deaths, followed by tree nut allergy. Combined food related data from 1994-1999 and 2001-2006 showed that of the reactions that resulted in

anaphylactic deaths, in 58.7% (37/63) the culprit allergen was most probably peanut and in 28.6% (18/63) of the cases, it was likely to be a tree nut [12]. In the UK from 1992-1998, of the food allergy related fatalities documented, 68% (25/37) were due to peanut and/or tree nuts combined [13] and over the following seven years, a further 48 deaths were documented due to food anaphylaxis of which 19% (9/48) were due to peanut and 37.5% (18/48) were due to peanuts and/or tree nuts combined [14]. As PA has been identified as one of the most common foods related to anaphylaxis, a lot of research has focussed on understanding how it develops but also identify ways in which it can be prevented.

The natural history of peanut allergy

The median onset of PA is 14 months [15] and it most often persists into adulthood and it was previously thought to be a lifelong problem. However, several studies have shown that between 20-50% of children outgrow their PA [16-19]. In a study by Fleischer et al, 55% of children who had a specific-Immunoglobulin-E (sp-IgE) to peanut of 5 kUA/L or less, 63% who had a sp-IgE to peanut of 2kUA/L or less and 73% who had undetectable sp-IgE to peanut had a negative oral food challenge (OFC) to peanut which suggested that 50% of patients with a history of peanut allergy but had a sp-IgE to peanut of 5kUA/L or less were likely to outgrow their allergy [16]. However, many of these studies confirmed resolution of PA by OFCs but the initial criteria for peanut allergy diagnosis was based on clinical reaction or positive skin prick test (SPT) or sp-IgE testing with no history of peanut ingestion [18]. This could have falsely elevated the rate of PA resolution if children who were sensitized to peanut rather than being allergic were included in the data. A more recent population-based study (Health-Nuts cohort) conducted by Peters et al on 1 year old infants with challenge-confirmed PA, found that 22% of children had OFC-confirmed resolution of their PA at 4 years of age [19]. They also found that decreasing SPT wheal size predicted tolerance and that increasing SPT wheal size was associated with the

persistence of PA. It has also been shown that there is the possibility of reoccurrence even with negative SPT and OFC results, especially if there is a lack of regular peanut intake [10].

Fleischer et al found that patients who ingested peanut infrequently or in limited amounts were significantly more likely to have recurrence of their PA compared to those who ingested peanut regularly ($p=0.025$); they reported a recurrence rate of 7.9% [20]. Interestingly, patients who have a history of peanut anaphylaxis are not likely to develop tolerance to peanut [18].

Therefore, peanut allergy management is currently limited to avoidance and the provision of a management plan in case of accidental exposure. Peanut desensitisation studies are only conducted in the research setting and can increase the threshold of peanut tolerance whilst on treatment but do not provide a cure. In order to work towards finding a cure, we need to understand how people become allergic to peanut.

The immunological process of peanut sensitization

Allergen exposure can occur via a variety of routes. The most obvious route for food allergen exposure is through the oral route; however, food allergen exposure may also occur through exposure of allergens via the respiratory tract and/or the skin. To develop peanut allergy, one must be exposed to peanut allergen in order for the immune system to be primed in order to produce peanut specific IgE. In the body, this process begins when antigen-presenting cells in the body engulf peanut allergen and a naïve CD4⁺ T-helper lymphocyte. This sets off a cascade of the T-helper lymphocyte activating and maturing B cells to produce antigen-specific antibodies to peanut and IgE-secreting plasma cells [21]. These plasma cells continue to produce and secrete sp-IgE antibodies against specific peptides of the peanut protein, which bind to surface receptors of mast cells in various tissues in the body including the skin, gastrointestinal tract, respiratory tract and basophils circulating in the blood. Therefore, on repeat exposure to peanut, the peanut peptides bind to sp-IgE antibodies on these mast cells

and basophils which result in degranulation and release of inflammatory mediators causing an allergic reaction. The clinical reaction seen depends on which target tissues are affected - for example skin symptoms include hives and angioedema, respiratory symptoms include wheeze, stridor, difficulty in breathing, cardiovascular symptoms include hypotension, pallor and possible collapse and gastrointestinal symptoms include vomiting and diarrhoea.

Routes of peanut sensitization

In utero exposure

There are a multitude of factors that are likely to contribute to the development of peanut sensitization and PA. There is a strong genetic influence on the development of PA as shown by the 64% concordance rate in monozygotic twins [22]. Similarly in a Chinese cohort study, concordance rates for food sensitization were higher in monozygotic twins compared to dizygotic twins [23]. Ethnicity has also been studied to see if this might contribute to developing food sensitization, more specifically, Black ethnicity has been shown to be associated with peanut sensitization [24, 25].

The potential routes of peanut sensitization have also been researched to try and determine at what point sensitization occurs. Research has shown that foetal cells are capable of producing IgE from the second trimester onwards although IgE producing cells are quite rare until 9 months after birth [26]. IgE has been found in umbilical cord blood and it has in the past been used to predict atopy in children [27, 28]. The Avon Longitudinal Study of Parents and Children (ALSPAC) was a large birth cohort study in which 14000 pregnant women were recruited over a 1-year period [29]. Children of these mothers who had developed challenge-confirmed peanut

allergy by 38 months of age had their cord blood assessed retrospectively. The study found no detectable peanut sp-IgE in the cord blood (using a cut-off of 0.35kUA/L) of the peanut allergic children, which suggested that peanut sensitization had not occurred in the antenatal period [29]. It is possible that IgE found in cord blood may be reflective of maternal IgE production as found in the Copenhagen Studies on Asthma in Children (COPSAC) cohort [30]. They found allergen sp-IgE in 14% of cord blood samples that was no longer detectable in the infants' blood at 6 months of age [31]. Also, sp-IgE in the cord blood correlated with cord blood-IgA (used to measure maternal blood contamination of cord blood as IgA cannot cross the placental barrier) which supports that the sp-IgE present is likely to be maternal in origin [31]. In summary, it seems that children are not sensitised to peanut in utero and therefore interventions during pregnancy may be less effective.

Breastfeeding

There has also been research performed to see whether peanut allergen exposure occurs through exposure from breast milk. Studies have shown that cow's milk (β -lactoglobulin) and egg (ovalbumin) proteins can be found in breast milk [32, 33]. Vadas et al looked at the transmission of peanut allergen via breast milk by measuring the presence of total peanut protein and 2 major peanut allergens (Ara h1 and Ara h2) in breast milk at hourly intervals after women consumed 50g of dry roasted peanuts. They found that within 3 hours of ingesting peanut, peanut proteins (both Ara h1 and Ara h2) were detected in breast milk [34]. A different study looked at transmission of peanut protein Ara h6 in breast milk and found that it was detected as soon as 10 minutes after maternal peanut consumption in breast milk and although there was a reduction over time, there was still some present at 26 hours post ingestion [35]. Schocker et al found that Ara h2 was detected in breast milk post maternal consumption of peanut within 1-12 hours but the concentration of Ara h 2 secreted seemed to be individually regulated [36]. Given the presence of peanut allergens in breast milk post maternal

consumption, it is possible that peanut sensitization can occur in the breastfeeding child.

However, studies have looked for an association between maternal peanut consumption and the development of peanut sensitization or PA in children and there is conflicting evidence.

There are large cohort studies (ALSPAC study n=13971 and Isle of Wight study n=4156), which did not find an association between maternal consumption during pregnancy or lactation with peanut sensitization or PA in children [29, 37]. Similarly, the CoFAR study (n=512 infants with egg or cow's milk allergy or moderate to severe eczema with cow's milk or egg sensitization) found no significant association between peanut consumption during breastfeeding and the development of peanut allergy [38]. However, a dose-response relationship between maternal peanut consumption during pregnancy and a serological diagnosis of PA was noted, and more specifically the infants in the group who did not breastfeed were 5-times more likely to have peanut sp-IgE $\geq$ 5kUA/L (p=0.004) if their mothers consumed peanut at least twice a week during pregnancy [38]. This suggests that household exposure to peanut in the absence of the protective effect of breastfeeding is associated with the development of PA. There have been randomized controlled trials (RCT) looking at maternal dietary manipulation during pregnancy to prevent against the development of eczema, food and respiratory allergies to children [39]. However, meta-analysis of these studies does not support recommending maternal dietary restriction during pregnancy or lactation due to lack of efficacy of the intervention from studies so far and the potential impact on infants' nutrition and growth.

Household peanut exposure

Fox et al conducted a study comparing 133 peanut allergic children against 160 atopic egg allergic controls and 160 non-atopic controls from general paediatric clinics and looked specifically at the route of peanut exposure in the development of PA [40]. They found that

household peanut consumption (quantified as the combined peanut consumption of all household members in the child's first year of life) during infancy increased the probability of developing PA in children. Household peanut consumption was ten times higher in peanut allergic children (18.8grams/week) than high-risk egg allergic children without PA (1.9grams/week) ($p<0.0001$) and three-times higher than non-atopic children without PA (6.9grams/week) ($p<0.0001$) [40]. They reported a dose-response relationship between environmental peanut exposure (non-oral) in the development of PA of which peanut butter was strongest. The authors thought that as peanut butter is stickier, there was an increased likelihood of transfer by hands and therefore exposure to an infant's skin directly or onto their bedding or play area. A limitation of the study was that they did not measure environmental peanut levels in dust to objectively quantify household peanut levels but instead used food frequency questionnaires for each household member.

Cutaneous sensitisation

Eczema is often described as the first step in the allergic march [41] and there is research that has shown that 50% of infants with eczema develop food allergy by 1 year of age [42]. The Melbourne Atopy Cohort (MAC) study, in which 620 children were recruited at birth looked at the link between eczema and IgE-mediated food sensitization [43, 44]. These children were "at risk" of allergic disease based on a first-degree relative having eczema, asthma, allergic rhinitis or IgE-mediated food allergy. They found that at 1 year of age, children with a history of mild eczema had a three-fold increased risk of IgE food sensitization compared to infants without eczema (36% versus 11% respectively). In children with a history of severe eczema, the increase was six-fold compared to children without eczema (65% versus 11% respectively) [43].

Research has shown that filaggrin (filament aggregating protein) plays a crucial role in the strength and integrity of the skin of which filaggrin loss-of-function mutations are associated with eczema, skin barrier dysfunction (which can be measured using transepidermal water loss (TEWL)) as well as allergic sensitization [45, 46]. A recent study has shown that filaggrin expression in umbilical cord blood is associated with eczema development in the first year of life [47]. In the Australian Health nuts cohort, filaggrin loss-of-function mutations were more commonly found in children who had food sensitization compared to those who did not [48]. Flohr et al showed that early onset atopic dermatitis and skin barrier impairment (TEWL) were associated with food sensitization at 3 months of age [49]. In fact, Kelleher et al measured TEWL at birth (day 2) and at 2 and 6 months and found that impairment of skin barrier function at birth and at 2 months was predictive of clinical atopic dermatitis at 1 year of age [50]. In a second study, they found that skin barrier impairment as measured by TEWL at birth (day 2) predicted food allergy at 2 years of age [45]. More specifically with regards to PA, Lack et al used data from the ALSPAC study and identified that exposure to topical Arachis (peanut) oil during infancy was associated with the development of PA but only if the infants who also have eczema [29]. Brown et al showed that children with filaggrin loss-of-function mutations had a significant association with PA and even after controlling for coexistent atopic dermatitis, this association remained significant ($p=0.0008$) [51]. Brough *et al* found that children who carried a filaggrin mutation had an increased risk of peanut sensitization and challenge proven peanut allergy [52]. Skin barrier dysfunction seems to have a role in the development of allergic disease and cutaneous sensitisation may explain how environmental allergens are exposed to individuals.

Peanut sensitization and the environment

Environmental exposure to inhaled allergens is known to be a risk factor for the sensitization and development of allergic disease. Sporik et al showed that infants exposed to up to 10 micrograms of house dust mite (Der p I) was associated with the development of asthma at 11 years of age, more specifically the relative risk of asthma was 4.8 [53]. With regards to peanut allergen in the environment, studies have been performed to look at the amount present in the home and school environment [54]. Perry et al assessed the amount of peanut remaining on surfaces after spiking them with peanut butter and then cleaning them by different methods [55]. Peanut protein was quantified using a monoclonal ELISA directed against Ara h 1. They found that the major peanut allergen Ara h1 was easily cleaned from hands and household surfaces using a variety of cleaning methods (i.e. washing with liquid soap, bar soap or commercial wipes for hands and common household cleaning agents for surfaces) and it did not seem to be widely distributed in preschools and schools. They also could not detect any airborne peanut allergy using a model where participants wore personalised air sampling monitors and ate and stamped of peanuts on the floor in an enclosed room [55]. Brough et al quantified peanut protein in the home environment using a more sensitive polyclonal ELISA directed against whole peanut protein [56]. In this study they tried to detect airborne peanut with a personalised air-sampling monitor using a number of experimental set-ups: 1cm above peanut butter, dry-roasted peanut packet, whilst eating peanuts (on shirt, breathing onto air sampling head) and simmering satay sauce on a stove and they were unable to detect any peanut protein. The only experimental design that could detect peanut was when the sampling head was placed directly above peanut being shelled (1cm and 1m). In this experiment peanut protein was detected in the sampling head during active peanut shelling but disappeared immediately after peanut de-shelling stopped. This suggested that airborne peanut was not likely to remain airborne (unlike for example cat allergen [57]), and therefore would be less

available for inhalation and potential sensitization. More recently, Sheehan et al analysed dust for peanut protein from students' homes and the school environment (i.e. cafeteria and classrooms) using an ELISA directed against whole peanut protein [58]. They found that peanut was widely detectable in dust samples from classrooms and cafeterias at schools, which could have an important role in environmental peanut exposure to children. The presence of peanut in dust has also been demonstrated in other countries and study centres using a variety of methodologies such as different sampling techniques, ELISA or dot blot analysis [59].

The home areas at which dust samples have been taken from has been investigated; for example, Trendelenburg et al reported a positive correlation with peanut levels in the eating area but not on bed sheets [60]. Brough et al found that peanut consumption correlated highly (Spearman rank >0.8) with peanut protein in bedroom and living room dust and on kitchen and bedroom surfaces. This is important because Fox et al showed previously that household peanut consumption is a risk factor for the development of PA [40]. They stipulated that peanut protein might be transferred from hands to the environment as they found that household consumption of peanut butter (which is sticky and easily transferable) during the child's first year of life was the form of peanut-containing food that was the most highly associated with the development of PA. Brough et al evaluated potential routes of peanut protein transfer into the environment after peanut consumption in separate experiments. Hands and saliva were found to be potential routes of peanut transfer in the environment as peanut was still present on hands and saliva three hours after peanut consumption. Even after being cleaned with detergent, household surfaces (table surfaces, appliance handles), furnishings (sofa covers) and bedding (pillows) were still found to have detectable peanut protein [56]. Thus once present peanut protein remained on household surfaces and bedding despite cleaning measures leaving it potentially available to sensitize children. Other food proteins have been measured in household dust such as milk, fish and egg but the clinical relevance of this has not been evaluated yet [61].

Further investigation into an infant's environmental exposure to peanut was performed, as it is during infancy that peanut sensitization is occurring. There was a positive correlation found between peanut protein found in the infant's environment (i.e. bed, crib rail, play area) and household peanut consumption at 1 month old and 6 months old [62]. Thus even though the infant was not consuming peanut, peanut was still finding its way into the infant's bed, where, the child could be exposed to peanut, either transcutaneously or via inhalation.

Are environmental peanut levels in dust sufficient to elicit an allergic reaction in peanut allergic individuals?

Simonte et al conducted a study on children with peanut allergy (inclusion criteria of sp-IgE peanut >50 kIU/L and clinical anaphylaxis, reported inhalation-contact reaction or positive OFC to peanut) in which they exposed them to peanut via the skin and inhalation by holding masked peanut butter 12 inches from the subject's nose [63]. They reported with 96% confidence that at least 90% of highly sensitive children with peanut allergy would not experience a systemic or respiratory reaction from casual exposure to peanut. Of those that did react, it was more likely to lead to a local skin reaction rather than a significant allergic reaction [63].

This finding was further supported by another study, which looked at skin exposure to peanut. They found that 41% of children sensitized to peanut (positive SPT) developed localized urticaria from prolonged skin contact (applied under an occlusive dressing to an area skin free of eczema for 15 minutes) with peanut but none developed a systemic allergic reaction [64].

There has therefore been a lot of focus into the dose of peanut protein required to elicit an objective response in patients undergoing OFC. In a review article of 12 studies, the lowest doses predicted to elicit objective symptoms ranged from 11mg for threshold studies, 18mg for diagnostic studies, and 65.5mg for immunotherapy challenges [65]. However, other studies

have shown that objective reactions have occurred on consumption of as little as 0.1-5mg of peanut protein [66, 67]. Hourihane et al conducted a study in 378 peanut allergic children that found that single administration of 1.5mg of peanut protein was clinically safe and tolerated by the children, with fewer than the predicted 5% of patients having an objective reaction (defined as having 3 or more concurrent episodes of noncontact urticaria persisting for at least 5 minutes, perioral or periorbital angioedema, rhinoconjunctivitis, diarrhoea, vomiting or anaphylaxis occurring 2 hours from ingestion) [68].

Interaction between environmental peanut and skin barrier function

There are children who are more at risk for peanut sensitization via environmental peanut exposure. Brough et al looked at the effect of environmental peanut exposure in children with filaggrin loss-of-function mutations [52]. They found that in children carrying at least one filaggrin loss-of-function mutation, a dose-response relationship between early-life environmental exposure to peanut protein in the household and peanut sensitization and PA. For every *ln* unit (2.7 fold) increase in house dust peanut exposure during infancy, these children had a 6-fold increase of school-age peanut sensitization and a 3.3-fold increase in developing school-age PA.

This data supports the hypothesis that PA develops through transcutaneous sensitization in children with a weakened skin barrier. This is further supported by data from another study by Brough et al, which looked at peanut sensitization and PA development from exposure to peanut antigen in dust in children with atopic dermatitis [69]. In this study, they found there was an increased exposure-response relationship between peanut protein levels in household dust and peanut SPT sensitization (odds of 1.97) and PA (odds of 2.34) in children with atopic dermatitis. Again this supports the idea that environmental exposure to peanut through an impaired skin barrier is a potential route for peanut sensitization and PA.

Dual Allergen Exposure Hypothesis

The most common theory that is thought to be the way in which food sensitization develops in infants is the Dual Allergen Exposure Hypothesis. It suggests that early sensitization to food and aeroallergens, occurs via exposure to allergens via the cutaneous route [70]. Recent advances in the last few years have demonstrated that early consumption of peanut in infants can be protective against the development of PA via the development of oral tolerance. Fox et al found that high levels of oral exposure to peanut in infants led to tolerance irrespective of environmental exposure [40] similar to what has been found in animal models; once the mice have had oral exposure to peanut it is no longer possible to sensitize them via the skin [71]. Although environmental exposure to peanut in the form of the presence or consumption of household peanut during infancy, does increase the risk of peanut sensitization; exposure via the oral route has an important role in the child developing peanut tolerance [72, 73]. The oral tolerance induction route therefore seems to be a much stronger effect than the sensitising effect of cutaneous exposure.

Conclusion:

The prevalence of PA is high and accounts for a significant proportion of fatal allergic reactions. Environmental peanut exposure that occurs from the presence of peanut allergen in dust, likely secondary to household consumption of peanut does increase the risk of peanut sensitization and PA in infants if they have additional risk factors leading to a disrupted skin barrier such as FLG loss-of-function mutations and/or eczema. It is not clear if the peanut in dust is directly responsible for peanut sensitisation or if this is just a marker of peanut being transferred around the house and onto the infant through skin contact. However, exposure to peanut via the oral route can have a protective role in a child developing peanut tolerance, even in the

presence of environmental peanut exposure. Further research is required to determine whether a reduction in environmental exposure to peanut prior to oral peanut consumption can protect against the development of peanut allergy.

Key summary points:

1. Peanut allergy (PA) remains one of the most common causes of food-related anaphylaxis and can be fatal.
2. Peanut protein levels in dust in an infant's bed and play-area are highly correlated with levels of household consumption of peanut.
3. The combination of cutaneous sensitization through a disrupted skin barrier (i.e. people with eczema especially with filaggrin loss-of-function mutations) and environmental peanut exposure may influence the development of PA.
4. Peanut levels in dust may be able to directly sensitize children to peanut if they have an impaired skin barrier or may be a marker of cutaneous transfer of peanut onto the infant's skin.
5. Although research has shown that environmental exposure of peanut during infancy is associated with the development of peanut sensitization and PA in children with a disrupted skin barrier, a causal relationship has not yet been proven and would require a randomised controlled trial.
6. Oral tolerance induction appears to have a stronger effect than cutaneous sensitization on the development of PA.

Conflicts of interests:

Dr. Ru-Xin Foong does not have any conflicts of interest. Dr. Helen Brough reports grants from Food Allergy & Research Education (FARE), research support from Stallergenes, ThermoFisher Scientific and Meridian Foods and Honoraria for provision of lectures and expert focus groups from Allergy Therapeutics, Nutricia Advanced Medical Nutrition, Nutricia Early Life Nutrition. She is also a Consultant for Mead Johnson Nutrition.

Abbreviations:

PA = peanut allergy

Sp-IgE = specific immunoglobulin-E

OFC = oral food challenge

SPT = skin prick test

ALSPAC = Avon Longitudinal Study of Parents and Children

COPSAC = Copenhagen Studies on Asthma in Children

CoFAR = Consortium of Food Allergy Research

RCT = randomized controlled trial

MAC = Melbourne Atopy Cohort

TEWL = transcutaneous epidermal water loss

LEAP = Learning Early About Peanut allergy

QoL – quality of life

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