

EU Forum

A EuroPrevall review of factors affecting incidence of peanut allergy: priorities for research and policy

Peanuts are extensively cultivated around the world, providing a foodstuff that is both cheap to produce and nutritious. However, allergy to peanuts is of growing global concern, particularly given the severity of peanut-allergic reactions, which can include anaphylaxis and death. Consequently, it is important to understand the factors related to the prevalence of peanut allergy in order to inform efforts to ameliorate or pre-empt the condition. In this article we review evidence for the relevance of factors hypothesized to have some association with allergy prevalence, including both genetic and environmental factors. Although our analysis does indicate some empirical support for the importance of a number of factors, the key finding is that there are significant data gaps in the literature that undermine our ability to provide firm conclusions. We highlight these gaps, indicating questions that need to be addressed by future research.

**A. Boulay¹, J. Houghton¹,
V. Gancheva², Y. Sterk², A. Strada³,
M. Schlegel-Zawadzka³, B. Sora⁴,
R. Sala⁴, R. van Ree⁵, G. Rowe¹**

¹Institute of Food Research, Norwich Research Park, Colney, Norwich, UK; ²Association APPEL EUROPA, Sofia, Bulgaria; ³Jagiellonian University Medical College, Krakow, Poland; ⁴Centro de Investigaciones Energeticas, Medioambientales y Tecnologicas, Madrid, Spain; ⁵Department of Experimental Immunology, Academic Medical Centre, Amsterdam, the Netherlands

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A. Boulay
Institute of Food Research
Norwich Research Park
Colney
Norwich NR4 7 UA
UK

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The peanut (*Arachis hypogaea*), also known as the groundnut, earthnut, monkey nut or goober, is a legume (1). Archaeological records suggest it was first encountered and used by humans in Peru between 2500 and 300 BC (2, 3). At the time of the Spanish and Portuguese conquests of America, peanuts were being grown widely in the West Indies and South America. Nowadays, the peanut is widely distributed, with the most important producing countries being India, China, USA, Argentina, Western and Southern Africa, and Brazil (4). *Arachis hypogaea* has four main cultivars, known as Virginia, Peruvian Runner, Valencia and Spanish (believed to have originated from different locations in South America), though breeding programmes to improve yields and disease resistance have subsequently produced many different varieties [Maleki (5) numbers 14 000 of these]. Peanut seeds are nutritious, containing many important nutrients, such as vitamin E, niacin, folacin, calcium, phosphorus, magnesium, zinc, iron, riboflavin, thiamine and potassium. They are also a good source of protein and a rich source of edible oil. Furthermore, peanuts are

cheap to produce – an important factor in the context of world hunger.

On the negative side, the prevalence of food allergy related to peanuts has reportedly increased in recent decades, particularly in western countries (6). Peanuts are among the highest food producers of IgE-mediated allergic reactions following ingestion (7) and they are one of the most common foods that cause an allergic reaction, both in children and adults (8–14). Allergic reactions arise as a result of immunological responses to particular proteins: in peanuts these proteins are Ara h 1 (*vicilin*), Ara h 2 (*conglutin-homologue protein*), and Ara h 3/Ara h 4 (*glycinin*). These proteins are considered major allergens because they are recognized by over 50% of peanut-allergic patients in the USA (13, 15), although interestingly, Ara h 1 may be only a minor allergen for some European patients (16). More recently three additional minor allergens – Ara h 6 and Ara h 7 (both *conglutin-homologue proteins*) as well as Ara h 5 (the plant *pan-allergen profilin*) – have been identified (17). Recently, Mittag et al. (18) identified,

cloned and expressed a new peanut allergen, Ara h 8 which is the Bet v 1 homologue in peanut and a major allergen in patients with combined birch pollen and peanut allergy.

Peanut allergy is one of the most severe food allergies because of its sometimes life-threatening characteristics (14, 19) and also because it is rarely outgrown. Additionally, people suffering from peanut allergy often react to smaller doses of food than people with other food allergies: peanut allergy can be triggered by a very small amount, and even the smell of peanut can be enough to trigger an allergic reaction in extreme cases (20–23). Furthermore, diagnosing peanut allergy is difficult as the Double Blind Placebo Controlled Food Challenge (DBPCFC) is expensive and time consuming, and hence most recorded cases of peanut allergy are self-reported. Over the last 30 years, the prevalence of peanut allergy in the western world is reported to have increased (6, 24) and has been estimated at from 1 in 10 000 up to 1 in 200 (24–36). However, there is a lack of time series data and uniformity in data collection, making comparisons difficult. Indeed, some researchers have argued against there having been such an increase, noting that similar rates of allergy exist in children and adults (27). Regardless, allergic diseases as a whole are now the most common chronic disorders in childhood in the developed world (37), and the major increase over the last 25 years has highlighted the need to develop more definitive preventative or curative strategies.

The EuroPrevall project (a European multidisciplinary and multicentre research project funded by the EU) has been set up to study the prevalence, cost, and basis of food allergy and to ameliorate quality life for food allergic people. After all, food allergy can have a significant impact on an individual's quality of life, and at the population level, there are economic consequences in terms of medical costs and working days lost (38). While it would seem likely that the prevalence of food allergy within a given population has some connection to the eating behaviours within that population, causality is not straightforward. Indeed, there appear to be many factors (both food-related and nonfood related) linked to the development and incidence of food allergies. In this paper we set out to identify factors linked to peanut allergy in particular, looking first at potential factors influencing peanut sensitization, and then focusing on aspects of the peanut food chain that may be relevant to allergy incidence. In reviewing the research evidence, it may be possible to identify patterns or trends in peanut production, processing and consumption that can be used to create hypotheses about the causal factors influencing the prevalence of peanut allergy, which may be tested at a later time. At the very least we hope this review exercise will highlight data gaps, pointing to a series of research questions that need to be addressed in order to enhance allergy prevention and management. We conclude our analysis with recommendations for future research.

Method

In order to identify factors related to the incidence of peanut allergy, a systematic literature review was undertaken. Relevant publications from Science Direct, Blackwell Synergy, Ingenta Connect, Web of Science, Taylor and Francis, Scopus, Medline, Google and Google scholar were identified between 16 May and 6 July 2007. To select relevant articles, keywords used included 'peanut' and its synonyms along with the terms: *Africa*, *allergen(s)*, *allergenicity*, *allergic*, *allergy*, *Ara h 1*, *Ara h 2*, *Ara h 3*, *blanched*, *boiling*, *breast milk*, *consumer*, *consumption*, *cooking methods*, *countries*, *crush*, *cultivars*, *cultivation*, *definition*, *earth-nut*, *Europe*, *export*, *fried*, *frying*, *geography*, *grinding*, *history*, *import*, *incidence*, *India*, *infant*, *lactation*, *milling*, *newborn*, *prevalence*, *processing*, *production*, *roasting*, *sensitization*, *temperature*, *time*, *tolerance*, *trade*, *UK*, *utilization*, *wean*, *weaning* and any combination of these terms. The literature search was largely conducted on English language articles, but also included articles in French, Spanish, Polish and Bulgarian, reflecting the composition of members of our research project. The most relevant abstracts (related to peanut production/processing or consumption/utilization in relation to peanut allergy) were subjected to a more detailed scrutiny. Publications (scientific and nonscientific) that did not focus exclusively on peanuts were excluded from the review. From the literature review, key factors were identified as important with regard to their potential role in peanut allergy.

Figures 1–3 summarize the results of this literature review, highlighting the various factors potentially related to peanut allergy, and the strength of evidence for their association. Figure 1 indicates factors related to peanut sensitization, providing a simplified representation of the main categories of factors that may influence this, without showing the potentially complex interrelationships between these (e.g. it does not show links between genetic and environmental factors, but these do, of course, exist). Our main interest is in the peanut food chain, as will become apparent later on. Figure 2 thus focuses on production, processing and uses (consumption), but provides an added level of detail to show the strength of evidence that exists for the relationship of the identified factors to allergy. Figure 3 goes even further in detailing the evidence of those factors in the peanut food chain that may be more important for allergy. In the subsequent sections we elucidate the relationships shown in these figures, looking at genetic and environmental factors, as well as aspects of the peanut food chain (e.g. cultivars, processing, early exposure and dietary habits).

Factors involved in peanut sensitization

Research shows that prevalence of peanut allergy varies with geographic location (39). This may be explained by differences in genetics (between and within populations) and/or environments (including cultural differences in behaviour between different populations, in terms of different processing/cooking methods and different environmental patterns of utilization, consumption and exposure in terms of both food and nonfood uses, and in terms of the time at which peanuts are introduced into the diet, e.g. weaning practices) (see Fig. 1). Other factors underlying geographical variation may include different frequencies/prevalence of transplants, variations in incidence of certain atopic diseases, and different rates of transmission via caesarean sections. Our analysis therefore does not consider geography *per se* as a relevant factor for allergy, but attempts to identify the underlying factors that explain geographical variance.

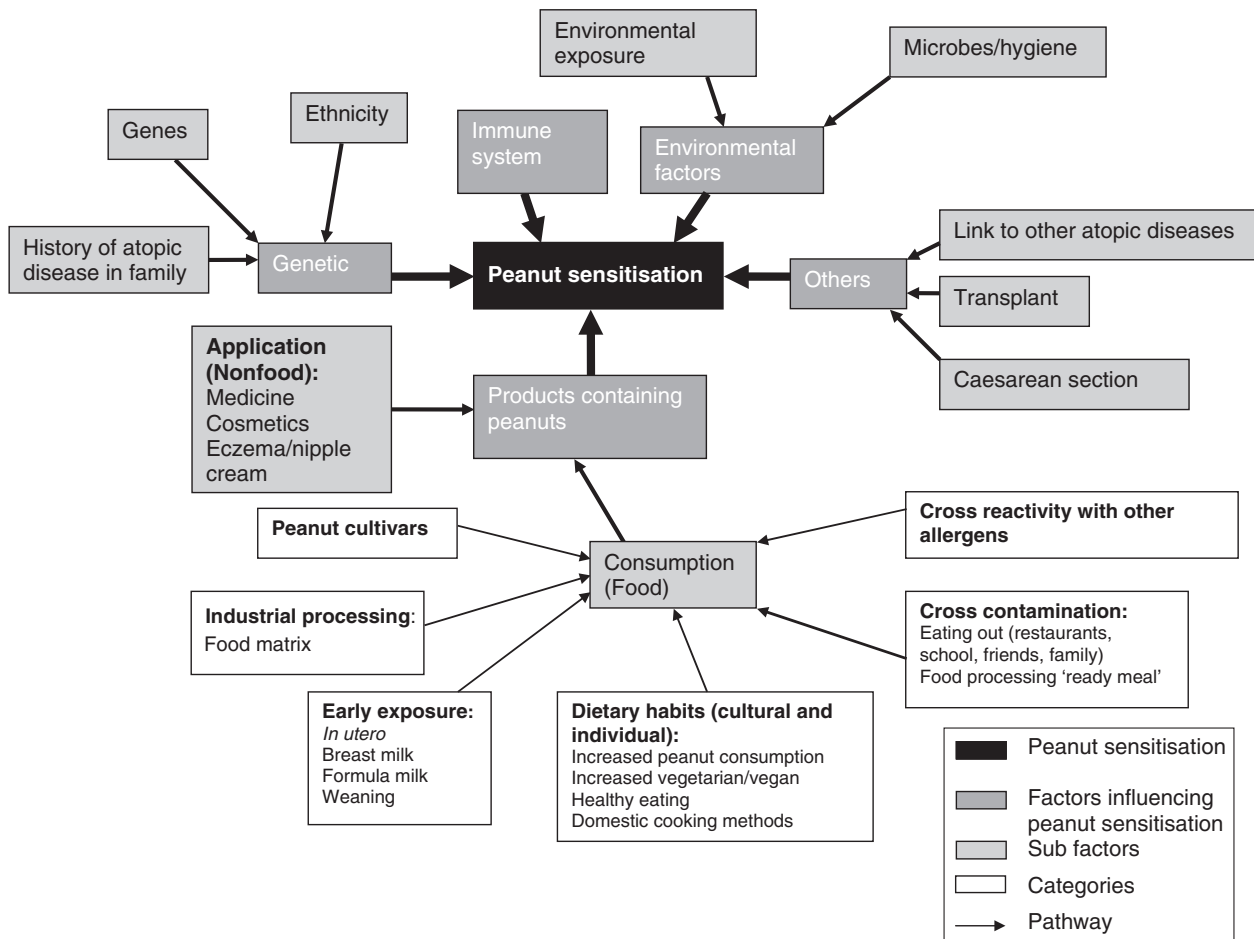


Figure 1. Factors influencing peanut sensitization.

Genetic factors

Genes and history of atopic disease. It has been established that genetic factors may exert an influence on the development of peanut allergy (see Fig. 1), although allergen-specific inheritance for peanut is less well known or accepted than nonspecific inheritance (e.g. asthma, atopic dermatitis and rhinitis). In studies carried out in the UK, the frequency of peanut allergy has been found to be significantly higher in relatives of peanut allergy patients than in the general population (7% vs 0.5%) (40). Children of allergic mothers are more likely to develop allergies than children of allergic fathers, but if both parents are allergic then there is a much higher tendency to develop allergies. A survey of the families of 622 peanut allergic probands (the first person being allergic and studied in a family) in the UK noted an increased prevalence of peanut allergy in succeeding generations. However, increased prevalence also occurs in those with no apparent family history of allergy (41), and so a genetic explanation provides only part of the story. A study carried out in 58 pairs of twins showed that 7% of dizygotes and 64% monozygotes shared peanut allergy, suggesting a significant genetic influence. The probability of inheriting peanut allergy was estimated to be 81.6%, a percentage similar to other allergic diseases, such as asthma (87%), atopic dermatitis (74%) and allergic rhinitis (74–82%) (42).

There is also a possible association with Human Leucocyte Antigen (HLA) class II genes (43). Howell et al. (43) concluded that while other genetic factors may be important, results from their study (individuals from 37 families and nine unrelated patients)

indicated that HLA class II genetic polymorphism may play a role in determining susceptibility to peanut allergy.

Ethnicity. Though it appears that peanut allergy is increasing in prevalence, little evidence speaks to the ethnicity of children suffering from it. It is unclear whether the general trend reflects changing referral patterns, a change in all allergic conditions, or an effect specific to peanut allergy. Anecdotally, over the past 10 years, there has been a disproportionate increase in the proportion of children diagnosed with peanut allergy from nonCaucasian ethnic groups in the UK (44). In contrast, it has been noted that the high occurrence of peanut allergy in the UK may not be typical of all countries in the world, with peanut allergy reported only rarely in countries in Africa and Asia (45). The lower occurrence in these countries could be explained by differences in the genes of the population, or they could be due to some other environmental factor, such as different types of infections or consumption practices (see *Environmental factors*).

Environmental factors

Environmental exposure to peanut. It has been observed that in countries in Africa and Asia where environmental exposure to peanuts is high, there is nevertheless a low reported prevalence of peanut allergy (45). One possible explanation is that oral tolerance induction through early infant feeding protects these populations against allergic sensitization (46, 47). Some data suggest that

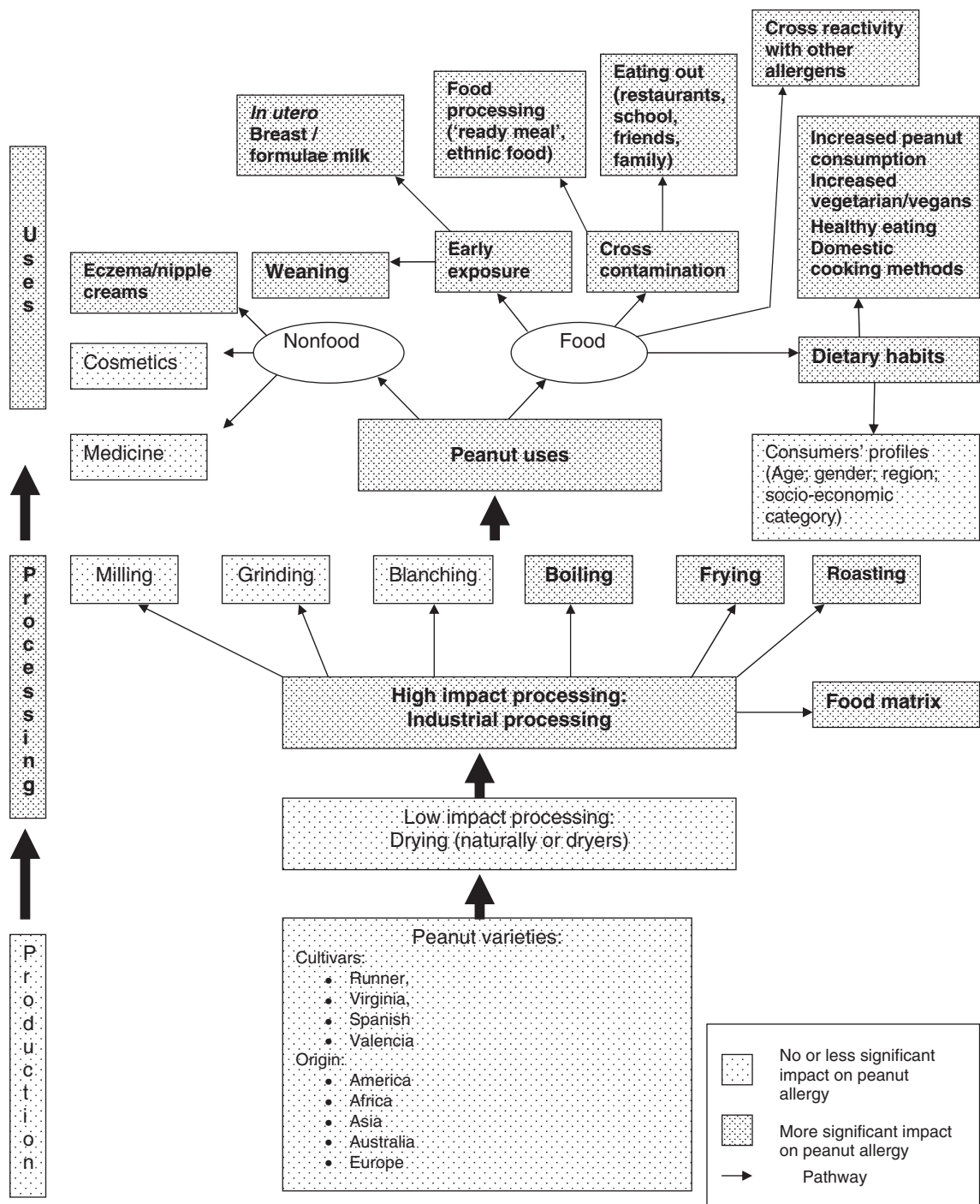


Figure 2. Generic peanut food chain schema.

exposure to environmental peanuts during infancy promotes sensitization and that low levels may be protective in atopic children (see Fig. 3). This supports the hypothesis that peanut sensitization occurs as a result of environmental exposure (44). No special effect of maternal consumption during pregnancy or lactation has been observed.

Perry et al. (48) describe the presence of environmental peanut allergen, which could potentially represent another source of topical exposure. Perry et al. (48) measured by enzyme-linked immuno-

sorbent assay (ELISA), the Ara h 1 peanut content on cafeteria tables and on hands and tabletops, as well as aerosolized peanut allergen during the consumption of peanut. Whereas Ara h 1 was undetectable on hands after washing with soap and water, it was detectable on a quarter of hands after washing with water alone and half of hands after washing with a hand sanitizer. Most cleaning agents removed peanut allergen from tabletops, but Ara h 1 was detectable after dishwashing liquid cleansing on a third of tabletops. Interestingly, airborne Ara h 1 was undetectable in simulated real-

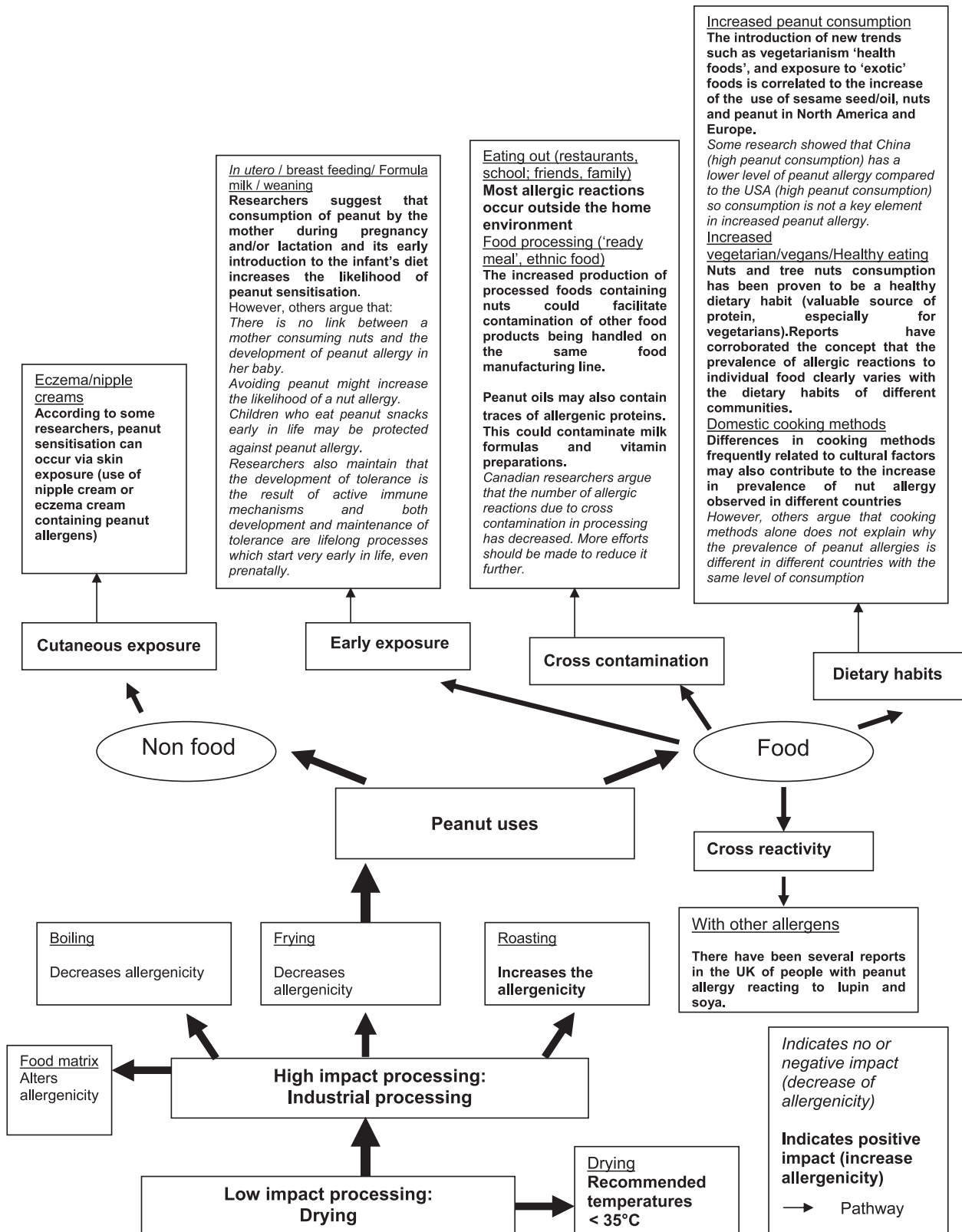


Figure 3. Literature review finding of factors influencing peanut sensitization.

life situations. These data can be interpreted in two ways. On the one hand they imply that it is relatively easy to take environmental measures (e.g. hand washing and cleaning of surfaces) to protect against environmental exposure and allergic reactions. This is good news for the allergic sufferer. On the other hand, the detection of low-level peanut allergen on hands and surfaces that are not washed represent a risk for atopic infants exposed to peanut-eating parents and siblings. This environmental exposure could represent a potential source of cutaneous sensitization (45).

Microbes. Epidemiological investigations have identified that early exposure to microbes may be an important factor for allergy and asthma, perhaps acting as an 'immune educator' (46). It has been suggested that babies are born with an immune system tending towards allergic patterns of response. This acts as a survival mechanism by protecting against infection from faecal matter that could be present at birth. Warner believes that exposure to ordinary microbes is the key to switching off this mechanism, and that this should happen just after birth (49). The 'hygiene hypothesis' suggests that scarcity of microbial exposure during childhood interferes with the development of the immune system and may be one cause of the allergy epidemic in Western countries (45, 50, 51). Growing concern over the adverse immunologic effects of progressively more hygienic environments has led to enormous interest in the role of microbial products such as probiotics in the prevention and treatments of allergic disease (52).

The hygiene hypothesis has two aspects. Firstly, exposure to microbes (pathogenic or nonpathogenic [commensal and dietary]) can inhibit the process of sensitization. For example, a study of asthma in a farming community showed that farm exposure may reduce the risk of asthma in adults (53). Although it is not clear which farming-related factors give protection, several studies have suggested that contact with livestock may play an important role (54, 55). Indeed, livestock farming is known to be associated with increased exposure to bacterial endotoxin and/or other microbial agents which may inhibit Th2 cell immune responses and the subsequent development of Th2-dependent diseases, including allergic asthma, hay fever and eczema (56, 57). However, the exact mechanisms by which the process of sensitization is inhibited are less clear and the subject of some debate.

Of course, nutrition provides factors, including nutrients, that can influence immune system maturation and responses. It also provides factors that influence intestinal flora and this, in turn, affects antigen exposure, immune maturation and immune responses. Through these mechanisms it is possible that nutrition early in life may affect later immune competence, the ability to mount an appropriate immune response upon infection, the ability to develop a tolerance response to 'self' and to benign environmental antigens, and the development of immunologic disorders (46).

The second aspect of the hygiene hypothesis relates to chronic infections (e.g. with parasites). In this case, there is no inhibition of sensitization to allergens (including peanut) but inhibition of clinical allergy in the presence of sensitization, most likely by anti-inflammatory Treg responses. In a study conducted in Ghana, Yazdanbakhsh and Boakye (58) observed that allergies may be partly explained by differences in the burden and chronicity of parasites or parasite species.

Aspects of the peanut food chain

Role of cultivars. According to the literature, different peanut cultivars grown in a particular location do not lead to greater or more frequent allergic responses. Koppelman et al. (59) analyzed four different peanut cultivars, cultured in various parts of the

world, for protein content and composition. Peanut allergens Ara h 1 and Ara h 2 were quantified and IgE-binding properties were assessed. The results suggested that peanuts of different varieties and from different parts of the world contain similar proteins, and consequently, that the IgE-binding properties are similar to a great extent. Koppelman et al. (59) concluded that differences in serology between peanut allergic patients from different parts of the world are not explained by the allergen composition of different peanuts. Another study by Riecken et al. (60), analysing an Indonesian variety, concluded that the allergenicity of peanuts containing less Ara h 1 might be compensated by other allergens, such as Ara h 3 and Ara h 4.

Nevertheless, scientists are searching for peanut cultivars that would be less allergenic than others (61). An *in vitro* study showed that high-oleic peanuts were not different from other peanut cultivars in allergenicity, though Chung et al. (62) suggest that high-oleic peanuts could be less allergenic than other peanuts if analyzed *in vivo* (i.e. in mice or humans). This is because the intake of linoleic acid is lower with high-oleic peanuts than with other peanuts. While this is only a hypothesis, the high-oleic peanuts are thought to warrant further investigation.

Role of processing methods. While the research literature on peanut processing methods is not extensive, there is some evidence that specific aspects of processing may contribute to peanut allergy. In particular, as identified in Figs 2 and 3, thermal processing appears to play an important role in enhancing the allergenic properties of peanuts. The literature indicates that roasting tends to increase peanut allergenicity while boiling and frying have a lesser effect, and perhaps even decrease allergenicity (61, 63–69). Peanut processing methods vary with geographic location, with some countries (e.g. USA) mainly consuming roasted peanuts and others (e.g. China) mainly consuming boiled peanuts. (And hence, we might suppose that the dominant regional processing method matches consumption patterns, though imports may also play a role.)

Many authors have noted that roasting peanuts at very high temperatures rapidly increases allergenicity by altering the protein conformation (7, 61, 63, 64, 70). Moreover, Schmitt and Maleki (71) have reported that roasting, frying and, to a lesser extent, boiling increase IgE binding and advanced glycation end (AGE) modifications while decreasing the solubility and digestibility of peanut proteins. Ara h 1 is more susceptible to thermal processing, due to modification by AGE. Peanut components such as proteins, sugars, and fatty acids may react, particularly during roasting, to give different kinds of end-product adducts (i.e. products covalently linked to the lysine residues of proteins). These include AGE products, which are formed as a result of protein-sugar reactions (i.e. Maillard reaction) (72, 73) and/or protein-lipid reactions (74). Such proteins that are stable to digestion tend also to be the major allergens of foods (75). Like allergens, adducts are capable of stimulating T-cell and antibody responses (76–80).

Boiling peanuts at relatively low temperatures reduces allergenicity (81). Mondoulet et al. (82) reported that the IgE binding capacity of the boiled peanut protein extract was reduced by 50% compared to raw and roasted peanut extracts). Mondoulet et al. (82) reported that while roasting peanuts does not modify their allergenicity boiling decreases it considerably. This decrease of boiled peanut allergenicity comes from a loss of some allergens into the boiling water. It may also be due to structural modifications of peanut proteins that occur in boiling water.

Other processing methods (heat or nonheat related) also appear to be related to peanut allergenicity. Chung et al. (62) suggested that maturation and curing processes may be important. During these processes (which involve heat, dehydration and lack of oxygen),

new types of proteins, namely 'stress' proteins, appear (83) and these stress proteins impact allergenicity (62, 84, 85). More specifically, Chung et al. (62) showed that mature peanuts exhibited higher levels of IgE binding and AGE products compared to immature peanuts. Moreover in curing using drying, their results suggested that higher temperatures provoked higher IgE binding and AGE levels. These authors therefore recommend cooking with temperatures lower than 35°C to avoid peanut allergenicity.

There is also evidence that the food matrix plays a role in the allergenicity of foods. The structure of the food matrix affects the release and stability of allergens and this impacts on the elicitation of reactions in food allergic individuals (86). With fat-rich matrices, such as chocolate, food allergic individuals do not get the same warning symptoms as they would if the allergen was in a low-fat food or eaten in its natural state and this results in more of the food being eaten before a reaction starts [see, for example, Refs (85, 87)]. Clearly, then, differences in the ways in which peanuts are prepared and cooked in different countries and communities might impact on apparent allergy incidence (at least, in the frequency of recorded allergy episodes, though also perhaps in terms of differing exposure levels). However, we are aware of no research that specifically compares dominant national or cultural processing methods with allergy prevalence.

Early exposure. There are a number of factors related to the consumption or uses of peanuts that may be important for allergy (see Figs 2 and 3). The first of these we consider is early exposure – which was hinted at earlier. According to the literature, peanut allergic reaction occurs during first exposure, with a number of researchers suggesting that consumption of peanuts by the mother during pregnancy and their early introduction to the infant's diet increases the likelihood of sensitization (41, 88–91). There is some evidence suggesting that *in utero* exposure to peanuts and/or exposure during lactation can trigger sensitization, as food allergens have been identified in breast milk. This is particularly true where there is a family history of atopy (24, 29, 41, 50, 92–104).

Whilst the latest research suggests that mothers with the lowest dietary intake of vitamin E have the greatest risk of having babies with an allergic tendency in general (105), there have been no studies showing that increasing the dietary intake of vitamin E in mothers decreases the likelihood of their children being allergic. Sasenthaler et al. (100) suggest that maternal diet during the last four weeks of pregnancy has an effect on the development of allergic diseases in the offspring. In particular, high maternal intake of margarine, vegetable oils, deep-frying vegetable fat, celery, citrus fruit and raw seed peppers were positively associated with either eczema or allergic sensitization in children at two years of age, though high fish consumption seemed to *decrease* the risk of eczema (100). It is unclear whether maternal diet has an effect on peanut allergy specifically.

Some researchers claim that prolonged breastfeeding reduces the incidence of atopic diseases, especially in high risk children (6, 30, 41, 90, 91, 106–109). Researchers have also hypothesized that sensitization may occur through traces of proteins in peanut oil that are contained in some infant formulae and Vitamin D preparations (40, 47, 65, 89, 106, 110–118). Increased early exposure may also come through more food products containing small amounts of peanuts, especially in foods frequently consumed in childhood, such as peanut butter (29, 34, 40, 41, 106).

However, the concept of fetal and breast feeding sensitization has been challenged. A recent expert review (119) has questioned the clinical evidence for a protective effect of maternal allergen avoidance [see Ref. (103) for supporting evidence]. According to Lack (45), there is no link between a mother consuming peanuts and the development of peanut allergy in her baby, and indeed, avoiding peanuts might *increase* the likelihood of an allergy. Lack

argues that recent evidence shows that children who eat peanut snacks early in life may in fact be protected against peanut allergy. US-based researchers have suggested that feeding small amounts of a food allergen to children could build up tolerance (120). Researchers also maintain that the development of tolerance is the result of active immune mechanisms and that the development and maintenance of tolerance are lifelong processes which start very early in life, even prenatally (45, 46, 121–126). (See earlier discussion about the hygiene hypothesis.) In summary, although it is frequently claimed that early exposure – whether *in utero*, via breast feeding or during weaning – may increase sensitization, the evidence is contested, and some researchers suggest that the reverse may be the case.

This state of confusion is reflected in the status of advice on this topic in certain countries, and indeed, cross-nationally. Since 1998, advice in the UK has been that pregnant women should avoid eating peanuts if they, the baby's father, or a previous child is allergic to peanuts or has an atopic disease such as eczema (127). Furthermore, it has been advised that children under the age of three should avoid eating peanuts and peanut products, not only to reduce the risk of allergic reaction but also to lessen the risk of choking. However, in the light of suggestions that consuming peanuts while pregnant might build up tolerance, a new report from the House of Lord has recently recommended that the existing UK advice be withdrawn immediately pending a comprehensive review (128). Although we have not considered international recommendations systematically, our analysis has found that in Bulgaria, Poland and Spain (the countries of the non-UK co-authors) official advice regarding peanut consumption during pregnancy or breastfeeding is non-existent. For example, the Bulgarian Ministry of Health issues no formal recommendations, though information on this subject is being exchanged on a personal basis via chat-forums and web sites such as <http://www.bg-mamma.com> and <http://www.alergii.com>. (It is our perception that the issue is receiving growing attention from young and future parents and might invite appropriate governmental measures in the years to come.) Likewise in Spain, there are currently no recommendations or laws that exist regarding peanut consumption during pregnancy or in weaning practices. Recommendations from the national health system concerning babies' general diet do not contain any specific discussion of peanuts. Indeed, up to now the Ministry of Health does not seem to have provided information concerning food allergies in any advertising campaign at national level. Nevertheless, the Catalan Autonomous Government has organized a training session about allergy. Moreover, an allergic people association organizes training sessions about allergy in schools. In this light, the European Academy of Allergy and Clinical Immunology is trying to get a new law passed so that schools are prepared and trained to cope with different allergies (129). What is clear is that further investigation is needed to clarify whether or not allergic food avoidance while pregnant is necessary.

Dietary habits. Several studies have associated dietary intake of various types of fatty acid¹ with risk of the development of allergic diseases, but overall the available data are equivocal (46). As

¹Peanut components such as proteins, sugars, and fatty acids may react to give different kinds of end-product adducts (i.e., products covalently linked to the lysine residues of proteins). These include advanced glycation end products (AGE) which are formed as a result of protein-sugar reactions (i.e. Maillard reaction) (72, 73) and/or protein-lipid reactions (74). In peanuts, AGE adducts are particularly likely to occur during roasting due to heat-induced protein-sugar reactions. Such proteins that are stable to digestion tend also to be the major allergens of foods (75).

mentioned previously, differences in peanut allergy prevalence have been associated with certain dietary habits, such as early introduction into infant diets and heavy peanut consumption [see earlier, and Ref. (130)], as well as different cooking methods (63) and other, as yet unidentified, factors related to peanut-containing products (in the form of peanut butter) in the regular diet. Other reports have supported the concept that the prevalence of allergic reactions to individual foods clearly varies with the dietary habits of different communities (131). These results imply a need to study peanut consumption patterns and to relate these to allergy incidence.

In the developed world, the introduction of new trends, such as vegetarianism, 'health foods', and exposure to 'exotic' foods, have contributed to the increase of peanut consumption (132). Peanuts have, after all, been shown to be a good source of protein and a good component in a healthy diet. Peanuts are generally eaten either as a whole, in spreads, or in hidden sources (i.e. processed food, commercial products). However, data on peanut consumption is difficult to obtain. The literature provides little detail on *how* peanuts are consumed and by *who*, and dietary surveys typically confound peanuts with other categories.

For example, in Poland, there have been no consumer surveys regarding the peanut market specifically: the only available materials refer to whole markets, namely, the 'nuts and dried fruit market' (133, 134); and the 'salted snacks market' (<http://www.poradnikhandlowca.pl>). Peanuts may belong to both categories, and therefore none of these surveys is satisfactory for making definite conclusions on Polish peanut consumption. A similar pattern occurs in other countries. For example, in the UK the National Dietary survey refers to peanut consumption in the 'nuts and seeds category' (135), and in Spanish dietary surveys peanuts are included within the category of 'nuts and dried fruits' (136). Furthermore, these categories do not reflect all possible ways in which peanuts can be consumed: more research is needed on the consumption patterns of products with peanut-based ingredients (i.e. confectionary products, peanut butter), as well as nonfood products (i.e. cosmetics).

While details on peanut consumption are brief, it is possible to identify some patterns in the literature. For example, in the UK there is evidence to suggest, unsurprisingly, that males eat more peanuts than females, and vegetarians eat more than nonvegetarians (135), while data from Spain suggest that peanut consumption is higher in large towns and varies according to the household's characteristics (136). In addition, data from a report in Bulgaria points to a national preference for roasted peanuts (137). Clearly, however, this data is of limited usefulness, and more systematic data acquisition is necessary with respect to changing patterns of peanut consumption.

Exposure through cross contamination. Research suggests that cross contamination may play a role in peanut allergy incidence, being another pathway of exposure (see Fig. 3). Peanuts can be present in processed foods (not all of which are obvious), such as ice creams, cakes, chocolates and other confectionery products (138), as well as frequently occurring in certain types of cuisine (e.g. Indian and Chinese foods). The production of processed foods containing peanuts as components has increased, which could facilitate contamination of other food products being handled on the same food manufacturing line (139). Eating outside the home can also bring risks of cross contamination: food allergy sufferers appear to experience more reactions to food prepared by others (in restaurants, ice cream shops and bakeries), due to the risk of accidental ingestion of nonlabelled foods (minimal amounts present) than food prepared at home (130). For example, 'buffet' restaurants can be a potential source of cross contamination between different foods because the same cutlery is used for servings and there is re-use of containers that have previously

contained peanuts. Other cross contaminations are linked to peanut oils which may contain traces of allergenic proteins. This could contaminate milk formulas and vitamin preparations. Although it is generally assumed that refined (hot pressed) peanut oil contains no proteins and thus is not allergenic in peanut sensitive patients, Moneret-Vautrin et al. (114) reported two cases of infants being allergic to infant formulae that contained peanut oil and linked the allergy directly to that ingredient, hence, there might be traces of proteins in refined peanut oil (140). Furthermore, it is important to note that some peanut allergy sufferers react to different concentrations of allergen protein. For these people, any traces of peanut could trigger a reaction and cross contamination is a particular problem. Geographical differences in prevalence may thus be due in part to the sources and nature of cross-contamination, and future research ought to look at this potential pathway.

Cross reactivity. Cross reactivity is problematic for anyone suffering from an allergy to a specific substance. Cross reactivity is the ability of an antibody to react with or bind an antigen that did not stimulate its production. As such someone suffering from peanut allergy may also react to soya containing products. There have been several reports of people with peanut allergy reacting to lupin and soya (141–143). The identity of cross reactive agents, and their role in sensitization to peanuts, needs to be established prior to assessing the role of this factor in allergy prevalence.

Cutaneous exposure. Sensitization to food allergens may not occur through oral exposure but rather through other routes, such as low dose topical cutaneous (skin) exposure (45, 47) or exposure in other, diverse, settings such as the home, restaurants, schools and other public places (89, 144–146). Lack et al. (47) showed in a prospective birth cohort study that peanut allergy is associated both with severe atopic dermatitis and cutaneous exposure to topical *Arachis* (peanut) oil. Sensitization to peanut protein may occur in children through the application of peanut oil or eczema cream to inflamed skin or the use of nipple cream with breastfed children. The importance and relevance of these products to allergy incidence clearly requires much greater study.

Other factors

Other factors may impact on the increased prevalence of peanut allergy. For example, some researchers have investigated whether delivery by caesarean section is a risk factor for later allergy. According to Laubereau et al. (147), infants born by caesarean section (17%) had a greater risk of diarrhoea and sensitization to food allergens, both in adjusted and stratified analyses (by cord blood IgE). It is speculated that the different gut flora present in infants born by caesarean section, or other factors, like antibiotics given to the mother, may put the child at risk of allergic sensitization. Caesarean rates vary greatly across the world, and hence this factor could hypothetically explain some part of the variance in allergy prevalence.

Other researchers have looked into the role of transplants in allergies. Peanut allergy can be transferred with a liver transplantation from an allergic donor (148, 149). Food allergy, particularly of peanuts, has also been documented in organ recipients receiving immunosuppressive treatment with Tacrolimus. In contrast, the resolution of peanut allergy following bone marrow transplantation has been reported (150). In each of these cases, operation rates are sure to vary around the world, although given that these procedures are not ubiquitous the transplant factor is unlikely to explain much of the difference in allergy prevalence.

Discussion

Peanuts are a nutritious and tasty foodstuff of especial value to the developing world. However, allergy to peanuts can lead to severe and even life-threatening symptoms – a particular concern given that allergy prevalence appears to be increasing (6). Unfortunately, what actually causes peanut allergy (the mechanism/s involved) is currently unclear. In this light, establishing associations (correlations) between different rates of prevalence and different potentially influencing factors may help to inform the generation of explanatory theories. This paper has started from the position that prevalence rates around the world differ and are undergoing change (although these facts in themselves would appear to require further evidence), and has sought to identify associated factors. While there is evidence of genetic predisposition to allergic disease, researchers such as Barnes (131) argue that the presence of certain polymorphisms (i.e. many forms of genes) is unlikely to explain the increase in allergy prevalence alone, and that environmental, social, cultural and economic factors should not be ignored. Consequently, our analysis has examined genetic and environmental factors, including aspects of the peanut food chain (incorporating production, processing and consumption), with most emphasis on the latter. Figures 1–3 detail the factors that have been mooted to be of relevance and the varying levels of support for their association with peanut allergy prevalence, and our review has elaborated on these. Perhaps the main finding of this review, however, is that significant data gaps exist that undermine our efforts to identify the most significant allergy factors. For example, though exposure to peanuts (particularly at an early age) may be a relevant factor (though whether exposure is good or bad now seems an issue of contention), there is a general absence of relevant high-quality data to enable sound correlations. In short, it is unclear to what extent high and low prevalence populations are exposed to peanuts – either as a food or nonfood source, whether directly or via cross contamination, whether early in life

or not, and in what form (in what matrix; processed through what method, etc.).

We suggest that research needs to focus on the systematic collection of data on allergy prevalence across both developed and developing countries, and on patterns of exposure within these. This would require appropriate dietary surveys (that focus on exposure to peanuts and other potential cross-reactive agents, without subsuming peanuts within other categories), and social surveys to chart different populations' 'peanut experiences'. Given that early exposure and route of exposure may be particularly important, we suggest a need to pay especial attention to aspects such as maternal diet and weaning practices. There is also a need to consider the ways in which peanuts have been processed and otherwise incorporated within food products, and how these vary across different populations. Additional exploration of cross contamination pathways and exposure to nonfood sources is also required. Furthermore, given the hygiene hypothesis, it is important to establish the rates of infection of populations with particular infections (45, 50).

In conclusion, we hope this paper may encourage the conduct of more rigorous studies to fill the identified knowledge gaps. The findings from such extended research are liable to have significant implications, not just for understanding the causative mechanism/s of peanut allergy, but for various relevant stakeholders, from peanut allergy sufferers and their families, to policy makers (regarding setting legislation or recommendations, such as about weaning practices), farmers (regarding choice of cultivar types), processors (regarding preferred processing methods and cross contamination), and so on. Research within the EuroPrevall project is currently attempting to take initial steps in this direction.

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