

Food Allergy: International and Developing World Perspectives

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Abstract

Purpose of Review Epidemiological data on food allergy worldwide suffer from the challenges of variability in methods of diagnosis, sampling, and response rates. There are little data on food allergy in the developing world and populations with food allergy in such settings may suffer from challenges that are different from those experienced by subjects with food allergy in the developed world.

Recent Findings Data based on IgE-mediated food allergy established by food challenge in unselected childhood populations exist only from the USA, Europe, China, Thailand, Australia, and South Africa. In the developing world, barriers to food allergy diagnosis and care include lack of public awareness of food allergy, poor education of health care providers, under- and over-diagnosis of food allergy, lack of access to care, inadequate availability and affordability of testing, insufficient trained health care providers and emergency medication, inadequate labeling legislation, poor availability of food substitutes, and cultural or language issues. Recent data question the use of internationally derived 95 % positive predictive values of

specific IgE and skin prick tests for food challenge outcome in children in developing world settings.

Summary The little data on food allergy from rural and developing world settings suggest that the prevalence may be lower but challenges experienced by patients may be higher than that in the urban developed world. Differences in food sensitization and food allergy rates between populations may reflect genetic variation, unique environmental exposures or both, via epigenetic modulation.

Keywords Food allergy · Epidemiology · Developing countries · Ethnicity · Urban–rural differences

Introduction

Globally, 220–250 million people may suffer from food allergy [1]; however, large areas in the world lack good epidemiologic data, services for diagnosis and managing food allergy, legislation on food labeling, and treatment availability.

The prevalence of allergic disorders such as asthma, allergic rhinitis, and eczema has been rising rapidly across the world. Some evidence exists that there has been a further increase in the developing world but stabilization (of higher rates) in many developed countries [2]. Although it seems likely that food allergy has also been increasing, particularly in first world settings, significant limitations in the quality of the global evidence make that assertion difficult to prove conclusively [3]. Despite the limitations, some authors have already dubbed the increase in food allergy prevalence in westernized countries as the ‘second wave’ of the allergy epidemic following on from the

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increase in allergic respiratory conditions by several decades [4].

Difficulties of and Pitfalls in Food Allergy Studies

Data on the prevalence of IgE-mediated food allergy must be carefully scrutinized to assess whether the studies are reporting reliably on true food allergy in a general population. Many studies have investigated food allergy in selected populations, such as people with other atopic diseases or patients referred to specialist clinics. Furthermore, as studies conducted in different environments may yield different results, it is important to consider whether a population is an urban or rural sample. Studies with small sample sizes may have such wide confidence intervals that they yield no real meaningful information and data may not be applicable to the general population. However, other sampling issues may mar prevalence studies such as selection bias from non-random sampling frames, participation bias due to lower recruitment rates from non-allergic subjects, or attrition bias from non-allergic subjects in longitudinal studies who drop out because of lack of interest.

The frequency and timing of assessments will also affect prevalence rates. Cross-sectional studies reporting on allergy prevalence at a specific age may reflect different results from cohort studies. In addition, cohort studies can either report on the prevalence of food allergy at a specific age or report on the cumulative prevalence of allergy up to that age. This is because food allergy is not static and over the course of time subjects within a cohort will outgrow their food allergy, while other subjects will acquire new food allergies.

The most important consideration, however, is what definition is used for the labeling of a subject as having food allergy. Clinical diagnosis of IgE-mediated food allergy may be difficult and the steps for evaluation include a thorough history and examination; evidence of sensitization by either skin prick tests or food-specific serum IgE antibodies and oral food challenge. The gold standard for diagnosis of food allergy is the double-blind, placebo-controlled food challenge (DBPCFC) since bias is minimized, especially in older children and adults who may report subjective symptoms with open food challenges (OFC). However, a positive SPT or s-IgE with a clear history of food-related allergic response is often used as confirmatory of food allergy, especially when using “cut-off levels” with ≥ 95 % positive predictive value for SPT or s-IgE [5, 6].

Epidemiology is, however, different from clinical practice and outcomes reported in the literature include self-reported food allergy, food sensitization alone (and at

different levels of sensitization), a combination of sensitization and symptoms, as evaluated by OFC and DBPCFCs.

Questionnaire studies on self-reported food allergy are relatively common as they are generally easy and cheap to perform. However, self-reported allergy rates far exceed rates of both sensitization and true challenge-proven food allergy. Other obstacles to such studies in developing world settings may be lack of awareness of food allergy and local language, culture, and belief systems.

Although IgE-mediated food allergy requires the presence of sensitization, sensitization studies may significantly overestimate the prevalence of food allergy as many subjects with raised food-specific IgE may be tolerant to those foods. This may be particularly important in developing countries where high allergen sensitization levels are seen in the absence of clinical reactivity [7]. Factors that may be associated with this phenomenon are concurrent helminthic or parasitic infections and cross-reactivity with aeroallergens. Other issues with studies reporting on skin prick testing include interoperator variability, lack of the use of a single standardized lancet/tool, non-standardized reagents, the panel of agents that is selected for testing, and ethnic differences in histamine response.

Despite being less subject to operator and patient bias, DBPCFCs are often substituted by open challenges (particularly in younger children) with preset criteria relying on objective rather than subjective signs. The form of the test food used for the food challenge may affect prevalence rates, for example the use of raw egg, whole (scrambled) egg or “baked” egg (cupcakes) as reflecting egg allergy. In addition, the method of blinding required in DBPCFC may affect the allergenicity or absorption of the foods resulting in a measured lower rate of true food allergy, or differences in threshold doses with matrix effect of blinding agents. The more onerous time requirements for DBPCFC may result in lower response rates and higher drop-out rates in those studies using these challenges as the outcome measure. Finally, the requirements for diagnosis of delayed-type food allergy make assessment of this form of allergy extremely rare in large epidemiological studies.

Quality assessment criteria for the robustness of food allergy prevalence data include the method of diagnosis used and the sampling method, and reasons for non-response, withdrawal, and loss to follow-up have been considered and reported upon [8]. Studies considered at low risk of bias use food challenges (open or double-blind) with or without clinical history as a method of diagnosis or alternatively report on sensitization (skin prick test and/or serum-specific IgE) with a good clinical history. Whole population studies that are randomly selected and with good participation rates, low drop out, or loss to follow-up (or where those not recruited or lost do not differ from those who are finally reported on) are at low risk of bias.

Studies based on sensitization alone, clinical history alone, clinician diagnosed, or self-reported food allergy are considered at high risk of bias. Studies in non-random populations that do not account for low participation rates have significant drop out or loss to follow-up or have differential patient characteristics to the general population may also be at risk of bias.

Food Allergy in Different Parts of the World

North America

In North America, the bulk of published data is from the USA. Between 1997 and 2007, the percentage of children with reported food allergy increased by 18 % and hospital discharges with a diagnosis of food allergy numbered 2615 in 1998–2000, 4135 in 2001–2003, and 9537 in 2004–2006 [9]. While these methodologies are not good at measuring the absolute prevalence of true food allergy, those studies are good enough to show the increased trend in perceived and reported food allergy over time, although this may be effected by increased awareness, increased diagnosis, and reporting bias.

The sole study in North America using food challenges as an outcome considered an urban birth cohort recruited in 1980 and studied until 1983 [10]. This large study showed 7.7 % of subjects had challenge-proven food allergy within the first 3 years, with 4.4 % being proven using OFC and 3.3 % using DBPCFC. There was a clear difference between reported (28 %) and proven food allergy. Other noteworthy studies in the USA have demonstrated differences in food sensitization and/or reported food allergy according to ethnicity and social class [11, 12].

Europe

Of 1341 infants followed from birth in Iceland to age 1 year, 170 reported symptoms and 40 were sensitized to foods. Food allergy was confirmed in 25 (1.9 %) by DBPCFC [13].

Of 609 participants recruited in a birth cohort in Norway, 512 were followed up until age 2 years by which time 35 (6.8 %) had been diagnosed with food allergy either by a history and skin prick test >3 mm or 2 OFC or 1 DBPCFC [14].

A Danish urban birth cohort established in 1998–99 showed food allergy proven with OFC of 3.6 % at age 18 months and 2.3 % at age 3 and with DBPCFC of 1.2 % at age 6. Siblings (of various ages) had a prevalence of 1 % and parents a prevalence of 3.2 % proven with DBPCFC [15, 16].

From a random sample of 6600, adults in Utrecht, Holland, sent screening questionnaires during 2006–2009, 3864 responded and 416 reported adverse food reactions to one of the “priority foods” of egg, milk, peanut, hazelnut, celery, apple, peach, fish, or shrimp. Of these 416, 154 were willing to undergo a more detailed questionnaire and skin prick testing and 58 subjects were sensitized (classified as probable food allergy). Of 18 DBPCFC performed, 14 were positive. Taken as a proportion of the total population who responded, this reflects a “probable” (lowest estimate) of FA as 1.5 % and DBPCFC confirmed FA as 0.36 %. The low response rate and high drop-out rate may have affected the veracity of these figures in reflecting the true community prevalence [17].

The Isle of Wight birth cohort from 2001 to 2002 found a prevalence of IgE-mediated food allergy of 4 % at 1 year, 2.5 % at 2 years, and 3 % at 3 years and a cumulative prevalence of FA of 6 % at any time in the first three years of life [18–20]. At age six, the prevalence had dropped to 2.5 % when measured by OFC or history of a reaction with SPT >3 mm and 1.6 % when DBPCFC or a history with SPT >3 mm were used as the criteria. A population-based study in 2002–2003 found a prevalence of 0.1 % of DBPCFC-proven FA in 11 year olds. In 15 year olds, prevalence varied according to classification methods, OFC-proven FA 1 %, OFC-proven FA or history with SPT >3 2.3 %, and DBPCFC-proven FA 0.5 %.

An urban birth cohort conducted in the UK in 2006–2008 investigated cumulative allergy rates at age 2. 2.6 % of children had IgE-mediated food allergy proven by DBPCFC and 2.4 % had non-IgE-mediated food allergy diagnosed by DBPCFC. No subjects had both IgE- and non-IgE-mediated food allergy [21].

A German study found a prevalence of DBPCFC-proven allergy of 3.7 % in adults in Berlin in 1999, with the highest prevalence (4.3 %) in 20- to 39-year-old adults [22].

A Turkish study in analyzing the adolescent ISAAC phase 2 cohort in 2005 recorded an OFC-proven FA rate of 0.16 % [23]. A further study using recruitment from random telephone calls in Istanbul in 2006 recorded a rate of 0.1 % DBPCFC-proven allergy and 0.3 % rate with a criteria of history with SPT >3 mm [24].

Little data are available from Eastern Europe. In Lithuanian, food allergy among school children (self-reported) was diagnosed in 16.4 % [25].

Australasia

Asia is an extremely populous region with diverse populations, environments, and levels of affluence. Data using food challenges are available from China, Thailand, and Australia.

In Chongqing, China, children attending baby clinics for routine immunization visits were recruited into two studies 10 years apart on food allergy sensitization and prevalence. Although parent-reported food allergy did not change significantly between the two studies, food sensitization increased from 9.9 % in 1999 to 18 % in 2009. In 1999, the prevalence of open challenge-proven food allergy in 0- to 2-year-old children was 3.5 %, whereas in 2009 it had increased to 7.7 % (and 3.8 % within the first year of life). This is the first study to show an increase in challenge-proven food allergy prevalence in the same population with the same robust methodology at different time points [26, 27].

A Thai study in Chiang Mai recruited children aged 3–7 from schools during 2010. By open food challenge, 1.1 % were confirmed as food allergic [28]. By screening for sensitization and confirming with open food challenges, 0.45 % of 6-month- to 6-year-old children were found to have food allergy predominantly to shellfish (0.3 %) and egg (0.15 %) [29].

In Australia, a cross-sectional study on infants aged 11–15 months was performed at baby clinics in Melbourne from 2007 to 2010. This large study recruited 2848 infants and found the prevalence of open food challenge-proven allergy to be at least 10.4 %. Milk and shellfish challenges were not performed. The bulk of subjects were diagnosed as allergic to raw egg (8.9 %) and a lower proportion (1.4 %) were allergic to baked egg (cake). Allergy to the intermediate form of cooked whole (e.g., scrambled) form of egg was not reported. Peanut allergy was found in 3 % and sesame in 0.8 % of the participants. This study published extremely clear preset objective criteria by which to judge whether a challenge was passed or failed. Some infants were classified as food allergic on the basis of a reaction occurring within 2 h of food ingestion in the previous 1 month before a scheduled challenge (or 2 months for peanut and sesame), if the subject had a positive (>1 mm) SPT and had been subsequently avoiding the food [30•]. A further study in Australia has demonstrated lower prevalence of nut allergy in families with lower maternal education, lower maternal socio-economic index, rural areas, and Asian children born in Asia rather than Australia [31•].

Although many of the common food allergens are also common in Asia, shellfish allergy seems to be disproportionately frequent [32] and several unusual allergens are encountered such as buckwheat in Japan [33], birds nest in Singapore [34], and chickpeas in India [35].

South America

Little data exist on the prevalence of food hypersensitivity in the 12 countries comprising South America. Most

studies evaluate sensitization (without history of symptoms) and others describe self-reported food allergy prevalence.

Brazil is the largest country with several studies on food allergy epidemiology. Food sensitization has been shown to be more frequent in subjects with irritable bowel syndrome [36] than controls and in atopic children below 12 years (79 %) than controls (25.8 %) [37]. The prevalence of self-reported symptoms in patients with atopic dermatitis has been documented at 22.3 % [38]. More recently, a large parent-reported food allergy study in preschoolers and infants in Brazil reported a prevalence of food allergy of 17.6 and 23.5 %, respectively. The most frequently reported food was cow's milk with a 52.8 % in infants and 42.7 % in preschoolers. The most frequent symptoms reported were rash, diarrhea, vomiting, abdominal pain, and swelling of the mouth and eyes [39].

In Chile, two studies have evaluated sensitization by SPT in pediatric populations and one study by parent-reported food allergy in school-aged children. A high prevalence of food sensitization (38 %) was shown in children with suspected peptic disease referred for endoscopy [40]. In Santiago de Chile, children between 8 months and 15 years evaluated by SPT for 14 food allergens showed the most frequent food sensitization occurred by milk and varied according to age: children under 3 years of age being 7 %, between 3 and 5 being 2 %, and after the age of 5 being 5.9 % [41]. Most recently, 13 % of children in private schools from Santiago reported recurrent symptoms to a food and 6 % reported food allergy. The most commonly reported foods were milk (25 %), chocolate (14 %), egg [11], walnut (10 %), avocado (10 %), banana (10 %), peanut (8 %), shellfish (8 %), fish (6 %), citrus fruits (6 %), and wheat (6 %) [42].

In Colombia, a cross-sectional study of unselected children and adults in Cartagena showed an overall prevalence of self-reported food allergy of 14.9 %. Fruits/vegetables (41.8 %), seafood, (26.6 %) and meats (20.8 %) were the most reported food allergens, and the most frequently reported reactions were skin (61.4 %), gastrointestinal (29.1 %), and respiratory symptoms [43].

In unselected children from Bogota tested for sensitization to fruit extracts, 23 % were sensitized to one food, most commonly corn followed by banana and guava [44].

Recently, a study food sensitization in patients with suspected IgE-mediated food allergy in Medellin showed 29.7 % were sensitized to any food extract [45].

In a phone survey in Argentina, Bozzola et al. found approximately a million people over 18 years old were diagnosed with food allergy, and another million suspected that they have food allergy. The survey postulated that more of 5 % percent of Argentina population have some type of food adverse reactions, and estimated that

the prevalence in children was higher, around 6 %. (<http://www.abcc.org.ar/health-issues—our-hospital/food-allergies>).

Africa

There has been an exponential increase in FA research in Africa [46]. Despite this, most of the data from the continent report food allergy from selected (non-random) cohorts or using sensitization or self-reported food allergy.

Studies in which food allergy was diagnosed by clinical history AND evidence of sensitization to that food have been published by asthmatics from Southern Nigeria [47], self-reported seafood allergy sufferers from South Africa [48], fish processing workers from South Africa [49], Ghanaian school children [7], South African teenagers [50], atopic children from Botswana [51], and asthmatic adults from Northern Nigeria [52].

The first cases of eosinophilic esophagitis in Africa were reported in South African children, referred to a tertiary allergy clinic [53].

Unusual allergens have been reported from Africa such as abalone, mopane worms [54], the wild ‘mogwagwa’ fruit, (*Strychnos madagascariensis*), marula nut (*Sclerocarya birrea*), and black-eyed pea (*Vigna unguiculata*) (Kung SJ, Personal correspondence).

Studies in Africa have clearly demonstrated the fall-off between self-diagnosed allergy and proven FA. As an example, from 22 subjects with perceived fish allergy who were studied further, 15 had evidence of sensitization but only 1 of the remaining 7 who did not, went on to have a positive challenge DBPCFC [55].

The first study in Africa assessing OFC-proven FA in infants with atopic dermatitis recruited 100 children from a dermatology clinic and recorded an IgE-mediated FA prevalence of 40 % in this highly selected population [56].

The sole study from Africa investigating OFC-proven FA in an unselected population is the South African Food sensitization and Food Allergy (SAFFA) study [57]. This study is ongoing in urban Cape Town and the rural Eastern Cape. 1- to 3-year-old infants recruited from schools/creches are tested using questionnaire and SPT for sensitization to peanut, egg, cow’s milk, soya, wheat, fish, and hazelnut. History of a reaction with sensitization is not used as the criteria for diagnosis and an OFC is used to confirm the diagnosis in all children with SPT >1 mm who are not clearly tolerant to an age appropriate portion of that food. Preliminary data from the urban cohort show 2.5 % with OFC-proven FA, most to raw egg (1.8 %) (cooked egg allergy was 0.4 %), followed by peanut (1.2 %), milk (0.2 %), and fish (0.2 %). The (as yet unpublished) results from the rural cohort showed a lower OFC-proven FA rate

of 0.5 % to raw egg (but not to scrambled egg). Both sensitization and OFC-proven FA were significantly lower in rural versus urban communities.

Food Allergy in the Developing World

There are a number of challenges to providing optimal diagnosis and management of food allergies in the developing world, especially in countries which suffer from a “triple burden” of disease, viz. communicable diseases, non-communicable diseases, and trauma/violence. These include lack of public awareness of food allergy, poor education of health care providers leading to inability of health care workers to manage food allergy adequately, both under- and over-diagnosis of food allergy, lack of access to care, inadequate availability and affordability of testing, trained health care providers and emergency medication, inadequate labeling legislation, poor availability of food substitutes, and cultural or language issues.

A major factor is the lack of data from these regions. Much of the research on food allergy has been performed in first world settings and the results “generalized” to other settings without verification of the applicability of the data [58]. Recent data has shown that food allergy and sensitization may be effected by urbanization [59], socio-economic class [60], ethnicity [11], and migration patterns [31, 61].

Laboratory Tests for FS/FA in the Developing World

Commonly used 95 % positive predictive values (PPVs) of specific IgE and skin prick tests for food challenge outcome in children [5, 6] may not be applicable to some developing world populations.

Studies from different parts of world result in different 95 % PPV results [62–64]. In part, this may be because patient selection of “less allergic” children may result in a lower specificity of raised skin prick tests [65]. Values have been determined in first world settings and predictive values for African children have not been determined.

A retrospective, descriptive study of children aged 0–14 years conducted in Cape Town between 2011 and 2014 reviewed the results of children who had undergone open food challenges [66]. Large numbers of patients had negative challenges despite IgE levels being above the internationally derived 95 % PPVs (37 % of patients with IgE >95 % PPV to egg, tested tolerant on challenge, 50 % with cow’s milk IgE >95 % PPV, and 25 % with peanut IgE >95 % PPV). There was not a long delay between laboratory results and food challenges; therefore, the cause

of this disparity is not children having outgrown their allergies, rather that they were inaccurately classified as having allergy by combination of history and high “predictive” cut-off levels. We postulate possible unknown mechanism of immune tolerance present in African children leading to higher levels of sensitization without clinically significant allergy.

Ethnic Differences in FS and FA

In the African setting, a marked disparity has been demonstrated in the drop off between sensitization and food allergy in different ethnic groups. In the study of FA in children with atopic dermatitis, 66 % of children were sensitized to foods but only 40 % were allergic on challenge. Black African children showed lower food allergy rates (34 vs. 46 %) despite higher proportion of sensitization (69 vs. 61 %) than children of mixed (African and Caucasian) ethnicity. This was evident for egg allergy, 24 versus 27 % despite sensitization of 59 versus 46 %; and for peanuts, 15 versus 38 % despite sensitization of 41 versus 50 %.

This results in poorer utility of internationally derived “95 % positive predictive values” in Black African children versus children of mixed ethnicity. Internationally derived “95 % PPVs” performed well in mixed ethnicity children (SPT >8; 88 % PPV, IgE >14; 90 % PPV, AraH2 ImmunoCAP >0.35; 93 % PPV, ISAC AraH2 >0.3 100 % PPV) but poorly in Black African children (SPT >8; 80 % PPV, IgE >14; 57 % PPV, AraH2 ImmunoCAP >0.35; 53 % PPV, ISAC AraH2 >0.3 58 % PPV) [67, 68]. Receiver operator curves for peanut IgE were acceptable in mixed ethnicity subjects (peanut ImmunoCAP 0.87; AraH2 0.91) but not in Black African subjects (peanut ImmunoCAP 0.76; AraH2 0.60).

In the SAFFA study there was, however, no difference in sensitization or FA according to ethnicity in the urban cohort, but there were marked differences in sensitization and food allergy between urban and rural Black African subjects. It is thus possible that ethnicity is a confounder for environmental influences or that there is epigenetic regulation due to environment that may differ according to the underlying genotype.

Environmental Factors in Food Sensitisation and Food Allergy

The possible reasons for the rapid increase in food allergy may include dietary factors such as types and age of food introduction, increased ingestion of “junk foods”, and decreased ingestion of fiber, prebiotics, fat soluble

vitamins, and polyunsaturated fatty acids. In addition changes in ecosystems (and birth practices) result in alterations of microbiome exposure and loss of rural environments, or rapid urbanization may result in reduction of exposure to rural protective factors. Increases in allergen exposure may occur via non-oral routes. The changing burden of infectious disease exposure may result in increased exposure to proinflammatory organisms and reduced exposure to protective infections including chronic parasitic infestation. There has been an increase in the use of medication that may affect allergy such as gastric acid suppressants and painkillers. Many of these changes have occurred predominantly in the developed world but are starting to occur in the developing world as well, perhaps presaging an upswell in food allergy in these settings.

Genetic and Epigenetic Factors in Developing Settings

In addition, populations that have coevolved with parasites may have developed strong genetic predisposition toward Th2 immunity in order to defend themselves, with the resultant increase in tendency toward allergic diseases being offset by their protective rural environments and/or the effects of current/recurrent parasite infestation [69]. If it is true that such communities have a greater predisposition toward allergy (as evidenced by the data suggesting more severe asthma in African Americans independent of socio-economic class and the large numbers of subjects in Europe and UK with allergies from the Indian subcontinent), then the possibility exists for a food epidemic in developing countries to be even more marked than that currently experienced in developed countries.

Conclusion

Developing countries have inadequate capacity to deal with the current burden of allergies and other chronic diseases. If it is true that they will experience a large increase in the prevalence of food allergy, such countries will be less prepared to deal with the increase in morbidity that they may experience and individuals will be less able to access nutritional foodstuffs while avoiding foods to which they are allergic. There is thus an imperative to encourage good primary prevention strategies for food allergy in developing world settings, focusing on those of proven value. The use of emollient therapy in children with atopic dermatitis is not controversial; however, food introduction during “tolerogenic” windows of opportunity is more difficult in settings at high risk of infectious diseases and with significant prevalence of HIV [70]. Therefore, international

protocols for primary prevention of food allergy through dietary interventions need to consider the careful patient selection that will be required in the developing world.

Compliance with Ethics Guidelines

Conflict of Interest Michael E. Levin, Claudia L. Gray, Javier Marrugo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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