



Food allergy in adults in Europe: what can we learn from geographical differences?

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Purpose of review

The aim of this article is to characterize the present state-of-the-art on the topic of food allergies across Europe.

Recent findings

A systematic review and metaanalysis on the epidemiology of food allergy in Europe have been performed by the Food Allergy and Anaphylaxis Guidelines Group of the European Academy of Allergology and Clinical Immunology. The authors had made an extensive search of four different electronic databases which retrieved thousands of hits. A critical appraisal of the documents reduced their number to just over 100 articles covering the period 2000–2012, revealing striking methodological inhomogeneity and blank areas on the map of the continent, particularly for the adult population. A major new development intending to fill in the gaps in the field of food allergy is the launch and implementation of the European Union-funded project 'Prevalence, Cost and Basis of Food Allergy Across Europe,' acronym 'EuroPrevall.' Among the deliverable of the project are several seminal articles on food allergy in adults which are presented in this review.

Summary

The EuroPrevall project confirmed much more reliably and in more detail the existing inhomogeneity in the prevalence of food allergy, which reflects environmental and climate differences between the separate countries, but possibly also the level of public awareness.

Keywords

confirmed food allergy, double-blind placebo-controlled food challenge, food allergy, prevalence of food allergy, sensitization to foods

INTRODUCTION

Europe is a relatively small continent. Still, it hosts a wide diversity in terms of geographical, ethnic, socioeconomic, cultural and culinary differences between the regions and countries constituting its political map. This inhomogeneity is a prerequisite for wide variations in all kinds of morbidities across its territory. The organization of the healthcare services in the separate countries and media-guided public awareness on health-related issues also model the perception of the general public on disease entities, which are deemed important.

Over the past decades, allergies along with climate change and environmental pollution have been invariably considered an adverse consequence of modern development [1]. Human activities have had a profound impact on the biosphere and biodiversity. The creation of genetically modified plant and animal species has raised concerns fueled by the media that foods containing transgenic products could increase the incidence of food allergies – a belief that is not supported by the existing research

evidence so far [2–4]. Still, the perception that food allergies are on the rise (along with all other kinds of allergic morbidities) in the countries of the developed world to which Europe belongs, has driven the topic high up the scale of public interest [5,6]. As a consequence, many people are led to erroneously believe that they are allergic to one or more foods and resort to restrictive diets with potential negative sequelae. Until the beginning of this century, reliable data on the prevalence of clinically manifest food allergy (especially in adults) were patchy and inconsistent, the study protocols used were not comparable, evaluation of intracontinental

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KEY POINTS

- A recent systematic review and metaanalysis on the epidemiology of food allergy in adults revealed huge inhomogeneity of the number of studies performed across Europe and in their methodologies.
- The estimates of the prevalence of food allergies are rather different if based on self-reported subjective data from questionnaires, or if combined with assessment of sensitization to foods with objective methods, or if confirmed with double-blind placebo-controlled food challenges.
- One of its kind project, EuroPrevall, using standardized questionnaires and objective methods has been initiated by the European Commission in 2005, providing a wealth of data on the epidemiology of food allergy in adults in countries from different geographic and climate zones.

differences was based on questionnaires rather than on objective criteria [7].

INVENTORY OF STUDIES ON FOOD ALLERGY IN EUROPE SINCE THE BEGINNING OF THE CENTURY

The European Academy of Allergology and Clinical Immunology has initiated through its Food Allergy and Anaphylaxis Guidelines Group a systematic review and metaanalysis on the epidemiology of food allergy and on the prevalence of common food allergies in Europe [8–10]. The team started searching four electronic bibliographic databases for systematic reviews and metaanalyses, cohort, cross-sectional, and case-control studies on both children and adults. The plethora of retrieved documents made the authors restrict their analysis for publications between the years 2000 and 2012. This was a major undertaking which required sieving through

thousands of articles, which were reduced to 75 publications of acceptable quality and moderate risk of bias to be considered in their systemic review of food allergy prevalence, with 30 studies used for the construct of random-effects metaanalyses. Another 50 articles were selected for analysis of lifetime and point prevalence of allergy to eight most common foods assessed by self-reported surveys, positive skin prick tests, specific Immunoglobulin E (IgE) and food challenges, with 42 studies included in a corresponding metaanalysis (Table 1).

The synthesized data in Table 1 conceal gross disbalances in the source data because of the patchwork of studies of different sizes using diverse protocols. Most studies were performed in children and in countries of northern and western Europe. Consequently, no consistent risk or prognostic factors for the development or resolution of food allergy could be identified, despite the suspected important role of sex, age, country of residence, familial atopic history, and the presence of other allergic diseases. Despite the claim that the reviews were the first to consider the frequency of food allergy by geographical regions, large areas of Europe remained un or underrepresented like the countries in Eastern and South-Eastern Europe. The highly significant heterogeneity in the pooled estimates indicated intrinsic incompatibilities between the studies in terms of the methodology for specific IgE sensitivity assessment and the protocols for food challenges. Thus, despite the abundance of data and the scope of the performed statistical analysis, these pooled results should be interpreted with caution.

BASIC DIFFERENCES BETWEEN FOOD ALLERGIES AND CHILDREN AND ADULTS

The cited systemic reviews on food allergy in Europe shows a deficit of methodologically robust studies in

Table 1. Pooled estimates of food allergy outcomes for all age groups in any European country, compiled from two systematic reviews [8,9]

Food	Overall life-time prevalence	Point self-reported prevalence	Skin prick test positivity	Specific IgE sensitivity	Food challenge positivity
Cow's milk	6.0% (5.7–6.4)	4.7% (4.2–5.1)	2.3% (2.1–2.5)	0.6% (0.5–0.8)	1.6% (1.2–1.9)
Egg	2.5% (2.3–2.7)	3.6% (3.2–4.0)	1.5% (1.3–1.6)	0.2% (0.2–0.3)	1.0% (0.8–1.3)
Wheat	3.6% (3.0–4.2)	1.5% (1.3–1.8)	0.7% (0.4–1.0)	3.9% (3.4–4.4)	0.1% (0.0–0.2)
Soy	1.5% (1.2–1.8)	1.5% (1.2–1.8)	–	3.2% (2.7–3.6)	0.3% (0.1–0.4)
Peanut	0.4% (0.3–0.6)	1.7% (1.5–1.8)	1.7% (1.6–1.9)	8.6% (8.2–9.0)	0.2% (0.2–0.3)
Tree nuts	1.3% (1.2–1.5)	1.8% (1.6–2.0)	0.6% (0.5–0.7)	0.5% (0.08–0.8)	0.1% (0.1–0.2)
Fish	2.2% (1.8–2.5)	0.6% (0.5–0.7)	0.6% (0.5–0.8)	0.7% (0.4–0.9)	0.1% (0.02–0.2)
Shellfish	1.3% (0.9–1.7)	0.7% (0.6–0.8)	–	–	0.1% (0.06–0.3)
Pooled altogether	17.3% (17.0–17.6)	5.9% (5.7–6.1)	2.7% (2.4–3.0)	10.1% (9.4–0.8)	0.9% (0.8–1.1)

adults: many of the otherwise age-stratified figures on the prevalence of allergies to the limited number of eight different foods lack results for patients older than 18 years [9]. Although children grow and gradually mature into adulthood, there are principle differences between the mechanisms and expression of food allergies in the pediatric and adult ages most clearly outlined for the lowest pediatric stratum (0–5 years). In young children, food allergy is usually acquired via the gastrointestinal tract shaping sensitivity toward eggs and milk. Alternatively, adolescents and adults, mainly develop food allergy through primary sensitization to inhalant allergens on the basis of cross-reactivity between proteins in inhalant sources and in some foods [11]. This type of food allergy is often mediated by sensitization to widespread allergens termed panallergens [12]. In adults the most prevalent allergenic foods are of plant origin: fruits, nuts, and vegetables, whereas cow's milk and eggs top the ranking in youngest children. It has been demonstrated that IgE recognition patterns in allergy to peanuts is age dependent [13]. There are also specific circumstances in adulthood predisposing to food allergy, like for instance the proposed link between use of antacids and an increased sensitivity to foods [14]. On the other hand, food allergic reactions in adult patients have a type and severity range similar to children, presenting with mild and local symptoms from the skin and oral mucosa, affecting on the other extreme any visceral organ with the development of a systemic reaction and possible fatal outcome. In adulthood patterns of food allergies change, with new allergies emerging to foods such as crustacean and molluscan shellfish as well as fresh plant foods associated with sensitization to pollen. The lack of a definitive cure means patients with food allergy have to practice lifelong stringent avoidance of the foods to which they react. Furthermore, those at risk of severe reactions must carry rescue medication in case of accidental consumption of their problem food [15].

Alleged reactions to foods in toddlers and young children are a cause of concern and anxiety for their families and are among the most common reasons for visits to the pediatricians' offices. This has prompted intensive research on food allergies in children, leaving at backstage food allergies in adults. Getting a better insight into all aspects of adult food allergy has been now recognized as an unmet need by the respective directorates of the European Commission of the European Union.

FILLING UP THE VOID: THE EuroPrevall PROJECT

Recognizing the importance of food allergies for the health and safety of the European citizens, the

European Commission of the European Union launched in 2005 the project 'Prevalence, Cost and Basis of Food Allergy Across Europe (acronym "EuroPrevall")' [16]. Its main objective was to 'examine the complex interactions between food intake and metabolism, immune system, genetic background, and socioeconomic factors, to identify key risk factors and develop common European databases.' Among the planned milestones were:

- (1) Establishing the prevalence of food allergies in adults and children, and the patterns of reactivity to the main allergenic foods across the climatic and cultural regions of Europe.
- (2) Establishing which environmental factors, such as allergies to pollen and food consumption patterns, are linked to the development of food allergy.
- (3) Providing information regarding the effect of the food matrix and food processing on the allergenicity of foods.
- (4) Ascertaining the socioeconomic impact and cost of food allergies and their treatments, to the European Community.
- (5) Establishing associations between food consumption/exposure to nutritional products specific for different countries and regions and the development of sensitizations clinical food allergy to them.

The project started in 17 European countries with other partners joining in during its course. The field activities lasted four years and seven months. The collected data are been continuously analyzed and have resulted in dozens of scientific publications, many still in preparation.

An epidemiological study involving adults (20–54 years of age) combined surveys in unselected populations and nested case-control studies in allergy out-patient clinics. It was conducted in eight centers, chosen to represent different geographical and climatic regions of Europe (Table 2).

The complex study design and methodology were described ahead of conducting the planned activities [17]. The design involved three phases:

- (1) Phase I: Administration of a screening questionnaire to determine patients with self-reported food allergies.
A community-based survey was conducted among patients randomly selected from the general population. The aim of this short questionnaire was to collect basic information on perceived allergic reactions to foods.
- (2) Phase II: Selection of cases and controls for blood extraction to characterize patients with probable food allergy.

Table 2. EuroPrevall participating centers in different parts of Europe: pronounced intercountry differences in self-reported food allergy symptoms (5th column); positive specific IgE sensitivity to the reported foods outlined the patients with probable food allergy (6th column) and reconfirmed the major differences between the countries [17,18]

City	Country	Region/ Climate	Responders in Phase I	Patients with self-reported food allergy	Patients with probable food allergy
Reykjavik	Iceland	Nordic	n = 2078	n = 295 (14.2%)	n = 173 (8.3%)
Utrecht	Netherlands	Maritime	n = 3865	n = 393 (10.2%)	n = 153 (3.9%)
Zürich	Switzerland	Alpine	n = 2229	n = 373 (16.7%)	n = 187 (8.4%)
Vilnius	Lithuania	Continental	n = 2589	n = 12 (0.5%)	n = 4 (0.2%)
Lodz	Poland	Continental	n = 1497	n = 211 (14.1%)	n = 92 (6.1%)
Sofia	Bulgaria	Continental	n = 2117	n = 23 (1.1%)	n = 4 (0.2%)
Madrid	Spain	Mediterranean	n = 935	n = 177 (16.7%)	n = 70 (7.4%)
Athens	Greece	Mediterranean	n = 1985	n = 116 (5.8%)	n = 18 (0.9%)

The patients who stated in the Phase I screening questionnaire that they experienced reactions to any of the priority foods (priority foods: these included 24 frequently consumed foods known for their allergenic potential: hen's egg, cow's milk, fish, shrimp, peanut, hazelnut, walnut, peach, apple, kiwi, melon, banana, tomato, celery, carrot, corn, lentils, soy, wheat, buckwheat, sesame seed, mustard seed, sunflower seed, and poppy seed), and a random sample of people who had not mentioned any reactions, were invited to take part in this phase. They completed more detailed questionnaires about their lifestyles and dietary habits; blood samples were withdrawn and tested for the presence of specific IgE against selected foods and common environmental allergens.

- (3) Phase III: Performance of double-blind placebo-controlled food challenges (DBPCFC) to determine patients with confirmed food allergy. The patients from the Phase I of the study, who self-reported symptoms of allergy to selected foods, and who had also specific IgE to these foods in the Phase II, were invited to this phase except for those who had a history of anaphylactic food reactions. Those who consented were subjected to DBPCFC with the alleged food(s).

SUBJECTIVE PERCEPTION VERSUS FOOD SENSITIZATION VERSUS CONFIRMED CLINICAL FOOD ALLERGY [18,19"]

The three phases of the EuroPrevall food allergy prevalence study demonstrate the substantial differences which occur when using three different methodological approaches of increasing sophistication and cost to estimate food allergy prevalence. By all means, the starting point is the subjective perception (and conviction) of the individual

patient, that one or more foods consistently cause symptoms when ingested, and these symptoms are deemed 'allergic.' This kind of 'food-allergy-oriented-mind-set' is formed under the influence of personal health-related experiences modulated by the level of 'food-allergy-awareness,' which seems to be different between the separate countries. This country-specific subjective perception of food allergy shaped the self-reported food allergy (life-long or point) prevalence. It can be seen from Table 2 that it ranges between 16.7% in Madrid and Zurich to 1.1% in Sofia and 0.5% in Vilnius. It exceeds manifold the prevalence of true clinically manifest food allergy. The estimates sink proportionally in the respective centers when specific IgE positivity is added to compute the prevalence of probable food allergy.

On top of this 'diagnostic pyramid' stand the results of the most sophisticated and expensive DBPCFC. They are considered the gold standard for confirming the true allergy to a certain food. Unfortunately, too few patients with probable food allergy from the EuroPrevall study consented to be subjected to oral challenges with six of the priority foods. (Priority foods for which food and matching placebo challenge meals were available: shrimp, peanut, hazelnut, peach, apple, celery, hen's egg, cow's milk, fish. No challenges were performed with the last three foods.) Overall, 40 out of 55 challenges (72.7%) turned out reactive, suggestive of a fairly good positive predicative value of assessing the 'probable food allergy status' of the patients first. This high number of patients declining to be subjected to challenge tests demonstrates the level of apprehension alleged food-allergy sufferers have for their allergic condition. The number of DBPCFC differed dramatically between the centers (1 to 29), which did not allow estimation of the prevalence of confirmed FA across the countries.

Table 3. Mismatch between self-reported causative foods and IgE sensitization to foods along with the leading self-reported symptoms [19**]

Top 5 ranking self-reported causative foods		Top 5 ranking IgE sensitizations		Bottom 5 ranking IgE sensitizations		Top 5 ranking self-reported symptoms	
Food	Prevalence (%)	Food	Prevalence (%)	Food	Prevalence (%)	Symptoms	Prevalence (%)
Milk	7.8	Hazelnut	9.3	Soya	2.3	Gastrointestinal	44.5
Apple	5.6	Peach	7.9	Mustard	1.6	Skin	38.8
Tomato	4.3	Apple	6.5	Egg	0.9	Oral allergy	34.8
Egg	4.2	Celery	6.2	Milk	0.8	Respiratory	12.0
Kiwi	3.8	Carrot	6.0	Fish	0.2	Cardiovascular	9.8

There has been a substantial mismatch between the self-reported symptoms of causative foods and the specific IgE sensitization to foods (Table 3).

The order of prevalence of IgE sensitization against different foods was similar between the separate centers and correlated with the prevalence of the pollen cross-reactive allergens Bet v 1 and Bet v 2 ($r=0.86$). IgE sensitization to plant allergen components unrelated to pollen allergens was more evenly distributed and independent of pollen IgE sensitization ($r=0.10$). The most common foods containing allergens not cross-reacting with pollens were sesame, shrimp, and hazelnut. Discussion: IgE sensitization to foods is common, but varies widely and is predominantly related to IgE sensitization to pollen allergens. IgE sensitization to food allergens not cross-reacting with pollens is rare and more evenly distributed.

ACHIEVEMENTS OF THE EuroPrevall PROJECT AND STILL UNMET NEEDS

EuroPrevall has achieved its overall aims and objectives and has delivered a large amount of data, collected in standardized ways. It has identified patients with well-characterized food allergies and made possible the development of a EuroPrevall Serum Bank [20]. A key contribution of EuroPrevall is the provision of good quality data to characterize the risk from allergenic foods. Combining extract-based serology with component resolved diagnosis against the specific clinical background of the patient allowed assessing the risk of severe reactions [21**]. Epidemiological data are already providing a clearer picture of the size of the population at risk in Europe and an indication of the relative importance of different foods. Most importantly the project has created a network of pan-European researchers spanning disciplines from epidemiology to economics, from molecular genetics to clinical science, risk management to food science. This would be a prerequisite for establishing better standards for

the diagnosis and management of food allergies across Europe. An important task would be to work out simpler patient-friendly methods to confirm alleged allergies to a huge diversity of foods. A difficult task to solve would be to identify the objective environmental influences which may help preventing the development of sensitization to different foods.

CONCLUSION

There exist substantial differences in the prevalence of self-reported food allergies in different regions of Europe which may be due to environmental and climate differences but may also reflect the level of public awareness on the subject of food allergy in the separate countries.

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Conflicts of interest

There are no conflicts of interest.

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