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Review article

The prevalence, cost and basis of food allergy across Europe

The development of effective management strategies to optimize the quality of life for allergic patients is currently hampered by a lack of good quality information. Estimates of how many individuals suffer from food allergy and the major foods involved vary widely and inadequacies of *in vitro* diagnostics make food challenges the only reliable means of diagnosis in many instances. The EuroPrevall project brings together a multidisciplinary partnership to address these issues. Cohorts spanning the main climatic regions of Europe are being developed in infants through a birth cohort, community surveys in school-age children and adults and an outpatient clinic study. Confirmatory double-blind placebo-controlled food challenge diagnosis is being undertaken using foods as they are eaten with titrated doses to allow no-effect and lowest-observable effect levels for allergenic foods to be determined. The cohorts will also facilitate validation of novel *in vitro* diagnostics through the development of the EuroPrevall Serum Bank. Complementary studies in Ghana, western Siberia, India and China will allow us to gain insights into how different dietary patterns and exposure to microorganisms affect food allergies. New instruments to assess the socioeconomic impact of food allergy are being developed in the project and their application in the clinical cohorts will allow, for the first time, an assessment to be made of the burden this disease places on allergy sufferers and their communities.

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IgE-mediated food allergy is a disease affecting all age groups and because the only treatment is still avoidance (1), it changes quality of life in a profoundly negative way (2). Allergy sufferers have to deal with disbelief about their condition and face difficulties in managing their social life. Patients' (or allergic children's parents') anxiety about severe reactions can lead to social isolation and mental health problems (3). Everyday activities become complicated, requiring forethought and preparation, even extending to the need for special diets during hospitalization. Clear food labelling regarding food allergens is essential to help allergic consumers manage their condition, although precautionary labelling can lead to unnecessary restrictions (4). Such social problems are compounded by the fact that, whilst knowledge of the diagnosis and treatment of food allergy by health professionals and dieticians should be standard, it is frequently inadequate (5). The majority of food allergies are IgE-mediated, but sensitization to a specific food does not always lead to clinical reactivity. Consequently serological tests for food-specific IgE cannot be used alone for diagnosis. As a consequence of inadequate diagnostic procedures, food allergy is sometimes over-diagnosed (6). On the other hand, food allergy is also often not recognized or incorrectly treated. Therefore, patients still leave the hospital without either a prescription for self-injectable adrenaline or even referral to an allergy specialist after treatment for acute anaphylaxis (7).

Within this context it is the objective of the EU-funded integrated project EuroPrevall (www.europrevall.org) to deliver the information and tools necessary for policy makers, regulators, clinicians and allergic consumers, together with the food industry, to effectively manage food allergies and the allergens that cause them. This is being undertaken in a pan-European manner with a view of improving the quality of life of food allergic consumers. The project includes 56 partners from 21 different countries (from 19 European countries, Ghana, India and China) with additional collaborating centres and partners from the USA, Australia and New Zealand.

Defining the size of the problem – patterns and prevalence of food allergies

It is generally accepted that rates of food allergy vary, estimates of the prevalence of food allergy being generally imprecise. A meta-analysis of studies has found that the incidence of self-reported food allergies ranges between 3% and 35%. The incidence was lower (2–5%) in studies where subjects were assessed for sensitization and symptoms towards foods (8). Very few studies have employed oral challenge procedures (either open or double blind placebo controlled) to confirm diagnosis. These have found that around 1–4% of individuals suffer from food allergy. The reasons underlying the marked heterogeneity are varied and include wide differences in response rates, problems in reliability and consistency of diagnosis across studies (R. Rona, unpublished data) and especially the poor clinical specificity of skin tests and measurement of food-specific IgE (8).

To address these issues, the EuroPrevall partnership is undertaking a series of studies using common protocols (including diagnosis of food allergy) to obtain good estimates of the prevalence of food allergy and identify the major foods involved. As the incidence of food allergy is age dependent, particularly affecting infants and young children, cohorts are being set up in different age groups with a birth cohort covering children from birth to the age of 2½ years, and community surveys in school-age children and adults. Studies in unselected populations are being complemented by a cross-sectional study in the allergy outpatient clinics (Fig. 1). They build on a number of predecessor projects including the Multicentre Allergy Study (MAS) (9) and Infabio (www.gla.ac.uk/infabio; accessed 17 May 2007) birth cohort studies and the ECRHS studies (10). EuroPrevall studies are being undertaken in different centres chosen to represent the different cultural and climatic regions of Europe from the Mediterranean to Iceland and from the UK to Bulgaria (Fig. 1). A set of on-line databases, restricted to the participating centres, have been set up to store and collate all the questionnaire information being collected.

Birth cohort

Birth cohorts have been set up in nine centres (Fig. 1A) and at least 9000 newborns will be recruited over 18 months, with over 5000 babies and their families enrolled into the study so far. Standardized questionnaires are used to collect baseline data from each mother about her pregnancy and the birth of her child, her family's history of allergies, environmental factors and quality of life. This will be followed by standardized telephone interviews when the child is 12, 24 and 30 months old. Any baby that develops symptoms of a possible food-related allergy during this period undergoes a full diagnostic protocol. Some of the babies have already been evaluated, along with age-matched babies as controls, using measurement of food-specific IgE, skin prick test and double-blind placebo-controlled food challenges (DBPCFC) as diagnostic instruments.

Community surveys

Studies in unselected populations are also being set up. The study in adults and in children aged 7–10 years is being undertaken in nine centres representing different climatic regions in Europe, including Alpine (Switzerland), Mediterranean (Spain, Greece), Central Europe (Bulgaria, Poland, Lithuania), Nordic (Iceland) and Maritime (UK, the Netherlands) regions (Fig. 1B).

Outpatient clinic studies

Studies have been started in 12 different centres in Spain, Italy, Greece, Bulgaria, Poland, Czech Republic, Switzerland, UK, the Netherlands, France, Lithuania and Iceland covering similar geographic regions to the birth cohort and community surveys (Fig. 1C).

In the community survey and the outpatient clinic studies, food allergies will be diagnosed by assessing sensitization a panel of 24 foods to foods using serum IgE measurements (Table 1), and complemented by skin prick testing. These foods encompass almost all those that have to be labelled because of their allergenicity as stipulated by Annex IIIa of the Labeling Directive (11), and others, like peach, which is known to be a problem food in the Mediterranean area but not northern Europe, and kiwi, an emerging food allergen. This will allow us to study geographic differences in food allergies in addition to the effects of introduction of new foods into the European diet.

In a second step, the clinical reactivity to foods will be assessed by standardized DBPCFC. These challenges will be done in those infants and children from the birth cohorts showing suspected allergic reactions to food using extensively hydrolysed or amino acid formula as matrices for delivering the allergenic food. For the outpatient clinic studies and a randomly selected sample of school children and adults from the community-based surveys, DBPCFC will be undertaken with priority 1 foods (Table 1). A dessert and a dark chocolate matrix have been prepared for adults and children in which priority 1 foods are hidden, and sensorially tested to ensure they are truly blinded. During DBPCFC, foods will be given in titrated doses which will allow us to obtain information on 'no-observed effect levels' and 'lowest-observed effect levels' for major allergenic foods.

In the future these cohorts offer the possibility of follow-up studies to assess whether rates of food allergy, along with other types of allergic disease, are increasing. Within the project a retrospective assessment of sensitization to selected foods will be undertaken by serological analysis of the ECRHS II of 2001 cohort biobank. However, unequivocal indications of changes in allergy

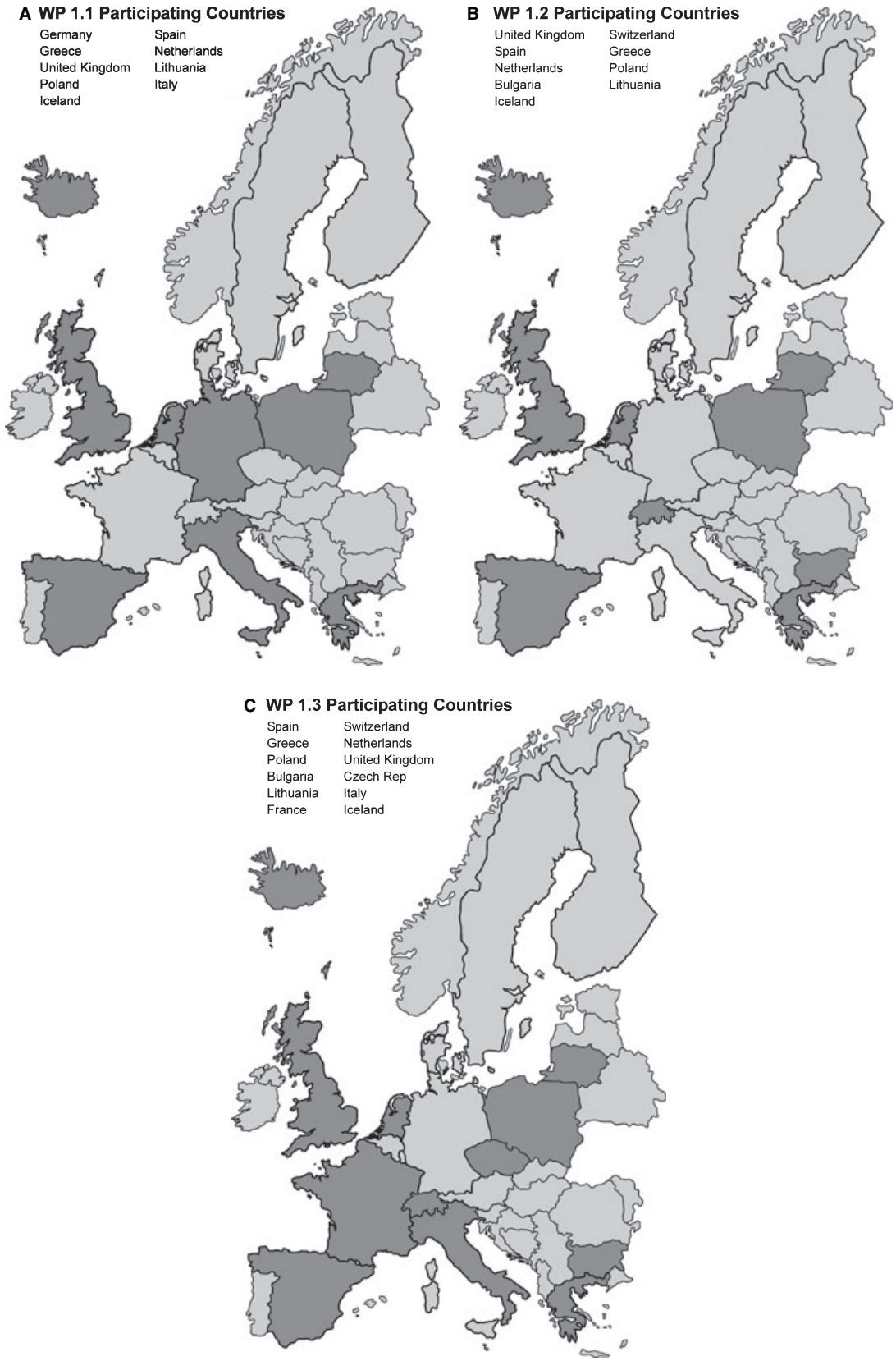

Figure 1. Centres in the pan-European EuroPrevall cohorts: (A) birth cohort study; (B) community surveys in adults and school-age children; (C) outpatient clinic study.

Table 1. Foods being used for serological analysis of food-specific IgE and skin testing in the EuroPrevall cohorts

Priority 1	Priority 2	Priority 3
Hen's egg	Kiwi	Sunflower
Cow's milk	Mustard	Buckwheat
Fish (cod)	Sesame	Banana
Shrimp	Soy	Carrot
Peanut	Walnut	Corn (maize)
Hazelnut	Wheat	Lentil
Apple		Melon
Peach		Poppy seed
Celery root (celeriac)		Tomato

rates will require more comprehensive studies undertaken across a wider timescale.

Socioeconomic impact of food allergies

Food allergy can have a profound effect on the quality of life of European citizens, as well as the European economy. The assessment instruments which are needed to quantify the socioeconomic impact of the disease are not currently available, and are being developed within the EuroPrevall project. Without understanding the socioeconomic consequences of food allergy, the policy community cannot assess its impact on people's experiences of health, or the European economy and industrial competitiveness (12,13). Understanding the complex links between sex, gender and their interaction is an important focus of research (14). In particular, there are gender issues regarding the burden of care for individuals (particularly regarding young children who may suffer from food allergies). Various interventions to improve the quality of life of food allergic patients have been proposed, for example, improved information provision about the disease and its management, better diagnostic techniques and improved allergen traceability through the food chain. The effectiveness of such interventions cannot be judged unless socioeconomic factors can be measured systematically, and subsequent improvements monitored.

Prototype instruments (in Dutch and English) have been developed to assess the impact of food allergy on quality of life and the economic costs of food allergy. This followed a comprehensive review of relevant (existing?) instruments and development of an extended prototype questionnaire which has been refined and reduced. The prototype questionnaires are now being cross-sectionally validated and will be applied in the EuroPrevall cohorts later during the project.

What are the causes?

Food allergy can result from either direct sensitization to foods or cross-reactive IgE responses to inhalant allergens. Patterns of allergy in the EuroPrevall cohorts will be related to patterns of pollen exposure and food consumption. Genetic predisposition plays an important role in the development of allergies, but very little is known about the genetics of food allergy. Genetic aspects will be studied specifically in relation to children with food allergies identified in the birth cohorts, and their parents in order to identify potential inherited factors.

The marked increase in the prevalence of hay fever and asthma over the past decades has been proposed to be caused by decreased exposure to infectious micro-organisms and/or changed commensal flora sometimes referred to as the hygiene hypothesis (15). It is also not known whether protective mechanisms against the development of respiratory allergies also play a role in food allergy. To address one aspect of this, a small study is being undertaken in rural and urban environments in Ghana to investigate the role of infections, particularly parasites, in the development of allergies to peanut, a food widely consumed in Ghana. This will be complemented by studies in India, China and Russia. Emerging economies where lifestyle is changing from a traditional to a modern one coupled with geographic variation in the prevalence of allergic disorders offer an unprecedented opportunity to study the impact of such changes on food allergies. The diverse socioeconomic and culturally heterogeneous populations living in Ghana, India, China and Russia provide unique populations with highly diverse dietary habits, microbial and parasitic exposures. The studies, based on the tools and know-how from the main population studies in the project, will allow us to better understand the role of exposure to microbes and microbial products in the development, persistence and severity of food allergies by studying a whole spectrum of microbial exposure.

Novel diagnostic tools

The EuroPrevall Serum Bank has been set up to collate serum samples for IgE testing in the outpatient clinic cross-sectional survey (Fig. 1C). This forms an important platform to characterize the components in foods, known as allergens, responsible for triggering allergic reactions. An allergen library, representing all the known allergens from all the priority foods identified in the project, is being prepared. To date over 30 natural and recombinant allergens from the priority 1 foods have been prepared and authenticated with regard to their identity (sequence information), folding and, where appropriate, their biological activity. This platform of allergens will be used to explore the feasibility of the 'component resolved diagnosis' concept. Using the EuroPrevall cohorts, studies will ascertain whether assessing patterns of sensitization to individual allergens permits food allergy to be diagnosed with greater sensitivity and specificity than is currently possible with serological analysis using food extracts. Tools for undertaking these studies currently being

developed include the Phadia CAP^{TM} (Phadra, Uppsala, Sweden) and the VBC Genomics allergen chip technology (VBC Genomics, Vienna, Austria). In addition cellular methods able to assess the biological activity of serum IgE are being developed and applied with a Reflab histamine assay using stripped basophils. In addition protocols, have been set up using an alternative histamine release assay based on a humanized rat basophil leukaemia cell line, with a view to undertaking a ring trial to assess its effectiveness and transferability across different laboratories in the project partnership.

Managing the problem

Communication, including the doctor–patient relationship and linking printed information linked with explanation, plays an important role in helping food allergic individuals manage their condition (16). It is also important in dealing with psychological distress and helping allergic individuals adopt the necessary treatment regimens (14). However, as allergy sufferers at present have to avoid problem foods, often for the reminder of their life, there is also a need for others involved in producing and serving food to become partners in the management of food. The responsibility for not eating the allergenic food is primarily that of the patient but to fulfil this task the patient has to be able to rely on information provided by food manufacturers, retailers or catering staff. Food manufacturers can help food allergic consumers protect themselves by informing them when the specific allergen is present in a product (labelling), or by ensuring that it is not present at a level that will cause harm to those consumers (17). However, total absence of a specific allergen in foods, where it is not intended to be present, is usually very difficult to achieve because of manufacturing practices.

Labelling allergens in foods, irrespective of the amount of an allergen present, implies extensive precautionary labelling with no regard to the actual risk. An alternative is to assess the risk arising from a particular level of exposure to an allergen. To do this, the risk must be assessed and characterized, and an estimate made of exposure to the hazard. This process requires knowledge of the amounts of allergenic food which do not trigger a reaction (thresholds). Whilst these can only strictly be determined for individuals, where enough individual data exist, they can be used to define population reactivity and to make predictions about the likely frequency of reaction in that population (18, 19). Adequate information on thresholds is currently limited largely to the most prominent allergens (peanut, milk, egg) and the data remain fraught with several limitations (20). In the EuroPrevall project individuals will undergo food challenges starting at very low doses, so that true individual thresholds can be established. Furthermore, these individuals will be drawn from a true random sample of the populations examined, and the studies will therefore permit conclusions to be drawn about the reactivity of the whole allergic population. They will thus answer not only the question 'what is the lowest amount of allergen X that people react to?' but also 'what is the proportion of the population that reacts to Y mg of allergen X?'. Furthermore, this information will be provided for all the priority 1 foods (Table 1).

Understanding how food processing and the food matrix may affect allergenic potential, in terms of either sensitization or elicitation of allergic reactions, is important in making effective risk assessments for novel foods as well as managing known defined allergenic risks. EuroPrevall will contribute to this body of knowledge through a limited study to compare the thresholds for a given food in the dessert and chocolate matrices. The effect of these food matrices on the release and stability of allergens to digestion is being studied using a subset of allergens from the allergen library drawn from the cupin [including the allergenic seed storage globulins from peanut (Ara h 1), soybean, hazelnut (Cor a 11), and pea (Pis s 1) and prolamin superfamilies, including the lipid transfer proteins from peach (Pru p 3), apple (Mal d 3) and wheat/barley]. Residual IgE reactivity (including the destruction of IgE epitopes or appearance of neo-epitopes) will be defined, along with impact on sensitizing potential in animal models.

Conclusion

Through this suite of interconnected studies, the EuroPrevall project partnership aims to obtain the objective information we are currently lacking to manage food allergens and allergies adequately on a pan-European scale. The project will provide knowledge about the prevalence of food allergies, as well as ranking of allergenic foods (food groups) as a function of the number of reactions they provoke both in the overall population and in specific population groups (regarding age and geographic location). These studies also provide a sound basis for studying the evolution of food allergies over time (10–15 years) and hence test the assertion that rates of food allergy, like those of other allergic disease, are increasing. The project will also generate knowledge on the relationship between allergies (sensitization) to environmental agents, such as pollens, and food allergy to establish which environmental factors, such as allergies to pollen, food consumption patterns, are linked to the development of food allergy. This will allow policy makers to address food allergy from a holistic public health perspective. It will also allow us to determine whether these are the same as those implicated in the development of allergic disease in general. An important aspect will be to link these data with those obtained on socioeconomic costs and hence determine the economic impact of food allergies cost on individuals and society.

The EuroPrevall cohorts will also allow us to establish the usefulness of novel methods (component resolved diagnosis, protein/peptide chip technology and cellular methods) for diagnosing food allergy when used in a hierarchical manner. All the data and tools will feed into the development of better strategies to manage allergens in foods, from understanding how different food manufacturing processes may affect allergenicity through to how best to convey allergen information to consumers in food labelling. Only through the breadth and scope of EuroPrevall, bringing together clinical researchers, social scientists, food chemists, plant biologists and risk assessors to study food allergies, can such ambitious goals be achieved and pave the way to improving life for allergic consumers.

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