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Original article

The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology

Background: The epidemiological surveys in children and adults of the EU-funded multidisciplinary Integrated Project EuroPrevall, launched in June 2005, were designed to estimate the currently unknown prevalence of food allergy and exposure to known or suspected risk factors for food allergy across Europe. We describe the protocol for the epidemiological surveys in children and adults. This protocol provides specific instructions on the sampling strategy, the use of questionnaires, and collection of blood samples for immunological analyses.
Methods: The surveys were performed as multi-centre, cross-sectional studies in general populations. Case–control studies were nested within these surveys. The studies in children aged 7–10 years and adults aged 20–54 years were undertaken in eight centres representing different social and climatic regions in Europe.
Results: After a community-based survey collecting basic information on adverse reactions to foods, all those stating they had experienced such reactions, as well as of a random sample of those stating 'no reactions' to foods, completed a detailed questionnaire on potential risks and exposures. Also a blood sample was taken to allow serological analysis to establish patterns of food and aeroallergen sensitization. We also included a questionnaire to schools on their preparedness for dealing with food allergy amongst pupils. Subjects reporting adverse reactions to foods and sensitized to the same food(s) were called in for a full clinical evaluation that included a double blind placebo controlled food challenge (DBPCFC), following a protocol which is described in detail elsewhere.
Conclusions: The outcome of these studies will help to improve our understanding of several important aspects of food allergies in the European Community, providing for more well-informed policies and effective measures of disease prevention, diagnosis and management.

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A substantial proportion of the population in Europe reports adverse reactions to foods. In the centres included in the European Community Respiratory Health Survey (ECRHS) (1) 19% of the population reported 'illness or trouble' caused by eating particular foods, and 12.2% reported that they nearly always

experienced this illness following ingestion of particular foods (2). There were significant differences in the incidence of food-related illness between the different countries ranging from just over 4% in Spain to 18% in Sweden and 19% in Australia. Most likely few of these complaints represent true immunoglobulin E (IgE)-mediated responses, but there are no reliable sources of information on the actual prevalence and the different types of sensitization to foods. Recent reviews of the literature (3, 4) have indicated heterogeneity in the results of different studies, but the conditions under which they have been undertaken are rarely standardized and as a result cross-site comparisons are confounded by many differences in study design and protocols. Nevertheless sensitization to foods may be quite common and appears to be increasing (5), as is true of sensitization to airborne allergens (6, 7). In the UK at least, reports of hospital admissions with food allergy and anaphylaxis, which is often associated with food allergy, are also increasing (8).

In comparison with objective measurements, self-reported adverse food reactions in adults tend to overestimate the prevalence of true food allergies (9), resulting in nutrionally-unbalanced or suboptimal diets and making it difficult to achieve government targets for improving health through better diets.

Given the impact of food allergy on public health and the wellbeing of individual sufferers with the considerable associated socioeconomic costs, improvement in the practices of diagnosis, treatment and prevention of food allergy presents a serious challenge for the European Community. It was for this purpose that the EU-funded multidisciplinary Integrated Project EuroPrevall was launched in June 2005 (10). The overall aim of the EuroPrevall project is to evaluate the prevalence, basis and costs of food allergy.

The EuroPrevall surveys on the prevalence of food allergies in children and adults set out to improve our understanding of several important aspects of food allergies in the European Community, providing for more well-informed policies and effective measures of disease prevention, diagnosis and management.

Methods

EuroPrevall community surveys

The surveys described here were performed as multi-centre, cross-sectional studies in general populations. Case–control studies were nested within these surveys. The studies in children aged 7–10 years and adults aged 20–54 years were undertaken in eight centres representing different social and climatic regions in Europe, including Alpine (Zürich, Switzerland), Mediterranean (Madrid, Spain; Athens, Greece), Central Europe (Sofia, Bulgaria; Lodz, Poland; Vilnius, Lithuania), Nordic (Reykjavik, Iceland) and Maritime (Utrecht, the Netherlands) regions (see Fig. 1). The specific objectives of the study were to estimate:

Figure 1. Map showing centres taking part in the EuroPrevall cross-sectional studies in children and adults.

1. Variation in the prevalence of food allergies in Europe; and
2. Exposure to known or suspected risk factors for food allergies, their association with specific food allergies and the extent to which they explain variations in the prevalence of those food allergies across Europe.

Identifying people with food allergies

The first objective of the EuroPrevall epidemiological surveys in children and adults was to obtain authoritative estimates of the prevalence of food allergies across different European regions. The study focused on IgE-mediated allergies to a number of foods most commonly reported to cause Type I allergic reactions. The foods selected included many which have to be labelled in the EU (11, 12) such as cows' milk, hens' egg, fish (cod, *Gadus morhua*), an example shrimp species (*Crangon crangon*, North Atlantic shrimp), peanut, two examples of tree nuts (hazelnut, walnut) and celery. In addition two stone fruits from the Rosaceae family (apple, peach) were selected since these represent foods involved in cross-reactive allergies between pollens and fruit and which show different patterns of sensitization in the North compared with the South of Europe (13, 14).

Furthermore we examined sensitization to a panel of other foods including soy, wheat, buckwheat, corn, carrot, tomato, melon, kiwi, banana, lentil, sesame seed, mustard seed, sunflower seed and poppy seed. Together these foods are called 'EuroPrevall priority foods' and there are 24 in total. The study aims to identify individuals who (i) report consistent adverse reactions to any of the listed priority foods, (ii) display specific IgE antibodies to any of the listed priority foods, and (iii) mount a specific food allergic reaction in double-blind placebo-controlled food challenge tests (DBPCFC).

Study design – the sample

Sampling areas. It would not have been feasible to select a random sample of areas to study from each country. However, the selection of highly unrepresentative samples is less likely if large areas are selected and if the populations/areas to be studied are defined by pre-existing administrative boundaries. For this reason, the following guidelines were given for the selection of areas for this study:

(i) areas should be selected by pre-existing administrative boundaries; (ii) areas should have total populations of at least 200 000 people; and (iii) areas should have up-to-date sampling frames that could be used to sample children aged 7–10 years and adults aged 20–54 years.

Selection of subjects for Stage I (Screening Questionnaire). A community-based survey was undertaken, aimed at collecting basic information on adverse reactions to foods, using a short questionnaire (Stage I). Subjects completing the questionnaire were intended to form a representative sample of 7- to 10-year-old children and 20- to 54-year-old men and women resident in each sampling area. For reasons of practical feasibility, subjects were recruited by locally adapted procedures of random selection from pre-existing sampling frames such as patients lists of general practitioners (GPs) (in countries where everyone has to be registered with only one GP), city council registration databases, City Health Authority/Hospital registration databases, and primary schools (children). In Athens, a suitable sampling frame for the adult study was not available and quota sampling was used instead, for which no sampling frame is required, with questionnaires administered over the telephone. Quota sampling ensures that certain groups are adequately represented in the study through the assignment of the quota. It tries to ensure representativeness by sampling individuals from known groups in the population or groups of interest to the survey design. We made sure that the subjects in the chosen areas in Athens were proportionally represented with regards to gender (male, female) and age (20–35, 36–44 and 45–54) based on data from Census statistics. A team of interviewers called numbers from a list of phone numbers in Athens and ensured that the quotas would match the proportions with each quota (area, gender, age). Telephone numbers where chosen from a generator in which the code of the area was set.

Individuals who filled in and returned a screening questionnaire were called 'responders' ('Responder I', see Fig. 2). Each study centre determined the strategy most likely to maximize the response rate using methods such as reminder letters or phone calls. As far as possible reasons for nonresponse were determined and coded. If known from the sample frame, information on age and gender was added to the database for all nonresponders. The recommended sample size for the child and adult studies was 3000 per centre (see below). However, taking into account the likely nonresponse rate, the target number was increased in some centres.

Selection of subjects for Stage II (Main Questionnaire and blood extraction). All those who stated in the Stage I screening questionnaire that they had experienced distinct reactions to any of the selected priority foods, as well as of a random sample (see below) of those stating 'no reactions' to these foods passed into Stage II of the study if they responded and agreed to take part in the study ('Responder II', see Fig. 2).

At this point subjects completed a detailed questionnaire on potential risks and exposures, and a blood sample was taken to allow serological analysis to establish patterns of sensitization. All sera were tested for the presence of specific IgE against selected foods (see below) and common environmental allergens. Stage II also included a questionnaire to schools on their preparedness for dealing with food allergy amongst pupils.

Selection of subjects for Stage III (double-blind placebo-controlled food challenge, DBFCFC). Following the Stage II survey, consenting subjects with both specific IgE to the selected foods and self-reported symptoms of allergy to specific foods (Stage I and/or Stage II) were called in for a full clinical evaluation that included a double blind placebo controlled food challenge (DBPCFC) ('Responder III', Stage III), except in those subjects with a history of anaphylactic food reactions. The objective of this stage of the study was to produce at least 30 cases of challenged confirmed IgE-mediated food allergy at each centre (see beyond). A detailed protocol for the EuroPrevall clinical evaluation of patients with food adverse reactions including DBFCFC will be described elsewhere (in preparation).

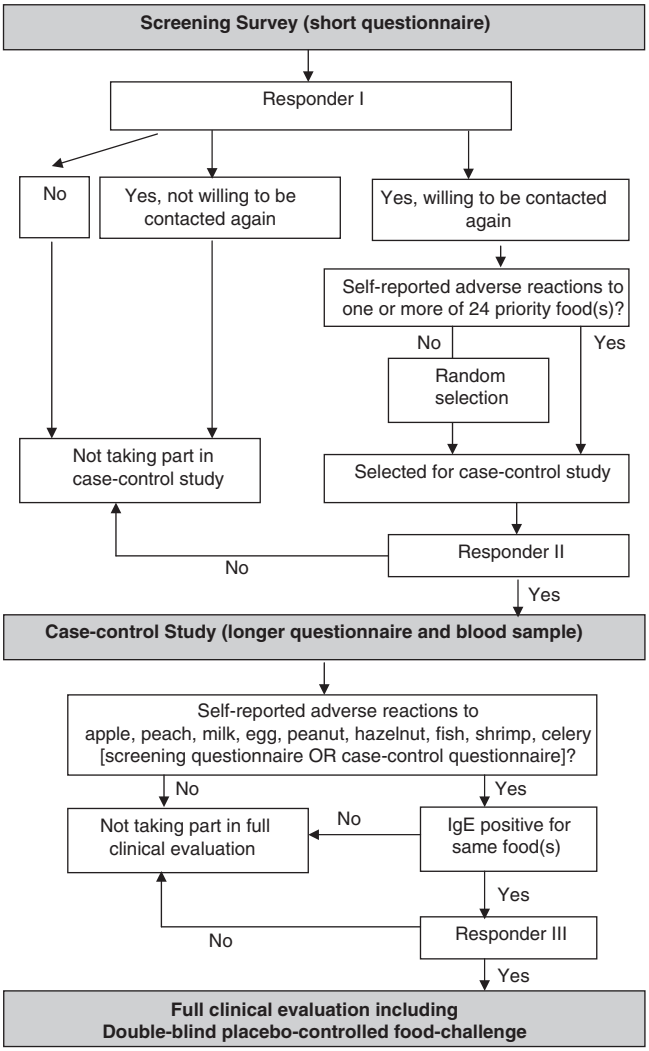

Figure 2. Study diagram showing how subjects were selected for the case-control study or Double-Blind Placebo-Controlled Food-Challenge.

Number of subjects per area

The main sample size was based on several considerations but the central estimate was based on the case–control studies. The most reliable evidence that was available was for the prevalence of reported food intolerance measured in the ECRHS, so the study was powered to assess a case–control study with this as the definition of a case. In the ECRHS only Spain had a prevalence of less than around 8% for intolerance that was consistently reported to a specific food, and most countries had higher prevalences.

A case–control with 240 cases and only one control per case would have 90% power to find an odds ratio of two to an exposure that 15% of the population were exposed to. Using these estimates the eight centres in the child and adult studies would have sufficient statistical power to detect variation between the centres if this existed. Assuming a nonresponse in the case–control study of 20% we needed to contact 300 cases. With an estimated overall prevalence of 10% for adverse reactions to foods, we calculated that we needed to screen 3000 subjects to finally find at least 30 cases of challenged confirmed IgE-mediated food allergy at each centre. For the initial case–control study we powered this to show a result in a single centre, in effect we planned to have eight centres and so there was plenty of additional capacity. This was deemed justifiable because (i) we had no idea of the eventual prevalence levels in some of the centres being studied, and (ii) we planned to undertake other analyses on the risk factors associated with sensitization, and for this we had no reliable data on which to provide a sample size.

The instruments

The questionnaires. Questionnaires were mostly developed based on relevant pre-existing questionnaires, which had already been used in national (9) and multinational studies (such as the European Community Respiratory Health Study; 1). The principle difference from previous questionnaires was that on top of questions of more general character, they also inquired about reactions to the specific foods of interest. The questionnaires were tested for comprehensiveness, translated to the national language of the respective centres, and the back-translated into English. The screening questionnaire was generally sent by post in both the adult and child studies and self-administered, although some centres found this was impractical and they used different approaches like home visits (Vilnius, Lithuania) or administering of the questionnaires by GPs in their office (Sofia, Bulgaria) instead. The clinical questionnaire was administered by trained interviewers in the clinics.

Serum IgE. The levels of serum IgE to twenty-five foods were measured using an ImmunoCAP 250 system (Phadia, Uppsala, Sweden) at a central laboratory, Amsterdam Medical Centre (Amsterdam, the Netherlands). A two step approach was taken to reduce the number of tests required to assess sensitization to all 25 foods. First, the samples were screened using five food mixes (Box 1) to identify samples with elevated specific IgE antibody levels. Samples testing positive ($\geq$0.35 kU_A/l) to a mix were subsequently tested against the individual foods of that mix. Rice is not an official EuroPrevall priority food, but was already included in the fx6 mix, a commercial made mix available at the time that the project started.

The common environmental allergens tested were birch, mite, cat, grass, mugwort, perietaria allergens and also total IgE was measured. Note that 'wheat' appears in two different mixes.

Box 1. Foods tested in CAP analysis (n = 25)

Commercial mixes
CAP mix 1 (commercial, fx5): hen's egg, egg's milk, soy, peanut, wheat, fish
CAP mix 2 (commercial, fx6): sesame seed, wheat, buckwheat, corn, rice

EuroPrevall custom mixes
CAP mix 3 (custom made): hazelnut, tomato, walnut, carrot, celery
CAP mix 4 (custom made): shrimp, poppy seed, lentil, mustard, sunflower
CAP mix 5 (custom made): apple, kiwi, melon, banana, peach

Study procedures

Prior to data collection, investigators from each centre attended a series of training seminars with the study co-ordinator, during which the protocols were explained and the standardized techniques demonstrated. Subsequently, an extensive quality control procedure was implemented in the study, comprising (i) weekly and monthly quality checks of data entries and study progress in each of the centres; and (ii) site visits by the co-ordinator to centres where specific issues needed to be dealt with locally (such as training of staff who had not been able to attend the plenary training seminars, assistance in setting up and monitoring the study in some centres).

The progress of the study

At the time of writing, all centres had completed the first screening phase of the study in children and adults and data cleaning was being conducted. Tasks remaining to be performed before the project can be brought to a successful conclusion include: (i) to complete the second more extensive phase of investigations in children and adults, (ii) a comprehensive analysis of all data collected; (iii) publication and disseminination of results; (iv) formulation of appropriate policy options based on the conclusions from the study. The studies are linked to a birth cohort study and an outpatient clinic study with many common participating centres. This coupled with detailed profiling of sensitization to the foods, including allergen profiling using allergen chip methodology, fuller assessment of dietary exposure to foods and geographic patterns of pollen exposure will ultimately lead to a most comprehensive description of food allergies undertaken in the European population to date (10).

The analysis

The following initial analyses will be undertaken:

1. The distribution of symptoms in relation to age, sex, smoking history, location;
2. The distribution of serum IgE to foods in relation to age, sex, smoking, the mother's and father's smoking histories in the first instance, and location;
3. Supplementary analyses to test which other risk factors are associated with symptoms or with serum IgE to foods. These factors include housing conditions, occupation, ownership of pets, diet, family structure as a proxy for early exposure to infections, and the use of medications; and, finally
4. The association between food allergies and different sensitizations and allergy-related symptoms such as asthma, hay fever and eczema.

Conclusion

The EuroPrevall surveys on the prevalence of food allergies in children and adults will provide unique data on regional variations of the prevalence and risk factors of food allergies in children and adults across major climatic and cultural regions of Europe. The results of this study will contribute to a better understanding of the disease and to the development of strategies for preventing and treating food allergies.

Organizational structure

EuroPrevall overall co-ordinating centre.
Project Leader: E.N.C. Mills

Survey in children and adults co-ordinating centre (described in this paper).
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Partner 48: Children's Hospital Iceland, Landspitali, University Hospital, Reykjavík, Iceland

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