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EUROPEAN STUDY PROTOCOLS

The European Community Respiratory Health Survey

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for the European Community Respiratory Health Survey

The European Community Respiratory Health Survey. P.G.J. Burney, C. Luczynska, S. Chinn, D. Jarvis. ©ERS Journals Ltd 1994.

ABSTRACT: The European Community Respiratory Health Survey (ECRHS) was planned to answer specific questions about the distribution of asthma and health care given for asthma in the European Community. Specifically, the survey is designed to estimate variations in the prevalence of asthma, asthma-like symptoms and airway responsiveness; to estimate variations in exposures to known or suspected risk factors for asthma, and assess to what extent these variations explain the variations in the prevalence of disease; and to estimate differences in the use of medication for asthma.

The protocol provides specific instructions on the sampling strategy adopted by the survey teams, as well as providing instructions on the use of questionnaires, the tests for allergy, lung function measurements, tests of airway responsiveness, and blood and urine collection. The principal data collection sheets and questionnaires are provided in the appendices, together with information on coding and quality control.

The protocol is published as a reference for those who wish to know more of the methods used in the study, and also to give other groups who wish to collect comparable data access to the detailed methodology.

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Background

Since 1990, the European Community's Concerted Action on Asthma Prevalence and Risk Factors (the European Community Respiratory Health Survey (ECRHS)) has been collecting information on the variation in asthma prevalence, known or suspected risk factors for atopy and asthma, and information on the management of asthma. The study has involved: 33 centres in 11 countries in the European Community; seven centres in five Co-operation in Science and Technical Research (COST) states in Europe; and 15 centres in seven other countries who are participating at their own expense. The aim of this article is to give a brief account of the background to the study and its methodology. A full protocol is available, published by the European Commission [1].

Asthma is a serious cause of morbidity in the European Community

Asthma is an increasingly serious cause of morbidity in many countries. When this programme of research began, mortality rates from asthma had been increasing since the mid-1970s and were a serious source of concern in several countries, including England and Wales [2], France [3] Germany, Denmark, the United States [4], and the Scandinavian countries (Bredkjaer, personal communication). The changes in mortality were particularly notable, as mortality from causes of death that were thought to be amenable to medical intervention had been falling rapidly since the early 1950s in almost all countries [5]. Although these increases in mortality now show signs of falling, they have been accompanied by even greater increases in discharge rates from hospitals, particularly among children. Again, this is a trend that has been noted in several countries, including England and Wales [6], the United States [7] and New Zealand [8], and is not a local phenomenon. In England and Wales, there was also a marked increase in consultations with general practitioners for asthma and hay fever between the early 1970s and the early 1980s [9]. Although these changes might have been explained by alterations in medical practice and in the criteria used to diagnose asthma, such an explanation seems unlikely to account for such widespread changes.

The hypothesis that these common trends were due, at least in part, to an increase in asthma prevalence now looks increasingly likely. Analysis of trends in mortality [10], and admissions [11] for asthma, both show "cohort effects" suggesting that the increase in both has been, at least in part, due to changes between generations, rather than simple changes over time that affect all generations equally and simultaneously. This is at

least compatible with the hypothesis that the incidence of disease has changed between the generations. More direct evidence comes from surveys of asthma. These have been criticized in the past, either because they have relied on a diagnosis of asthma, a diagnostic term that may have become more fashionable with time, or because they have been based on local surveys where the population may have changed between surveys. There is now more direct evidence that does not rely on diagnostic terms. Surveys that have documented increases in the prevalence of asthma-like symptoms over time in identifiable populations include studies from the United Kingdom [12–14], Australia [15–16], New Zealand [17], and the United States [18]. Although these studies could, individually, be due to migration or other changes in the local population over time, these are unlikely to explain such consistent results; and in England, the National Study of Health and Growth [19] has shown an increase in the prevalence of "persistent wheeze" in a representative sample of English school children since the start of the study in the early 1970s. This study is spread over a number of different locations and is unlikely to be strongly influenced by local effects of migration.

Asthma is a potentially preventable condition

These findings imply that asthma is a potentially preventable disease. The evidence for this comes from the wide variability of asthma prevalence in populations that are unlikely to have important genetic differences. This is most marked in the developing countries, where very large increases in asthma prevalence have been noted in the urbanized or more westernized areas. Again, this trend has been noted in several different areas of the world, including southern Africa [20, 21], West Africa [22], Papua New Guinea [23] and the Pacific islands [24]. These changes are far too rapid and large to be interpreted as genetic changes, and must be related to some environmental risk. Similar, though less dramatic, variation in prevalence has also been noted in England, where the annual prevalence of nocturnal dyspnoea, a symptom of moderately severe asthma, varied in men aged 20–44 yrs from 2.8–4.8% in different local authority districts sampled in 1986, a significantly greater variation than could be expected by chance [25].

The reasons for these variations are, however, unknown. They could, in part, be due to differences in the prevalence of atopy, a known risk factor for asthma. The Tokelau migrants, when living in New Zealand, [24] showed an increase in the prevalence of rhinitis and eczema, as well as asthma, and this supports this view. However, GODFREY [22] failed to show a comparable difference in skin sensitivity between urban and rural Gambians, to explain the difference he found in the prevalence of asthma. Even if there are wide variations in the prevalence of atopy, there may be other reasons for differences in asthma prevalence.

If the prevalence of atopy does vary, it could be partly due to variation in genetic susceptibility, but it is likely to be more than just this. There is reason to believe that the prevalence of atopy has been rising, as well as the prevalence of asthma. This evidence is based, in part, on evidence that clinically defined conditions, such as rhinitis and eczema, have also been increasing in prevalence [13, 14, 26, 27] and partly on less abundant evidence that the prevalence of atopy as measured by skin tests [28], or specific immunoglobulin E (IgE) [29] might be rising. This rapid increase implies an environmental cause. Exposure to allergens might be expected to have an effect on the prevalence of allergic symptoms, but the evidence for increasing asthma prevalence seems out of all proportion to any increase in exposure to common allergens. One alternative suggestion might be that maternal smoking during pregnancy has increased susceptibility to sensitization with allergens in early life, and that this partly accounts for the increase in asthma prevalence. Although not all studies have agreed with these findings, maternal smoking has been associated with a high cord IgE, a higher incidence of atopic conditions in the first year of life [30], and a higher prevalence of asthma in the early teens [31]. The increase in mortality from asthma has also occurred in England and Wales in generations whose mothers smoked increasing amounts of cigarettes.

As already stated, variations in atopic response are unlikely to account for all the variation in asthma prevalence. Another group of environmental risks that have recently received a great deal of attention are those that cause inflammation of the airway. These include respiratory infections, air pollutants and some occupational exposures. There is substantial evidence that all of these agents can and do incite bronchoconstriction in asthmatics. They would also, for that reason, be expected to increase the prevalence of symptomatic asthma. Whether they can induce asthma in previously normal subjects other than through some allergic mechanism is more open to dispute. Nevertheless, they are potential risks for asthma, and some account needs to be taken of them in a comprehensive assessment of risk factors for asthma in the community.

A further risk factor that has only recently been recognised is that of dietary sodium. This was initially linked to the geographical distribution of asthma mortality in England and Wales [32]. Although this relationship was an ecological association, based on crude estimates of regional sodium consumption, it has stood up well to subsequent investigation. The initial study showed significant associations between table salt purchases in different regions of England and Wales and asthma mortality in adult men and children of both sexes, but not in adult women. A subsequent survey of men living in two villages in Hampshire showed that the bronchial response to histamine was significantly associated with sodium excretion after adjusting for possible confounders, such as body size, smoking and skin sensitivity to common allergens [33]. Finally, two trials have shown that altering the dietary sodium will affect the response to histamine in men [34, 35] but not in women [34].

Reported asthma mortality rates vary markedly across Europe [36], as do treatment patterns [37]. Prevalence rates vary significantly between different areas of England

[25]. It is unknown whether this is true for Europe as a whole. Although a number of groups have completed prevalence studies, the methods used have not been consistent between countries.

Justification for co-ordination

The European Community Respiratory Health Survey (ECRHS) was designed to cover all areas of the European Community and has included other areas also. There were two reasons for such a design. The first was that the environmental and cultural variation across Europe was likely to be far greater than that across any individual area, region or country. The second was that the cost of such a study would have been prohibitive in any single country.

Specific objectives of the study

1. To estimate the variation in the prevalence of asthma, asthma-like symptoms and bronchial lability in Europe.
2. To estimate variation in exposure to known or suspected risk factors for asthma; to measure their association with asthma; and to further assess the extent to which they explain variations in prevalence across Europe.
3. To estimate the variation in treatment practice for asthma in the European Community.

Study design - the sample

Selection of 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: 1) areas should be selected by pre-existing administrative boundaries; 2) areas should have total populations of around 150,000 people; and 3) areas should have up-to-date sampling frames that could be used to sample adults aged 20–44 yrs.

Number of areas

At least 30 areas throughout the European Community were required, in order to allow for some ecological analysis of the differences between areas. The project aimed to collect data from at least three areas in each participating country or region, to reduce the confounding effects of countries and languages. At least some "within country" analysis would then be possible to take separate account of the "between country" differences.

Selection of subjects

Selection of subjects for Stage I (Screening Questionnaire). Subjects should be a representative sample of 20–44 yr old men and women resident in the areas. The selection of these subjects was ideally made by random selection from a suitable sampling frame, but it was recognized that this had to be adapted to local conditions. Individuals who returned a Screening Questionnaire were called "responders". Each centre decided the strategy most likely to maximize response. The point at which any individual was defined as a "nonresponder", for example, if an individual had not returned a third questionnaire after 40 days, was also defined locally. The reason for nonresponse was determined and coded, but if it was not possible to obtain information on all nonresponders, a random sample of these was investigated. It was suggested that the initial sample size should take account of the likely nonresponse rate in each area, with the aim of obtaining 3,000 responders, 1,500 of each sex.

Selection of subjects for Stage II (Main Questionnaire and further tests). The aim of sampling for the second stage was to provide: 1) a random sample of subjects to be studied; and 2) an additional sample of cases to be selected on symptoms.

The random sample was selected from all individuals who had been included in Stage I. This sample inevitably included nonresponders to Stage I. These subjects were not approached for Stage II unless, and until, they had become responders to Stage I, so that the reasons for the nonresponse to Stage I could be ascertained. The aim was to obtain 300 of each gender, that is a 20% sample. If response rates to the two stages were expected to differ, then Stage II could be separately over-sampled to take account of this. The reasons for nonresponse to Stage II were then determined.

The additional sample consisted of 100–150 symptomatic individuals in each area. These were selected from Stage I responders who answered "yes" to any one of Questions 3, 5 or 6 in the Screening Questionnaire and were not already in the random sample for Stage II. If there were too many of these, a random selection was made. If there were less, then all were eligible for Stage II.

Number of subjects per area

The sample size for the study was set at a minimum of 1,500 of each sex to be administered the Screening Questionnaire in each area, and a minimum of 300 randomly selected subjects of each sex to be administered each of the subsidiary tests, including the Main Questionnaire. Each of the two samples (men and women) were randomly selected from the sampling frame. These sample sizes were selected in order to have a 90% chance of detecting a twofold variation in the prevalence between any two areas. These sample sizes assume that the prevalence of symptoms is approximately 5%, and that the prevalence of hyperresponsiveness is approximately 14%.

Estimates of differences in variation in atopy are likely to be more sensitive than this.

The Instruments

The questionnaires

The questionnaires were developed, where possible, from pre-existing questionnaires, which had already been used in multinational studies. The questionnaires were tested for comprehensibility and translated, with back translation into English. The Screening Questionnaire was generally sent by post and self-administered, although some centres found that this was not practical. The Main Questionnaire, and the Screening Questionnaire where this could not be self-administered, was administered by trained interviewers.

Symptoms and medical history. These questions were taken from the bronchial symptoms questions of the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire [38–40]. A version of this questionnaire had already been used in an extensive survey of symptoms in England [25], and a preliminary study comparing the characteristics of the questionnaire in four European countries had been completed [41].

Occupation and social status. These questions were taken from the Office of Population Censuses and Surveys' (OPCS) questions on occupation and social status [42]. They are compatible with the European Community Socio-Economic Status Groups.

Smoking. Questions on smoking habit were adapted from the American Thoracic Society (ATS) Questionnaire [43].

Home environment. The questions on housing conditions were based on those used in the Children's Health Study (Harvard School of Public Health and Canadian Health and Welfare), which surveyed 24 communities in the US and Canada.

Questions on medication and use of services. There was no currently available questionnaire suitable for all countries of the European Community. A new questionnaire was, therefore, devised.

Allergy tests: skin sensitivity and serum IgE

Atopy is a predisposition to develop an IgE-mediated immune response to environmental allergens that do not sensitize nonatopic individuals. The expression of an atopic phenotype requires the interaction of a partly genetic predisposition with environmental allergen exposure. There are several climatic regions in Europe and each has a different distribution of allergens. Therefore, a broad selection of allergens was used in this study.

Skin prick testing. Studies of skin sensitivity are the most practical in epidemiological surveys and are generally acceptable to the public. They give a semiquantitative measure of sensitization and are relatively cheap. Skin testing was carried out using Phazets (Pharmacia Diagnostics AB, Uppsala, Sweden), which are lancets precoated with standardized lyophilized allergen extracts. Except where local regulations made this impossible, a standard list of allergens was used in all centres in the survey. Because there are cross-reactions between allergens, and sensitivity to regional allergens may be found outside the region of that allergen's usual distribution, this list included some allergens which are regionally restricted. The allergens that were selected for use in all areas included: *Dermatophagoides pteronyssinus,* cat, *Alternaria alternata, Cladosporium herbarum,* timothy grass, birch, *Parietaria judaica,* olive and ragweed, with a positive control (histamine) Phazet and a negative control (uncoated) Phazet. Each area could add up to two additional allergens of local importance.

Serum IgE. Specific and total IgE was measured using the Pharmacia CAP System. Specific IgE was measured against *D. pteronyssinus,* grass, cat, *Cladosporium* and a local allergen. These local allergens were birch for northern Europe, *Parietaria* for southern Europe, and ragweed for the US and Canada. Although total IgE has poor sensitivity and specificity for clinical atopy, BURROWS *et al*. [44] report that this is the single best predictor of "asthma".

Measurement of bronchial responsiveness (methacholine challenge)

As a consequence of the difficulties in interpreting the relative prevalence of symptoms elicited in different cultures and in different languages, it is necessary to have a more objective measure related to asthma. Although it is recognized that clinical asthma and bronchial responsiveness are not identical, bronchial reactivity has been shown to be a consistent feature of most asthmatics. Bronchial challenge with inhaled agents, such as histamine and methacholine, has been extensively used in epidemiological surveys. These tests have been widely conducted, particularly in Europe, and there are extensively published data available with which to compare results.

The principal objective of the challenge testing was to obtain standardized measurements between areas. The protocol was, therefore, designed to maximize the comparability of methods between areas, and it was most important that areas were able to use the same equipment for performing lung function tests. The following were selected for the standard methodology:

Dosimeter. Mefar MB3 Dosimeters (Mefar srl, Bovezzi, Italy) was used for the administration of methacholine.

Spirometer. Biomedin Spirometers (Biomedin srl, Padova, Italy) meet the European Commission standards [45] and

have computerized operating systems to ensure quality control to the same standard in each area.

Methacholine. Standard methacholine solutions were made up from lyophilized methacholine chloride (Provocholine, Hoffman La Roche, Basel, Switzerland) in local centres, either by pharmacy departments using standard procedures or by technicians using the agreed study protocol.

Urinary electrolytes

Urine was collected over a 24 h period from male subjects only, and aliquots were taken for the measurement of sodium, potassium, calcium, magnesium and creatinine. Specimens were collected over the weekend, if this was convenient to the subjects, as this has been shown to give equivalent results to collections taken during the week. Analyses were performed in a central laboratory (H. Kesteloot, Leuven, Belgium).

The execution of the study

Prior to data collection, investigators from each of the centres attended a series of training seminars, in which the protocols were explained and the standardized techniques demonstrated. Subsequently, there has been an extensive quality control procedure in the study. This has involved:

1) Visits by members of the central co-ordinating team to two centres in each region, with subsequent visits by members of those regional centres to the other centres in the region. These visits have checked that the protocol is being followed and have noted any deviations from the protocol.
2) Assessment of within-observer variation in results from skin testing with histamine phazets. Fieldworkers had to achieve a set standard before being allowed to undertake these tests on study subjects.
3) Monthly checks on the output of the nebulizers used for challenge tests.
4) High performance liquid chromatography (HPLC) assays of the methacholine solutions from the different centres, undertaken in a central laboratory to check the concentrations.

The progress of the study

At the time of writing, 36 centres have completed the first screening phase of the study and 10 centres have completed the second more extensive phase of investigations. The tasks which remain, in order to bring this project to a successful conclusion, are: 1) a full and co-ordinated analysis of the data collected; 2) the publication and dissemination of results; and 3) the formulation of appropriate policy options based on the conclusions from the study. These tasks present several general, and a number of specific, problems which can be solved but which will be labour intensive.

The analysis

The following initial analyses will be undertaken:

1. The distribution of symptoms and bronchial lability will be studied in relation to age, sex, smoking history, mean skin wheal diameter to all allergens, sodium excretion (after allowing for the confounding effects of height and creatinine excretion), with and without allowing for the independent effects of country and area.
2. The distribution of skin sensitivity and serum IgE will be assessed in relation to age, sex, smoking, the mother's and father's smoking histories in the first instance, with and without allowing for the independent effects of country and area.
3. Supplementary analyses will be run to test which other risk factors are associated with symptoms/bronchial hyperreactivity or with skin sensitivity/serum IgE. These factors will include housing conditions, occupation, ownership of pets, diet, family structure as a proxy for early exposure to infections, and the use of medications.

If independent country or area effects are still present at this stage, information on pollution levels, population density and climate, if available, will be tested for an association with the dependent variables.

Organizational Structure

Co-ordinating centre

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List of participating centres

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COST countries. W. Popp (Austria); T. Gislason (Iceland); A. Gulsvik (Norway); U. Ackermann-Liebrich (Switzerland); N. Lindholm (Sweden); G. Boman (Sweden); L. Rosenhall (Sweden).

Centres taking part at own expense. N. Ait-Khaled (Algiers); M. Abramson (Australia); J. Manfreda (Winnipeg and 5 other centres in Canada); R. Chowgule (India); J. Crane (Wellington and 3 other centres in New Zealand); I. Stepanov (Latvia); S. Buist (USA)

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