Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2010;152:255–263
DOI: 10.1159/000283034

Received: March 10, 2009
Accepted after revision: September 22, 2009
Published online: February 11, 2010

The Gene-Environment Interactions in Respiratory Diseases (GEIRD) Project

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Key Words

Genes · Chronic obstructive pulmonary disease · Asthma · Rhinitis · Case-control · Environment · Inflammatory biomarkers · Diet

Abstract

The role of genetic and environmental factors, as well as their interaction, in the natural history of asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD) is largely unknown. This is mainly due to the lack of large-scale analytical epidemiological/genetic studies aimed at investigating these 3 respiratory conditions simultaneously. The GEIRD project is a collaborative initiative designed to collect information on biomarkers of inflammation and oxidative stress, individual and ecological exposures, diet, early-life factors, smoking habits, genetic traits and medication use in large and accurately defined series of asthma, allergic rhinitis and COPD phenotypes. It is a population-based multicase-control design, where cases and controls are identified through a 2-stage screening process (postal questionnaire and clinical examination) in pre-existing cohorts or new samples of subjects. It is aimed at elucidating the role that modifiable and genetic factors play in the occurrence, persistence, severity and control of inflammatory airway diseases, by way of the establishment of a historical multicentre standardized databank of phenotypes, contributed by and openly available to international epidemiologists. Researchers conducting population-based surveys with standardized methods may contribute to the public-domain case-control database, and use the resulting increased power to answer their own scientific questions.

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Introduction

Allergic rhinitis and asthma affect a large proportion of children and adults [1, 2], and their prevalence rates are still increasing [3–5]. In addition, chronic obstructive pulmonary disease (COPD) represents a major and increasing global health epidemic [6], even in young adults [7]. It is estimated that more than 20% of the general population suffers from at least 1 of these conditions.

All the 3 diseases are characterized by systemic and local chronic inflammation of the upper or lower airways, and there is a considerable overlap in pathogenesis [8], clinical features [9, 10] and epidemiology [11–14]. Asthma and COPD seem to involve a marked oxidant/antioxidant imbalance [15, 16], and they are mediated by oxidative stress, which is caused by inflammation and environmental exposures [17].

Knowledge concerning the natural history of asthma, allergic rhinitis and COPD has made considerable steps forward in the last 20 years, thanks to multicentre surveys that have provided reliable data on their prevalence, incidence, severity and treatment around the world. However, many issues related to the epidemiology and the role of environmental and genetic determinants of the 3 respiratory diseases are still unsolved.

Some of the most interesting unanswered questions are related to:

- the real nature of the associations among asthma, allergic rhinitis and COPD [18, 19];
- the specific and differential role that some environmental exposures (air pollution and indoor exposures) [20], host features (like obesity and overweight) [21] and diet [22] play in asthma, allergic rhinitis and COPD;
- the relationships between oxidant/antioxidant exposures (like diet and occupation), endogenous inflammation and antioxidant gene-regulation [23];
- the reasons (and the determinants) for the large variation observed in the response to treatment [24–27] and in the short- and long-term effectiveness of inhaled corticosteroids [28, 29] in both asthma and COPD;
- the best epidemiological design for genetic studies: the failure to replicate the numerous associations found between genes, and asthma and COPD [30, 31] has been attributed to methodological features, such as insufficient power, genetic heterogeneity and poor definition of the phenotypes [32, 33].

Up to now, almost all of the main epidemiological studies of respiratory diseases have dealt with one disease at a time, defined according to simple epidemiological criteria, and they were generally cross-sectional and descriptive in nature. At this stage, the questions facing present day research indicate the need for powerful, population-based, analytical epidemiological designs covering the whole range of the 3 diseases. These investigations should be able to differentiate the various sub-phenotypes with respect to their: (1) inflammatory profile; (2) objective biomarkers of oxidative stress and history of their oxidant/antioxidant exposure; (3) duration of the disease; (4) treatment and achieved control; (5) genotype.

Aim

The present project is aimed at promoting the establishment of a multicentre 'historical' database and a multicentre biobank, related to phenotypes of asthma, allergic rhinitis and COPD and to controls (subjects without respiratory diseases), who will be accurately characterized according to their inflammatory and genetic profiles and risk factors. This database will be a unique instrument that will help in the investigation of gene-environment interactions in respiratory diseases, and it will be available to European epidemiologists of respiratory diseases who have contributed to the database.

Multicase-Control Design

The ideal epidemiological investigation of gene-environment interactions in respiratory diseases should be a very large study of 'unselected' specific (sub)phenotypes that are well characterized by the time-history of their diseases, exposures and treatment and by the use of objective measurements of markers of inflammation. No single research project would be able to simultaneously satisfy all these features, unless a huge quantity of resources, researchers and time was available.

For this reason, the GEIRD project will use pre-existing or ongoing population-based surveys carried out with similar 2-stage protocols (screening questionnaire and clinical examination), in order to produce an independent public domain database of cases and controls in the next few years. The database will be freely accessible to all scientists worldwide who are willing to share their cases and controls in exchange for the possibility to address their scientific questions with increased power.

The multicase-control design guarantees the possibility to simultaneously study all the inflammatory diseases

of the airways that have common genetic and environmental factors, and to assess the associations of each factor with all 3 diseases. A similar design has already been used in a genome-wide association study of 7 common diseases [34].

Although there are several other types of study that can be used in genetic epidemiology (cohorts, linkage studies, etc.), the population-based case-control study is considered to be the most powerful design to investigate genetic associations [35, 36] for complex diseases, due to its efficiency and the possibility to characterize outcomes and phenotypes more precisely than in other studies [37, 38]. Other designs that have been especially tailored to study the gene-environment interactions have been proposed [39]. However, estimation of the main effects of environmental and genetic factors, which is one of the aims of this project, is not possible in these studies.

The 2-stage strategy to select cases and controls from well-defined cohorts or from new random samples from the general population guarantees that cases and controls come from the same source population [40], and that they have the same degree of phenotypic and genotypic assessment [41].

Finally, the potential bias due to the 'dilution effect' in the relative-risk estimates (i.e. the misclassification bias due to the presence of 'diseased subjects' among controls) is less likely in the multicase-control study than in cross-sectional or case-control studies. In the multicase-control design, subjects belonging to 1 phenotype (e.g. asthma) are compared to controls who are free from all of the inter-related diseases investigated (i.e. subjects without asthma, allergic rhinitis, COPD or chronic bronchitis, CB). In the cross-sectional or case-control design, subjects affected by a specific disease are contrasted with subjects free of that disease. When the controls are affected by correlated diseases (as in the case of asthma, allergic rhinitis and COPD/CB) that share some risk factors, as well as genetic factors, a dilution bias occurs, and the size of this bias is considerable when the outcome is common in the underlying source population [42].

Selection and Identification of Cases and Controls

Because cases and controls have to be identified in pre-existing population-based cohorts or in cohorts whose recruitment is in progress, GEIRD involves a screening phase. Eligible subjects are administered a screening questionnaire, a modified version of a standardized questionnaire [2, 43], which investigates the presence of symptoms of asthma, allergic rhinitis and COPD/CB. According to their responses to the screening questionnaire (www.geird.org), subjects are classified as probable cases of asthma, allergic rhinitis, COPD/CB or probable controls (online supplementary text, www.karger.com/doi/10.1159/000283034).

All probable cases of asthma and COPD/CB, along with a 60% random sample of probable allergic rhinitis cases and a 30% random sample of probable controls, are referred to clinical centres where they undergo the 'phenotypization' protocol. The sampling fractions of 60% and 30% for allergic rhinitis and for controls (whose frequencies largely exceed asthma and COPD/CB), respectively, was adopted to guarantee that the mix of cases was almost balanced, and that the number of controls recruited for GEIRD is not lower than the maximum number of (asthma) cases enrolled in the study (a detailed explanation of the computation of the expected number of cases and controls is reported, see online suppl. text).

Based on clinical ascertainment alongside lung function and allergologic tests, a subject is classified as an asthma, rhinitis or COPD case, or as a control (see online suppl. text).

All cases and controls will be matched by study cohort (frequency matching) and centre.

Phenotypization Protocol

The phenotypization protocol is a set of tests and questionnaires performed in a clinical setting (table 1 gives the list of tests and questionnaires administered in the frame of the project). It consists of: (1) the identification protocol, which is the minimum set of tests necessary to identify cases and controls: the clinical interview, the lung function tests (slow and forced spirometry), the reversibility test, the methacholine test, a blood sample for genotyping and IgE assay, height, weight and blood pressure measurements, and the skin prick test for common allergens; (2) sub-phenotypization protocol, which comprises diffusing capacity of the lung and the 6-min walking test. Moreover, additional tests mainly related to inflammation and oxidative stress are included [44], such as fractional exhaled nitric oxide, exhaled breath condensate, exhaled alveolar air measurements and induced sputum cell count, urine collection for 8-hydroxy-2′-deoxyguanosine (8-OHdG) measurement [45]. One general quality of life questionnaire (SF-36) and specific questionnaires for asthma, allergic rhinitis and COPD will be administered: the Asthma Control Test [46], the Rhin-

asthma [47] and the St. George's Respiratory Questionnaire [48].

The clinical interview is a modification of the European Community Respiratory Health Survey (ECRHS) questionnaire (www.ecrhs.org); the other questionnaires are validated instruments, and all the measurements use standardized techniques according to the European Respiratory Society or the American Thoracic Society guidelines. Questionnaires and measurement protocols can be found at www.geird.org.

The skin prick test will be performed for a set of common allergens, and 33 ml of venous blood will be used for genetic analyses, a complete blood cell count and to extract the serum for IgE titration. A 50-ml spot sample of urine will be taken for 8-OHdG and creatinine determination (see online suppl. text).

Table 1. Tests and questionnaires administered at the clinical stage of GEIRD

	Asthma	Allergic rhinitis	COPD/ CB	Controls
Questionnaires				
Clinical interview	X	X	X	X
Quality of life (SF-36)	X	X	X	X
Asthma Control Test	X			
St. George Respiratory questionnaire			X	
MRC dyspnoea scale			X	
Rhinasthma	X	X		
Clinical laboratory tests				
Weight, waist/hip measure, height, blood pressure, oximetry	X	X	X	X
Spirometry (slow and forced)	X	X	X	X
Methacholine challenge test	X	X		X
Reversibility test			X	
Allergological test (SPT, RAST)	X	X	X	X
6-minute walking test	X	X	X	X
Biomarkers of inflammation[1]	X	X	X	X
Biomarkers of oxidative stress[2]	X	X	X	X
Genetic analyses	X	X	X	X

CB = Chronic bronchitis.

[1] Fractional exhaled NO; pH, hydrogen peroxide, leukotrienes, isoprostanes, TNF-α and interleukine-8 in exhaled breath condensate; percentage of eosinophils, neutrophils, macrophages and lymphocytes in the induced sputum.

[2] 8-hydroxy-2′-deoxyguanosine.

Genetic Protocol

The choice of the candidate genes, as well as the polymorphisms, will be based on literature data and will be updated according to the preliminary results obtained by analysing the Verona samples. Several molecular methods for the analysis of the polymorphisms will be used (see online suppl. text).

House (Nutritional and Environmental) Protocols

All the subjects involved in the phenotypization protocol will receive a home visit, during which they will be administered a nutritional questionnaire, specific occupational modules, a questionnaire about home characteristics and individual total exposure assessment (see online suppl. text).

Outdoor Pollution Protocol

The residential street address collected during the clinical interview will be geocoded by the GPS technology (see online suppl. text). Furthermore, annual summary statistics of air pollutants (NO_2, SO_2, O_3, CO, TSP, and PM_{10}) measured over the years of the study (2008–2010) will be collected in each centre, for ecological comparisons.

Public Domain GEIRD Database

This project will make it possible to establish a large database, including information on biomarkers of inflammation and oxidative stress, individual and ecological exposures (outdoor and indoor air pollutants), diet, early-life factors, smoking habits, genetic traits, and medication use in the cases of asthma, allergic rhinitis and COPD and in the controls. Not all centres and not all subjects will perform all of the measurements and tests described in the general protocol.

A subject will be included in the GEIRD database when he/she has performed the minimum set of tests and questionnaires to be identified as a case or as a control.

The Italian centres initially contributing to the GEIRD database (Ancona, Palermo, Pavia, Terni, Sassari, Torino, Verona) will carry out the clinical interview, the lung function test, the reversibility test, the methacholine test,

the skin prick test, the blood collection for genotyping and IgE assay. Moreover, each centre will have the possibility to extend the study according to its own scientific interests in the frame of the general project.

Other research teams, using case definition and measurement instruments similar to those used in this project, may provide their cases and controls; thus, increasing the size of this database and generating a public domain case-control database. In this way, the public domain database can become a new and innovative research instrument in the field of respiratory epidemiology. In fact, it will allow each researcher to answer his own research question with increased power. The comparability of the data among the centres is guaranteed by the use of standardized methods. However, a certain degree of variability between centres may persist. In order to overcome this problem, all the analyses will be based on the matching of cases and controls by centre and study cohort (frequency matching).

Analysis Strategies

The recruitment of both incident and prevalent cases (as well as controls) for the GEIRD project is currently in progress.

In agreement with the definition, an incident case of asthma and rhinitis is: (1) a member of a pre-existing cohort who fulfils the case identification criteria at the GEIRD follow-up, and who reported the first asthma or rhinitis symptom shortly before the GEIRD assessment (i.e. no longer than 2 years before) but not during the previous contacts; (2) a member of a new random sample who fulfils the 'case criteria', and who reported the first asthma or rhinitis symptom shortly before the GEIRD assessment [49].

As COPD is defined on the basis of lung function measurements, an incident COPD case is a member of a pre-existing cohort with normal lung function at baseline, but who had irreversible airflow obstruction at the GEIRD follow-up.

When studying the association between factors that do not change over time (e.g. genotype, sex, events or exposures in childhood) and respiratory diseases, or when evaluating the determinants of the severity and/or the control of the diseases, there is no need to disentangle incident from prevalent cases. Accordingly, all the cases (and if necessary, all the controls) will be included in the analyses.

When studying potential risk factors that could change over time (e.g. diet, pollution, home characteristics), a potential bias may result when prevalent cases are included in the study because the level of exposure measured in a prevalent case may not represent the level of exposure that a person experienced at the onset of the disease. In this case, the distribution of the determinants being studied will be compared in incident and prevalent cases. If a statistically significant difference is found, incident and prevalent cases will be analysed separately, or the analysis will be restricted to incident cases.

The choice of the appropriate statistical method will depend on the specific hypothesis being tested and on the kind of inclusion criteria (e.g. all cases and controls, only cases affected by 1 disease, only incident cases and controls). In general, all the analyses will account for the hierarchical structure of data (subjects nested into centres, taking the variability among centres into account) and for the different cohorts, using multilevel models [50] or meta-analysis techniques. In the main analyses, the associations of each environmental or genetic factor with all 3 respiratory diseases will be estimated simultaneously, using models for polychotomous outcomes (i.e. multinomial logistic models).

Centres, Cohorts Involved in the Study, Timetable and Organizational Structure

The Italian centres that will initially contribute to the GEIRD database are Verona, Pavia, Torino, Sassari, Ancona, Terni and Palermo. The screening phase will involve more than 25,000 subjects in the 7 participating centres. The pre-existing cohorts involved are: (1) the Italian branch of ECRHS [51] – a general population random sample (aged 20–44 years at enrolment), who were already studied in 1991 and 2000 [13]; (2) the ISAYA cohort [52, 53], made up of random samples from the general population aged 20–44 years in 1999, when they were first studied. Five new random samples aged 20–64 years (with the exception of the Palermo centre where the age ranged from 45 to 80 years), who were taken from the general population, and who were selected with the same sampling method used in ISAYA and ECRHS [43], will also be screened in the Ancona, Terni, Palermo, Pavia and Verona centres.

Using available estimates of prevalence, the expected number of probable cases and controls in the 7 Italian centres are 3,644 and 1,748, respectively (table 2).

Table 2. Expected number of probable cases and controls that will undergo the phenotypization protocol of GEIRD in the Italian Centres

	Verona	Turin	Pavia	Sassari	Ancona	Terni	Palermo[1]	Total
Asthma	465	177	339	112	169	150	196	1,608
COPD/CB	252	110	216	75	–	70	224	947
Allergic rhinitis[2]	325	136	260	84	160	124	–	1,089
Controls[3]	488	184	394	132	170	156	224	1,748
Clinical phase	1,530	607	1,209	403	499	500	644	5,392

Estimates based on the more reliable centre-specific prevalence estimates. In the computation, a response rate of 70% is assumed for the screening questionnaire and an attendance rate of 70% for the clinical stage of GEIRD.

[1] Random sample from the general population aged 45–80 years.

[2] A sampling fraction of 0.60 was applied.

[3] A sampling fraction of 0.30 was applied.

Table 3. Responders to the screening questionnaire, probable cases and probable controls in 3 Italian centres that have concluded the screening phase of the GEIRD project (Ancona and Terni) or completed 3 postal waves (Verona) by June 2009

	Ancona	Terni	Verona	
			pre-existing cohorts	new random sample
Eligible subjects	3,015	2,811	3,900	3,992
Respondents	1,866 (61.9)	1,660 (59.1)	2,559 (65.6)[1]	2,025 (50.7)[1]
Probable cases of asthma	242 (13.0)	244 (14.7)	373 (14.6)	235 (11.6)
Probable cases of COPD/CB	–	95 (5.7)	154 (6.0)	130 (6.4)
Probable cases of allergic rhinitis	260 (13.9)	230 (13.9)	360 (14.1)	296 (14.6)
Probable controls	722 (38.7)	586 (35.3)	992 (38.8)	792 (39.1)

Percentages are reported in parentheses.

[1] Respondents after 3 mail contacts.

Each Italian centre will start the screening phase before September 2009 and the clinical phase before February 2010. The initial databank is expected to be completed by June 2011. The study is managed by a provisional scientific steering committee that is responsible for the implementation, promotion and funding of the project, as well as the scientific use of the databank. This steering committee is also responsible for developing and seeking collaboration with other research teams with the aim of building an international databank. Before the end of the study (2011), a definite steering committee will be established based on all the centres that will participate in the project.

Ongoing Progress of the Study

Local ethics committees approved the study protocols. The screening phase has been completed in Ancona and in Terni with final response percentages of 61.9% (1,866 responders out of 3,015 eligible subjects) and 59.1% (1,660/2,811), respectively. The screening phase is currently in progress in Verona, Pavia, Sassari and Turin. In Verona, the mailed questionnaire was answered by 65.6% (2,559/3,900) of the historical cohorts and by 50.7% (2,025/3,992) of the new random sample after 3 mail contacts. In Pavia, the mailed questionnaire was answered by 30.9% of the new random sample after 2 mail contacts. In Sassari and Turin, people were contacted by mail for the

first time in December 2008 and April 2009, respectively. In Palermo, the screening phase started in September 2009.

The number of responders to the mailed survey, as well as the number of subjects reporting symptoms involved in case selection, are reported in table 3.

Selection Processes and Potential Biases

GEIRD is a 2-stage study. The first stage is aimed at producing representative series of 'probable cases and controls' through the screening of random samples or previous cohorts from the general population. Centres involved in GEIRD were not randomly chosen, but selected on a voluntary base. Nevertheless, they cover all the different regions of Italy (north, centre and south).

The success of the first stage will depend on the level of the response rate. Response rates to mailed epidemiological surveys on respiratory health have decreased in the last decades [54]. This negative trend will probably be confirmed by the present survey, as the response percentage in the first 2 centres (Ancona and Terni) at the end of the screening phase was only 60.5% (3,526/5,826).

A low response percentage could bias prevalence estimates because subjects reporting respiratory symptoms in Italy tend to be early responders, while current smokers tend to be late responders [55].

However, no significant difference between responders and non-responders was detected as regards sex and age in the centres that completed the postal survey: the proportion of women among responders (51.4%, 95% CI 49.8–53.1%) slightly exceeded 50%, which was the initial value in the selected sample. The mean age (SD) was 34.1 $\pm$ 7.0 years among responders and 34.2 $\pm$ 6.8 among non-responders ($p = 0.587$).

Moreover, the decrease in symptom prevalence across subsequent contacts was lower than expected. In the 3 centres where the 3 postal waves were completed (Ancona, Terni, Verona), the prevalence of drugs for asthma and chronic cough and phlegm did not change across subsequent contacts, while the decline in prevalence of asthma attacks and allergic rhinitis was much less pronounced than in a previous Italian study [55].

Similar findings were found in a previous follow-up of 1 cohort involved in GEIRD [13]: responders were slightly older and there was a greater percentage of women compared to non-responders. However, there was no statistically significant difference in symptoms at baseline.

Hence, preliminary data suggest that response to the GEIRD screening phase will be lower than in previous Italian surveys, but also less affected by response bias.

The main issue in the second stage (case-control design) of GEIRD is the comparability of cases and controls. A non-biased design requires that cases and controls come from the same source population, experience the same selection processes and are ascertained with the same accuracy. All these features are guaranteed by the GEIRD design, where potential cases and controls are identified through screening the same population and will undergo a concurrent assessment. Differential selection may occur if the participation rate in the clinical stage is different in probable cases and controls. Hence, this is a potential bias of the ongoing study; its presence, size and consequences can be fully assessed at the end of the study by comparing the screening data of participants and non-participants.

To sum up, the GEIRD design was devised to maximize the likelihood of obtaining unbiased series of cases and controls that are representative of the general population for genetic and environmental studies of respiratory diseases. The degree to which this expectation is actually reached will be fully assessed at the end of the study.

Conclusion

In contrast to cancer epidemiology, the epidemiology of respiratory diseases has scarcely used analytical epidemiological tools (like case/control studies). Consequently, many descriptive results have been obtained, but knowledge about the determinants of respiratory diseases is still limited and contrasting. The GEIRD project is based on a study design that is maximally efficient to answer the most important questions that have emerged in the research on determinants of asthma, allergic rhinitis and COPD. Moreover, the proposed instrument, i.e. the historical multicentre standardized database of cases and controls from the general population, may be enriched thanks to both the contribution of new centres and/or the contribution of new data (i.e. follow-up data). Consequently, the database may be periodically updated to deal with new research issues.

The GEIRD study group invites all the epidemiologists who are coordinating or promoting studies on respiratory diseases in general population to collaborate in establishing an international public domain case-control database to study the environmental and genetic deter-

minants of asthma, rhinitis and COPD. We can be contacted at www.geird.com.

Appendix: The GEIRD Study Group

Principal Investigators of the GEIRD Project

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Coordinating Centre

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Provisional Scientific Steering Committee

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Acknowledgments

The GEIRD Project was partially supported by grants from Fondazione Cassa di Risparmio di Verona, Vicenza, Belluno e Ancona and the Italian Ministry of University and Research.

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