Major long-lasting European studies of the general population

This online supplement includes short summaries of large-scale studies of the general population on the epidemiology of respiratory diseases and allergy that have been in progress for about 30 years or more and are still active. These studies have contributed significantly to our knowledge of respiratory epidemiology in Europe. The supplement also includes a summary of the European Community Respiratory Health Survey (ECRHS) although the life time of the ECRHS is so far somewhat shorter. The summary of the ECRHS includes also some major spin-off surveys of the ECRHS. The Dutch Vlagtwedde-Vlaardingen Cohort Study, started in 1965, is also included as it is still producing data and publications. The first study in the Bergen area of Norway also began in 1965, while a large-scale research program in Bergen started about 20 years later. Most of the studies included in this online supplement have received funding directly or indirectly both from the EU and the US NIH.

Long-term occupation-based studies, such as the Paris Area Workers Study, are not included.

The authors of each study are responsible for the text of their summaries. The included studies are:

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The Vlagtwedde-Vlaardingen cohort study on chronic airway diseases; the scientific impact of the first Dutch longitudinal population-based cohort study.

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The Vlagtwedde-Vlaardingen cohort study - background and goals

The Vlagtwedde-Vlaardingen cohort study, set up in 1965 by Professor Roelof van der Lende, is the first population-based prospective cohort study performed in the Netherlands. The study aimed to obtain data on the prevalence of chronic airway diseases and gain a deeper insight into their natural history, *i.e.* to study the effects of endogenous factors like age, sex, the tendency to allergy and bronchial hyperresponsiveness, and the effects of exogenous factors such as cigarette smoking and air pollution, on the development of chronic obstructive pulmonary disease (COPD) [1]. The study was conducted in Vlaardingen (a relatively polluted area near Rotterdam) and Vlagtwedde (a relatively unpolluted area in Groningen). The first surveys consisted of random samples of the inhabitants of both areas who were aged 40–64 years in 1965, and a random sample of all inhabitants aged 15–39 years in 1967 in Vlagtwedde and in 1969 in Vlaardingen. After the baseline surveys the cohort participated in follow-up surveys every 3 years. In Vlaardingen a closed cohort design was used: only participants who were included at baseline were invited for follow-up surveys. In Vlagtwedde an open cohort design was used: at every follow-up survey, new subjects aged between 20 and 65 years were invited to participate. In Vlaardingen 2790 participants and in Vlagtwedde 5675 participants were enrolled. The final surveys were performed in 1989 (Vlagtwedde) and 1990 (Vlaardingen), resulting in 25 years of follow-up with measurements of lung function, bronchial hyperresponsiveness (*i.e.* an exaggerated response of the airways to nonspecific triggers like cold air, tested using a histamine inhalation test), skin-prick tests for common aeroallergens, blood eosinophils, and standardised questions on respiratory symptoms, smoking habits, housing and occupation. At the final survey total and specific IgE were additionally determined, and neutrophil depot of spinned blood was collected and stored at -200C.

Given the study's state-of-the-art prospective epidemiological research design, with standardised and repeated measurements of potential risk factors, lung function indices and bronchial hyperresponsiveness, the study has led to identification of several host-related risk factors for the onset and course of chronic airway diseases like COPD.

Research highlights and novel knowledge derived from the Vlagtwedde-Vlaardingen cohort study after 25 years of follow-up

Analyses of the cohort data derived over a period of 25 years have identified bronchial hyperresponsiveness and allergy (*e.g.* increased number of peripheral blood eosinophils, higher level of serum total IgE, and/or positive skin prick tests) as important and significant factors related to respiratory symptoms, lung function impairment and COPD [2,3]. The results from these cross-sectional analyses were followed-up in the 1990s with more papers in which several potential risk factors as predictors for onset of disease were analysed, thus taking advantage of the full potential of the longitudinal data in Vlagtwedde-Vlaardingen, in which the risk factors are measured prior to the onset of disease. The endurance of the committed Vlagtwedde-Vlaardingen researchers and their consistent detailed data collection

in the 1960s, 70s and 80s enabled advancement of the research line in host and environmental factors in the aetiology of respiratory diseases into the 1990s, answering novel research questions that emerged, and identifying novel risk factors in the aetiology of chronic airway diseases.

These longitudinal analyses showed for example that increased bronchial hyperresponsiveness is an independent risk factor for an accelerated decline in lung function and, thus, for the development of COPD [2]. Longitudinal analyses also showed that increased bronchial hyperresponsiveness is positively associated with the development of chronic respiratory symptoms and negatively associated with the remission of these symptoms in adults [4], and that subjects who smoked and were bronchial hyperresponsive had an increased risk of developing respiratory symptoms, especially in the presence of eosinophilia [5].

Moreover, in 1995 the vital status of all 8465 subjects that were originally included in the Vlagtwedde-Vlaardingen cross-sectional study in 1965 (enriched with 2071 subjects from the linked cross-sectional Meppel study), was determined, opening a research line on medical characteristics like allergy, bronchial hyperresponsiveness and lung function level as predictors of all-cause, cardiovascular, respiratory and cancer mortality. This broadened the use of the Vlagtwedde-Vlaardingen data into relevant areas outside the scope of respiratory diseases. Positive skin tests were shown to be associated with reduced cardiovascular mortality in nonsmoking subjects with normal lung function and weight, and subjects with eosinophilia had an increased risk of cardiovascular death independent of other major risk factors. These analyses suggested a possible link between eosinophilia and positive skin tests and cardiovascular mortality [6]. Moreover, the studies established for the first time that increased bronchial hyperresponsiveness predicts mortality from COPD, independent of other mortality predictors like level of lung function, not only in smokers, but also in subjects who had never smoked [7]. This research line of predictors of mortality is still ongoing, and has recently led to new PhD research projects, using the updated vital status of the cohort in 2008, and enriching these updated mortality data with morbidity data in the form of hospital admissions. These current projects will provide an additional wealth of scientific knowledge related not only to the aetiology of respiratory morbidity and mortality, but also to other common diseases like cardiovascular disease and cancer, and more general, healthy ageing. Currently, this research line has largely extended its potential by incorporation of genetic data that became available through the new research line that was initiated at the beginning of the 21st century, namely the genetics study in Vlagtwedde-Vlaardingen. This newly started, successful and timely research line, focusing on the role of genes and environmental factors and their interactions in the onset of accelerated lung function decline and the onset of COPD, efficiently re-uses the wealth of data of the Vlagtwedde-Vlaardingen cohort study.

Genetics in Vlagtweddde-Vlaardingen: research into the role of genes, environment and gene–environment interaction in the onset of (respiratory) disease

In 2003/2004, DNA was isolated from 2467 subjects of the Vlagtwedde-Vlaardingen cohort participating in the last survey in 1989–1990 [8]. This was the start of the genetics research line in the Vlagtwedde-Vlaardingen cohort study, which focuses on the role of genetic susceptibility by studying germline genetic variants. By studying germline variants, and thus the genotypic make-up that subjects are born with, we can take full advantage of the over 25 years of follow-up with over 8000 lung function measurements, and thus use the full

power and potential of the Vlagtwedde-Vlaardingen cohort, still unique worldwide. This enables us to study the role of genetics in the aetiology of accelerated lung function decline and onset of COPD, but also the genetics of risk factors like bronchial hyperresponsiveness.

Research highlights and knowledge derived from the Vlagtwedde-Vlaardingen cohort genetics study

Smoking is considered the major risk factor for the development of COPD. However, since only a relatively small proportion of smokers (10–20%) develops symptomatic COPD and differences in cigarette smoke exposure account for only a small portion of the variation in lung function, genetic susceptibility is suggested to play a determining role in the development of the disease. Thus, the concept of the genetically 'susceptible smoker' has been put forward, *i.e.* a person who develops COPD upon smoking, whereas other smokers do not develop COPD. The huge societal and personal burden of disease as well as the lack of knowledge on the origins of the susceptible smokers had driven the research of me and co-workers. Initially we performed candidate gene studies in the Vlagtwedde-Vlaardingen cohort study, followed by GWAS studies and by relating genetics to protein expression in association with biopsy findings in COPD patients. This has resulted in many top publications on candidate gene approaches and gene–environment interactions (specifically smoking). Results of these studies were replicated in other population-based cohorts (*e.g.* the Doetinchem cohort study), allowing state-of-the-art independent replications of findings. Indeed some of the genetic effects of candidate genes were observed only in ever- or current smokers, which is in line with the theory of the 'susceptible smoker' as described above. For example, we identified variations in heme oxygenase-1 that were predictive of accelerated lung function decline in smokers only [9], and showed that the glutathione-S-transferase mu 1 and glutathione-S-transferase theta 1 null alleles confer a risk for accelerated lung function decline specifically in former and currently smoking males. Contrary, the Super Oxide Dismutase 3 Arg213Gly polymorphism was associated with slower lung function decline in non-smokers exclusively [10]. We showed that two SOD2 polymorphisms are associated with bronchial hyperresponsiveness, a risk factor for COPD, while SOD2 C5774T confers a risk for COPD in the total population. This study indicated that there is indeed a genetic basis for bronchial hyperresponsiveness, as also hypothesised by earlier researchers on the Vlagtwedde-Vlaardingen cohort study.

Apart from these confirmations of the concept of the genetically susceptible smokers, we also observed genetic effects on lung function decline that were independent of the effect of smoking; for example our studies showed that genetic variants in ADAM33 were associated with accelerated lung function decline in the general population [8], genetic variants in TGF-beta1 were associated with COPD, yet not with accelerated lung function decline in the general population [11], and a variant in the Tissue Inhibitor of MMPs 1 (TIMP1) also contributed to accelerated lung function decline [12]. Remarkably, all these early candidate gene studies showed that the genetic effects on lung function are independent of the deleterious effects of cigarette smoking.

Since so far non-smoking COPD patients had not been subjected to extensive studies anywhere, we proposed that studying their genotypes can provide extremely interesting information on the onset of impaired lung function and COPD. Clearly, genetic factors distinct from those involved in the onset of smoking-related COPD may determine non-smoking-related COPD. It should be possible to identify genetic factors that differentiate

between non-smoking-related COPD and smoking-related COPD. In line with the results that emerged from the Vlagtwedde-Vlaardingen genetics study on non-smoking-related COPD, only recently, population-based research confirmed that some individuals who have never smoked may also develop COPD and estimations currently are that 25–45% of COPD-patients have never smoked [13,14]. Therefore, other factors, both environmental and genetic, must contribute importantly to the development of COPD. Environmental factors that might be associated with COPD, besides active smoking, are: 1) passive smoke exposure; 2) air pollution (both indoor and outdoor); 3) occupational exposure to gasses, dust, or fumes; and 4) diet. These associations are currently studied in the Vlagtwedde-Vlaardingen cohort genetics study, and other cohorts available from, or to, our research group.

Conclusions

The genetics studies are of course in line with the traditions of the original Vlagtwedde-Vlaardingen research set up, focusing on both host-related (*e.g.* potentially genetic) factors and environmental factors, and their interplay through gene–environment interactions, on onset of chronic airway disease. Hereby, we fully benefit from the strength of the longitudinal design and wealth of the broad data collection of the cohort. Therefore, the Vlagtwedde-Vlaardingen cohort study still provides us with unprecedented information, unique worldwide, and is the basis for an exciting ongoing research line on the role of genes and environment on the onset and progression of chronic airway disease, and overall mortality and morbidity. Vlagtwedde-Vlaardingen is still fuelling research almost 50 years after its start, in 1965.

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Po Delta and Pisa epidemiological studies

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Introduction

The Pulmonary Environmental Epidemiology-EPAP Unit of the Institute of Clinical Physiology, CNR, Pisa, previously performed two large longitudinal studies on Italian general population samples living in the rural area of the Po Delta (North Italy) and in the urban and sub-urban area of Pisa (Central Italy) with the objective of studying the natural history of chronic obstructive pulmonary disease (COPD) and its risk factors; moreover, the collected data permitted to investigate the relationship between respiratory/symptoms diseases and environmental air pollution in Italy.

Material and methods

Study population:

Po Delta area:

The first cross-sectional study in the Po Delta area (PD1) was carried out in 1980–1982, before the installation of a large, oil-burning thermoelectric power plant.

The population sample was a multistage stratified, family-cluster design. Data on the population were obtained from the last census before the study. A total of 3284 subjects (78% of expected, 1573 males and 1711 females, aged 8–64 years) were investigated.

The second cross-sectional study in the same area (PD2) was performed in 1988–1991, on average 9 years later, after the installation of the power plant. Beside those participating in the first survey, other subjects were recruited to the study: children who were not yet born or were aged under 8 at the time of the first study, new spouses, and those who were not available in the first occasion due to military service, work, or refusal to participate. A total of 2841 subjects (66% of expected, 1342 males and 1499 females, aged 8–73 years) were investigated. (Viegi *Eur Respir J* 1988, Carrozzi *Eur J Epidemiol* 1990, Viegi *Am Rev Respir Dis* 1990, Viegi *Eur J Epidemiol* 1994).

Pisa area:

The first cross-sectional survey on the general population sample of urban and suburban residents of Pisa (PI1) was performed in 1985–1988. In this study the population sample was also a stratified, family cluster design: 3865 subjects (77% of expected, 1836 males and 2029 females, aged 5–90 years) were investigated.

The second cross-sectional study in the same area (PI2) was carried out in 1991–1993, on average 6 years later, after the construction of a new highway connecting Pisa to Florence, to which heavy traffic was displaced at a distance from the densely populated zones, and after improvement of the fuel quality and heightening of the exhaust stacks of the industrial installations. Changes in the composition of the recruited population sample were the same as in the Po Delta survey. A total of 2841 subjects (69% of expected, 1288 males and 1553 females, aged 8–97 years) were investigated (Viegi Environ Health Perspect 1991, Viegi Arch Environ Health 1992).

A third cross-sectional study (PI3) was carried out in 2009-2011, on average 18 years later, within the European study IMCA2 (Indicators for Monitoring COPD and Asthma in the EU). Beside those participating in PI1/PI2, other subjects were recruited: new spouses and subjects not available in PI1/PI2. A total of 1620 subjects (70% of expected, 767 males and 853 females, aged 18–103 years) were investigated.

Materials and methods

Information on respiratory symptoms/diseases and risk factors were obtained by a standardised interviewer-administered questionnaire developed by the National Research Council (CNR) Special Project on chronic obstructive lung disease (CNR questionnaire).

Other objective measurements were performed: in PD1/PD2 and PI2 lung function tests; in PD1 and PI2 bronchial responsiveness challenge to methacholine, allergological evaluation through skin prick tests, total IgE; in PI2 also mutagenetic determinations (sister chromatid exchanges, micronuclei), haemoglobin and DNA adducts to benzo(a)pyrene).

In PI3 a self-administered questionnaire on socio-demographic characteristics, respiratory symptoms/diseases and risk factors designed for such a project was used. All questions about asthma and COPD were obtained from previously used and validated questionnaires. A sub-sample performed lung function test, blood sample analysis, blood pressure, pulse oximetry, weight and height measurements.

Major results of the epidemiological surveys in Po Delta and Pisa

Prevalence rates of symptoms/diseases and lung function abnormalities

Comparing the prevalence rates of respiratory symptoms/diseases of PD1/PD2 and PI1/PI2 surveys, data showed a clear increasing trend between the two surveys within each area, in particular for wheeze and asthma. Moreover, the prevalence tended to be higher in males (except for dyspnoea and pleuritis) and in the urban area (more polluted) and increased with age (Viegi *IJTLD* 1999).

As regards the Pisa survey, a further comparison was performed between the 3 surveys (PI1, PI2 and PI3): with respect to PI1–PI2, higher prevalence rates of respiratory symptoms diseases were found, with increasing values from 6.9% (PI1) to 8.3% (PI3) for asthma, from 4% to 7.7% for asthma attacks, from 5.4% to 10.4% for COPD, from 15.1% to 18.8% for usual cough and from 13.4% to 21.4% for usual phlegm.

Moreover, Viegi *et al.* quantified the proportion of the general population with obstructive lung disease (OLD): about 18% of the Italian general population samples either reported the presence of OLD or showed spirometric signs of AO (Viegi *Chest* 2004).

Spirometric data collected in the surveys permitted quantification of the GOLD categories in the two general population samples. Prevalence rates of GOLD stages pre-0 (habitual symptoms cough or phlegm were present for less than 3 months per year or for less than 2 years), 0, I, II, III–IV were 3.5, 14.2, 12.3, 4.5 and 0.4% in men, 3.5, 10.1, 7.3, 2.2 and 0.3% in women, within the samples. The proportion of people with chronic bronchitis symptoms increased from near 30% in GOLD stage I to near 80% in GOLD stage III–IV in Po Delta men and from near 20% to near 75% in Po Delta women, respectively. Similar figures were shown in the Pisa sample (Zielinski *Eur Respir J* 2006).

In the Po Delta survey the influence of different spirometric COPD definitions on prevalence estimates was assessed. Applying different COPD definitions, rates of obstruction ranged from 11% to 57% of the study population. A disparity was found based on a large prevalence of mild obstructive abnormalities when the old ATS criterion (FEV1/FVC <75%) was applied, as compared to a clinical criterion later adopted by GOLD (FEV1/FVC <70%) and, especially, to the ERS criterion (FEV1/VC < 88% predicted in males and <89% predicted in females) (Viegi *Chest* 2000).

Normal values for lung function indices

The spirometric data collected within the PD1/PD2 and PI2 surveys permitted derivation of predicted equations for general population sample in age/sex groups: using the spirometric data of the 'normal' subjects (negative answers to questions on respiratory symptoms/diseases or recent infections, current/past tobacco smoking, and work exposure to noxious agents) the equations for slow vital capacity (VC) and variables from the forced expiratory maneuver were derived (Paoletti, *Bull Eur Physiopathol Respir* 1986, Pistelli *AJRCCM* 2000, Pistelli *Resp Med* 2007). The first equations were derived separately by sex and age groups, adjusting for height (PD1/PD2) (Paoletti, *Bull Eur Physiopathol Respir* 1986), the second one were derived separately by sex, adjusting for age, height and body mass index (PD1/PD2) (Pistelli *AJRCCM* 2000), the third applying natural cubic splines, one single smooth and continuous equation for the entire age range separately by gender, adjusting for age, height and body mass index (PI2) (Pistelli *Resp Med* 2007).

According to current recommendations from the ATS/ERS Task Force on the standardisation of lung function testing, our results reinforced the need to apply reference equations derived from samples of ''normals'' who are as similar as possible to the study subject/population on which such equations are applied, and based on measurements obtained by the same instruments and protocols. Variations in time, space, instruments or population characteristics may result in biased predictions.

Therefore it would be recommendable that such information be reported in detail whenever new reference equations are provided. Finally, our results confirmed the need to periodically update reference equations for lung function.

Association with risk factors (smoking, occupational exposures, residence/air pollution)

The relationship between respiratory symptoms/diseases and the main risk factors (smoking habits, occupational exposure and air pollution) was assessed.

Smoking is a known risk factor for incidence and exacerbation of respiratory symptoms/diseases and these surveys confirmed that the amount of cigarettes currently smoked may add a negative effect on respiratory symptoms and lung function (Viegi *Respiration* 1991).

Occupational exposure is strictly related to respiratory health: in the PD survey multiple logistic models showed that work exposure was associated with higher risk for all symptoms in men (Odds Ratio-OR- 2.76 for dyspnoea, OR 2.31 for asthma, OR 1.69 for cough and OR 1.64 for phlegm); in females, the relationship was significant for dyspnoea (OR 3.74) and asthma (OR 3.29); exposed men also had a significantly higher risk of airway obstruction (OR 1.45) (Viegi *Am Rev Respir Dis* 1991).

The prevalence of respiratory symptoms/diseases was always higher in the urban area (PI) with respect to the rural one (PD) (Baldacci *JEPTO* 1997) and bronchial reactivity level was higher in the urban area, with an higher risk of increased bronchial responsiveness (OR 1.41, CI 95% 1.13-1.76) (Maio *Chest* 2009). Moreover, long-term effects of the exposure to traffic air pollution in Pisa were shown: people residing near a major road (within 100 metres) had significantly higher risks (ORs ranging from 1.61 to 1.83) for persistent wheezing, dyspnoea, attacks of shortness of breath with wheezing, asthma, atopy and airflow obstruction (Nuvolone *Environ Health* 2011).

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The Copenhagen Studies

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Description

The two sister studies in the Copenhagen area include The Copenhagen City Heart Study and The Copenhagen General Population Study. Both studies investigate risk factors for and prognosis of different chronic diseases with main focus on heart and lung diseases.

Copenhagen City Heart Study (CCHS)

The CCHS was initiated in 1976–1978. A sample of 19,698 subjects aged 20–100 years was selected at random from the national Danish Civil Registration System, after age stratification in 5-year age groups, from residents of inner Copenhagen, and 14,223 subjects participated in the initial survey. They were all reinvited to participate in later surveys along with additional subjects in the youngest age-groups. The later waves constitute three subsequent examinations in years 1981–1983, 1991–1993, 2001–2004 and the ongoing 5th examination, which will be completed in 2014.

Copenhagen General Population Study (CGPS)

CGPS is a prospective epidemiologic study that aims to recruit more than 100,000 individuals representative of the general population of suburbs of Copenhagen and to collect genotypic and phenotypic data of relevance to a wide range of health-related problems. It is designed almost identical to the CCHS. Recruitment began in 2003 and is still ongoing.

Results

So far the studies have in total produced more than 900 scientific publications. The publications concerning respiratory diseases focused mainly on prevalence of respiratory symptoms and lung function impairment, risk factors for COPD and asthma and prognosis of these conditions.

Home pages

CCHS: http://www.frederiksberghospital.dk/menu/Afdelinger/Oesterbroundersoegelsen/

CGPS: http://www.cgps.dk/

Key publications with respiratory focus

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The Bergen Studies

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Description

The Bergen epidemiological studies of respiratory health comprise altogether eight surveys: The Bergen Chronic Respiratory Disease Survey; Hordaland County Respiratory Health Survey; Pneumoconiosis Survey of Western Norway; EC-Respiratory Health Survey in Bergen; The Second Oslo and Hordaland Asthma Survey; Bronchodilatation Survey in Hordaland Health Study; the Bergen part of the Respiratory Health in Northern Europe, and the Bergen part of the Burden of chronic obstructive lung disease.

Details of the surveys including objectives, design, methods, quality control and response rates have been given elsewhere (1). Briefly, the data sampling period covers four decades from 1965 and includes altogether 138 692 subjects aged 15–74 years at baseline. Spirometry results were available from 41 335 persons at baseline. A biobank for DNA and blood markers has been established. Six of the surveys have follow-up data while two (Pneumoconiosis Survey of Western Norway, and Bronchodilatation Survey in Hordaland Health Study) are cross-sectional. Response rates at baseline vary from 90% to 68% of those invited. In general the response rates have declined during these four decades of sampling.

Results

The studies have provided data on prevalence and incidence of respiratory symptoms, as well as asthma and chronic obstructive pulmonary disease (COPD). Also risk factors, both environmental and genetic, for these disorders have been published. The natural history and prognosis of asthma, COPD and respiratory symptoms have been studied. The studies have given data on various type of lung function impairment. Finally, reference values of spirometry, bronchodilatation, gas diffusion capacity and exercise testing have been provided. It should also be mentioned that these general population studies have formed the bases for COPD cohorts that have been followed extensively. The advantage of these cohorts is that they are community based. Hence the representativity of the findings to the COPD population at large is those known. The COPD cohorts include the GenKOLS study, and the Bergen COPD cohort study.

Altogether about 450 papers from these studies have been published of which some key publications are given below (2) (3-15)

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The OLIN Studies

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Description

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies is the name of several studies in progress on the epidemiology of asthma, allergy, COPD and OSAS. The overall aim is to identify modifiable risk factors for the diseases and factors promoting health. The studies started in 1985 with a cross-sectional survey on prevalence of asthma, respiratory symptoms and chronic bronchitis (1). This first sample of 6610 subjects has been followed up by questionnaires or clinical examinations by four surveys. Today, nine randomly selected or stratified cohorts including children, adults and elderly from the general population are under study. More than 20% of the population of the most northern county of Sweden, Norrbotten, which covers 25% of the area of Sweden, participates. The methods include mainly prospective longitudinal studies but also cross-sectional and case-referent studies. The methods used cover from basic epidemiologic methods including lung function and other clinical examinations to molecular epidemiology and genetics. Studies on health economics of asthma and COPD were included in the 1990s.

The large scale surveys based on the general population and the high participation rates of 69–97% guarantee a high representativeness and a validity of the results for society (2).

The OLIN Studies have influenced clinical epidemiology in Sweden (3) and also in other countries, mainly Finland and Estonia, and have attracted PhD fellows from several countries including the USA in the west and Vietnam in the east.

Results

The studies have provided data on prevalence and incidence of obstructive airway diseases and allergy and determinants associated with the diseases. The OLIN Studies were among the first verifying that about 50% of smokers sooner or later develop COPD (defined by BTS or GOLD 2-4) if they continue to smoke (4). Population study-based results on the incidence of COPD, societal costs of COPD, incidence and remission of asthma and incidence of allergic sensitisation in children and adults were also among the first published worldwide (5-15).

Data from the OLIN Studies have been used in about 20 PhD theses. The number of original and review articles including OLIN data amounts to about 200.

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European Community Respiratory Health Survey

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Introduction

In the 1980s, treatment patterns of asthma and asthma mortality had been found to vary considerably in Europe. This raised the question whether the variation in mortality was due to geographical differences in the prevalence of asthma or differences in asthma mortality (1). The information available on the variation in the prevalence of asthma and allergy at the beginning of the 1990s had been collected through several studies using different protocols. The European Community Respiratory Health Survey (ECRHS) was the first study that assessed the prevalence of asthma and allergic disease in a large number of countries using an identical and standardised protocol (2). The three main objectives of the survey were:

1. To estimate the variation in the prevalence of asthma, asthma-like symptoms, atopic sensitisation 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 assess further the extent to which they explain variations in the prevalence across Europe.

3. To estimate the variation in treatment practice for asthma in the European Community.

Material and methods

ECRHS I

The ECRHS I was conducted in 1990–1993 (2). A randomly selected population of at least 1500 men and 1500 women, aged 20 to 44 years, was invited to the study in each centre. In stage I, subjects were sent the ECRHS screening questionnaire asking about symptoms suggestive of asthma, the use of medication for asthma, and the presence of nasal allergies. In stage II, a smaller random sample of subjects who had completed the screening questionnaire was invited to attend for a more detailed interviewer-led questionnaire, skin prick test, blood tests for the measurement of total and specific IgE, spirometry and methacholine challenge. An additional sample of subjects who had not been included in the random sample but who had symptoms indicating asthma, were also invited to the extended examination. The total number of subjects that responded to stage 1 was 137,619 subjects from 48 centres in 22 countries, while 21,809 subejcts from 38 centres in 18 countries particpated in stage 2.

ECRHS II

The ECRHS II was carried out 2000–2002. In this follow-up study participants of the ECRHS II stage 2 were invited to a new clinical investigation large similar to what was done in the ECRHS I. The protocol also included genetics and measures of air pollution, indoor environment (3). All in all 13,470 subjects from 30 centres in 15 countries participated in this

follow-up. A follow-up of participants of ECRHS stage 1 by postal questionnaire was also done in some of the centres (4)

ECRHS III

A second follow up of participants from ECRHS I was made in 2008–2012. The target populations was once again participants from ECRHS I stage 2. The participants underwent a clinical investigation that in large parts was identical from what had been carried out in ECRHS I and II. The number of participants was 8834 subject from 29 centres in 14 countries. A postal questionnaire was used to follow-up stage 1 participants from ECRHS I in the Nordic countries and in some other centres.

Major results of the ECRHS

Up to date almost 400 papers have been published from ECRHS (www.ecrhs.org). The major results from the ECRHS I have been summarized in a review (1) and included demonstarting large geographical differences in the prevalence of asthma and allergy with high prevalence rates in English speaking countries and low prevalence rates in the Mediterranean region and Eastern Europe. The ECRHS I also highlighted the importance of occupational exposure for adult onset asthma and showed that the treatment of asthma varied widely between countries.

The longitudinal design of the ECRHS II enabled us to study aspects such as change (or rather lack of change) in specific IgE status with aging (5), the effect of smoking and obesity on lung function decline (6) the effect of occupational (7) and indoor expossure (8) on onset of asthma as well as risk factors for developing COPD (9,10). The study has also shown association between asthma symptoms and traffic related air pollution (11) and as part of the GABRIEL consortium made a large contribution to the genetics of asthma (12).

The questionnaires and examination procedures developed have also been implemented in other large international studies such as the Global Allergy and Asthma European Network (GA2LEN) survey (13) and the Burden of Obstructive Lung Disease (BOLD) study (14).

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