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Asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and respiratory symptoms among adults in Estonia: Prevalence and risk factors – comparison with Sweden and Finland

The "FinEsS" Studies – Estonia I

by

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Stockholm 2005

To my dear family

Published and printed by Karolinska University Press
Box 200, SE-171 77 Stockholm, Sweden

ISBN 91-7140-537-2

ABSTRACT

The thesis is based on original research data of the Estonian part of the "FinEsS" studies, which are cross-sectional comparative studies between Finland, Estonia and Sweden aiming to estimate the prevalence of respiratory symptoms, asthma, chronic bronchitis, COPD and allergy and to assess risk factors for the diseases and conditions. In Estonia the study areas included Tallinn, the capital of the country, Saaremaa, an agricultural island in the Baltic Sea, and Narva, a heavily industrialised town located at the Russian border. The study consisted of two phases, first a postal questionnaire survey from the late autumn of 1995 to the spring of 1996. The postal survey was followed up from 1997 to 2000 by a structured interview, clinical examination, lung function test, skin prick test and bronchial provocation test in randomly selected sub-samples. A further aim included comparison of postal questionnaire results from Tallinn, Stockholm and Helsinki, all capitals located at the Baltic Sea.

Totally 24,307 subjects in Estonia aged 15 - 64 years were invited to the postal survey. After exclusion of subjects who had moved abroad, were living elsewhere, or were dead, 22,579 subjects remained. Of them, 17,525 subjects (77.6%) participated. From the questionnaire responders, 2,676 randomly selected subjects after stratification by age and gender were invited to take part in the follow-up studies, and 1,432 subjects (53.1%) participated.

Of men, 57.2% were current smokers versus 28.1% of women. The most commonly reported respiratory symptom was sputum production, 29.5%, followed by longstanding cough, 24.0%. The prevalence of wheezing during the last 12 months was 21.7%, of recurrent wheeze 13.3%, and attacks of shortness of breath was reported by 12.5%. The prevalence of physician-diagnosed chronic bronchitis was 10.5%. Chronic bronchitis and all respiratory symptoms were most prevalent in Narva and the prevalence was lowest in Saaremaa. The prevalence of physician-diagnosed asthma was 2% according to the postal questionnaire without no major difference between the areas, and a few years later it was according to interview 3.8%. The prevalence of COPD was 7.8% with no statistically significant differences between the three areas. After adjusting for the age and gender distribution and for smoking habits in the population of each area, the prevalence was slightly lower. Measuring prevalence of asthma in Estonia based on postal self-administrated questionnaire and structured interview with results of functional and clinical data suggest that physician-diagnosed asthma in Estonia reflects a considerable under-diagnosis. Disease criteria for asthma based on symptom combinations yielded a prevalence of 5-8%.

Smoking and a family history of obstructive airway diseases were risk factors for all respiratory symptoms, while increasing age was a risk factor for chronic bronchitis and bronchitic symptoms. Family history of asthma was the major risk factor for asthma. Increasing age, male sex and smoking (in men only) were dominating risk factors for COPD. In Estonia, physician-diagnosed chronic bronchitis and all respiratory symptoms were significantly more prevalent in non-Estonians than in native Estonians.

Living in Tallinn compared with the Nordic capitals Stockholm and Helsinki was associated with an increased risk for most respiratory symptoms. For Estonia, the prevalence of chronic bronchitis was found to be much higher, of physician-diagnosed asthma much lower, and of COPD nearly similar compared with Sweden and Finland. The considerable differences in prevalence rates of physician-diagnosed asthma between the Estonia, Finland, and Sweden could be explained by differences in diagnostic practices. Asthma in Estonia and chronic bronchitis in Sweden and Finland seemed to be underdiagnosed.

Key words: epidemiology, asthma, chronic bronchitis, COPD, Estonia, the "FinEsS" studies

LIST OF PUBLICATIONS

This thesis is based on the following papers[1]:

I. **M.Meren,** L.Jannus-Pruljan, H.M.Loit, J.Põlluste, E.Jönsson, J.Kiviloog, B.Lundbäck. Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire. Respiratory Medicine 2001; 95: 954-964.

II. L.Jannus-Pruljan, **M.Meren,** J.Põlluste, H.M.Loit, J.Kiviloog, A.Baburin, B.Lundbäck. Postal survey on asthma, chronic bronchitis and respiratory symptoms among adult Estonians and non-Estonians. European Journal of Public Health 2004; 14: 114-119.

III. P.Pallasaho, B.Lundbäck, **M.Meren,** J.Kiviloog, H.M.Loit, K.Larsson, L.A.Laitinen. Prevalence and risk factors for asthma and chronic bronchitis in the capitals Helsinki, Stockholm, and Tallinn. Respiratory Medicine 2002; 96: 759-769.

IV. **M.Meren**, A.Raukas-Kivioja, L.Jannus-Pruljan, H.M.Loit, E.Rönmark, B.Lundbäck. Low prevalence of asthma in westernizing countries – myth or reality? Prevalence of asthma in Estonia – a report from the "FinEsS" study. Journal of Asthma 2005; 42: 357-365.

V. **M.Meren,** L.Jannus-Pruljan, E.Lillak, J.Põlluste, H.M.Loit, K.Larsson, B.Lundbäck. Chronic obstructive Pulmonary Disease in Estonia – an epidemiological survey. Submitted.

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CONTENTS

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physician
ATS	American Thoracic Society
BHR	Bronchial hyper-responsiveness
BMRC	British Medical Research Council
BTS	British Thoracic Society
CNSLD	Chronic Non-Specific Lung Disease
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Year
ECHRS	European Community Respiratory Health Survey
ERS	European Thoracic Society
ETS	Environmental Tobacco Smoke
EU	European Union
EVC	Expiratory vital capacity
FEV1	Forced Expiratory Flow in first second
FinEsS	Finland, Estonia and Sweden
FVC	Forced expiratory vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HEP	Histamine equivalent prick unit
ISAAC	International Study of Asthma and Allergies in Childhood
IUATLD	International Union Against Tuberculosis and Lung Diseases
MDI	Metered dose inhaler
NHBLI	National Heart, Lung, and Blood Institute
NHLI	National Heart and Lung Institute
OLIN	Obstructive Lung Disease in Northern Sweden Studies
PQ	Postal Questionnaire
SI	Structured Interview.
SOB	Shortness of breath
SPSS	Statistical Package for the Social Science
US	United States (of America)
VC	Vital Capacity
WBAC	Wheezing with Breathlessness Apart from Cold
WHO	World Health Organisation

INTRODUCTION

Respiratory disorders are steadily increasing in prevalence, and impose a significant economic burden all over the world. The interpretation and use of symptoms and diagnoses have been evolving with time due to improved knowledge among health care workers. Definitions for diagnoses have not been universal. In developing countries, chronic respiratory diseases are more frequent and severe because of limited health care recourses. In industrialised countries, focus is often on welfare-related specific conditions and diseases (Ait-Khaled et al, WHO, 2001). Improved understanding of disease processes, evidence-based medical decision-making, and international research collaboration can contribute to better public health and healthcare policy concerning respiratory disorders (WHO, 2001).

Respiratory diseases impose an enormous burden on our society. According to the World Health Organization (WHO) World Health Report 2000, respiratory diseases account for 17.4% of all deaths and 13.3% of all so-called DALY effects according to the Disability-Adjusted Life Years (DALY) methodology. Death and disability due to chronic obstructive pulmonary disease (COPD) are increasing, as is the prevalence of asthma, most rapidly among children, especially connected with the urbanisation of our populations. Asthma affects about 150 million people worldwide (WHO, 2003). In Estonia, according to the DALY methodology, the burden of respiratory diseases has risen to fifth position of all groups of diseases, inflicting an estimated 20,000 years of lost of life in the population each year (DALY Estonia, www.sm.ee).

During the last 2-3 decades, a large number of epidemiological studies have been performed world-wide with focus on the prevalence of allergy, asthma and other obstructive lung diseases. The use of different diagnostic criteria and different epidemiological methods in many studies make comparisons of the results difficult. A logical step to improve this situation is to standardise the methodology of investigations of populations living under different environmental conditions. Comparative prevalence studies of east- and west- European countries have demonstrated differences between asthma and chronic bronchitis: In east- European countries, the prevalence in asthma has been thought to be lower, and prevalence of chronic bronchitis higher compared with west- European countries.

Before 1990, very little was known about the prevalence of asthma, allergy and COPD in Estonia. In Estonia, the European Community Respiratory Health Survey, ECRHS, was performed in 1994-1995 in one town, Tartu. The study included a population aged 20-44 years, and the prevalences for asthma-related respiratory symptoms, type-I-allergy and hyper-reactivity were studied (Jõgi et al, 1995).

In the fall of 1995, a large cross-sectional study was initiated which aimed to estimate the prevalence of respiratory symptoms, asthma, chronic bronchitis, allergy and COPD and to assess risk factors for the diseases and conditions. The study was a part of comparatives studies between Finland, Estonia and Sweden labelled "The FinEsS Studies". The aims included also comparisons of the diagnostic practices for these diseases. As the study started only five years after the restitution of the independence of Estonia, when increased contact with 'Western' nations had only started, it was of particular interest to correlate the diseases with social and life-style factors using observations from the Nordic Countries to test this 'East-West' theory (Mutius et al,

1992, 1994; Bråbäck et al, 1994, 1995; Novak et al, 1996; Schafer et al, 1996; Duhme et al 1998).

Modern health policy is based on the understanding that public health can be improved only if the roots of the problems are understood and addressed. During recent years, Estonia has undergone an enormous development, and there is a strong need for follow-up studies to examine the effects on health of these changes in the community.

BACKGROUND

HISTORICAL, SOCIOECONOMIC AND ENVIRONMENTAL SITUATION OF ESTONIA

Epidemiology is a rapidly developing science which provides possibilities to assess and analyse processes with high cost-effectiveness. For decades, datasets with different methods and definitions have been collected. Large, population-based studies have also been initiated during the last decades. Demographic changes, environment, industrialisation, quality of life, poverty, schooling, tobacco use and other conditions have been demonstrated to have influence on the frequency of diseases. During the second half of the 20th century, the pattern of lung- and respiratory diseases has been changing rapidly.

In the beginning of the 20th century, Estonia was a developed agricultural farming country having a standard of living similar to Eastern Europe and Finland (Raun, 1991; Leinsalu, 2004). After World War II, the Estonian annexation by the Soviet Union resulted in a forced and radical transformation of its economy. The Soviet planned economy system was highly centralised. Heavy industry was favoured, and by the late 1950s the number of workers in industry outnumbered those in agriculture. Industrialisation also brought about relocation of large numbers of Russians in a reluctant local population. The pre-World War level of living standards was not reached again until the 1960s. Estonia enjoyed still the highest standard of living among the republics of the former Soviet Union, with a per capita national income 40-44% above the Soviet average (Misiunas and Taagepera, 1993; Leinsalu, 2004). The Soviet system prioritised the urban over the rural, the working class over the peasantry, Russians over other ethnic groups, the centre over regions, and Communist party elite above all (Leinsalu, 2004).

"Ethnic relations, in particular between Estonians and Russians, are an important social issue in Estonia. The majority of Russians have arrived in Estonia during the forced Soviet industrialisation program. For ethnic Estonians, Russians were, with few exceptions, the representatives of the Soviet colonial power. However, the notably transient nature of the Russian speaking colony in Estonia helped to reduce their vested interest and social power, even it also impeded their cultural integration (Misiunas and Taagepera, 1993)" (Leinsalu, 2004). During the Soviet time, poverty and the totalitarian regulation of the community impeded development of science and the implementation to health care. Industrialisation, urbanisation and disregard for the environment had a highly negative impact on society. At that time the importance of prevention and analysis of risk factors for illness were hardly performed. Health care was more focused on reduction of communicable diseases. X-ray examinations were well-organized, and once a year a prophylactic chest x-ray examination was performed on everyone. At the same time, spirometry was hardly known and only the main hospitals had old-fashioned simple equipments.

The start of the rapid change of the Estonian society has been summarised by Leinsalu: After restitution of the independence on the basis of the historical continuity its statehood in 1991 was re-established. Estonia started to rebuild the "normal", so-called westernised community with all pros and cons. "Independence changed political, economic and social realities; it was accompanied by a sharp decline in living standards.

By 1994/1995 the socioeconomic and political situation has started to stabilise. Life expectancy had improved little or not at all from the 1960s. At the beginning of the 1990s there was an unprecedented fall. From 1995, life expectancy started to rise again" (Leinsalu, 2004).

In the year 1995, when our epidemiological study started, already several of these changes had occurred, but the community was still 15-20 years behind the "west". During the next 10 years a large number of different changes took place, and today Estonia belongs to European Union with similar life standards and principles as other EU countries.

DIAGNOSING AND DISEASES

Epidemiologists, physiologists, clinicians and pathologists have tried to agree on the definitions of disorders associated with chronic airflow limitation, including emphysema, asthma, COPD and chronic bronchitis. Epidemiologists have contributed to the terminology and criteria based on functional status that can be monitored in population-based studies or studies of physicians' diagnoses (Lebowitz et al, 1976; Samet, 1978; 1987; 1989; Enarson et al, 1987; Pride et al, 1989; Vermiere et al, 1991; Venables et al, 1993; de Marco et al, 1998).

Symptoms and signs

Symptoms and signs are basic in diagnosing health problems and in monitoring the status and causes of the diagnosed diseases.

Symptoms are any subjective evidence or experience of disease, or a phenomenon that is experienced by an individual. They are sensations that only the patient can perceive. Medical symptoms are manifestations of an underlying illness that are experienced by the patient.

Sign is any objective evidence of disease. A sign can be detected by a person other than the affected individual.

Respiratory symptoms

Respiratory symptoms could be divided in two parts: temporary symptoms occurring during acute health problems like common cold or pneumonia, and intermittent or chronic symptoms which are not limited only to the acute phase of a disease. Intermittent and chronic symptoms have been studied in this thesis.

Cough is an important respiratory defence mechanism which protects the airways from unwanted inhaled particles. Cough is the major method of clearing excess mucus production (Fuller et al, 1990). Cough is evoked by stimulation of the vagal nerve endings in the respiratory tract from foreign particles, mucus or inflammation, and serves to expel obstructing material (Harrison, 1985). In epidemiology, different types of cough have been described as dry cough, productive cough, nocturnal cough, etc.

Sputum is the coughed-up secretions combined with foreign material such as dust and organisms of the respiratory tract. It is in essence mucoid due to chronic irritation of the trachea and bronchi, e.g. cigarette smoking and becomes mucopurulent or purulent related to infection.

Breathlessness is difficulty in breathing and occurs in lung and heart disease and in obesity. For respiratory diseases, two different types of breathlessness are important: breathlessness in general, which may be more common in COPD; and attacks of shortness of breath, which is a common symptom in asthma.

Wheezing is a musical sound more likely to be present on expiration when the airway narrows and is caused by narrowing of the bronchi due to oedema of the mucosa, bronchial muscle spasm, or material such as mucus or phlegm in the lumen. In epidemiological studies it is important to grade wheezing by frequency. Different meanings of the language of wheezing may be used, for instance wheeze or whistling and wheeze with breathlessness as well as wheeze in special circumstances, such as wheezing apart from cold, wheezing during exercise, wheezing during sleep and speech disturbed by wheeze.

In this thesis, *signs* have not been used to define diseases, but different methods like lung function test, skin prick test and hyper-reactivity test has been used to define respiratory disorders and diseases.

STANDARDISATION AND QUESTIONNAIRES IN EPIDEMIOLOGICAL STUDIES

In respiratory epidemiology questionnaires are the most commonly used instrument for assessment of conditions and diseases. The comparison of the results of a questionnaire with separate and independent criteria assesses validity. Validity and reliability express the quality of the data collected by questionnaires. The standardisation of the questionnaires aims to limit bias by maximising validity and reliability, and comparability. Validity in this context can be expressed as sensitivity and specificity. The degree of validity and reliability of the questionnaires may be reduced by bias, which may be due to the way of administration, and recall of investigated information (Samet, 1978; Armstrong et al, 1992; Liard et al, 2000; Bellia et al, 2003). Respiratory disease questionnaires usually have a high specificity but a low sensitivity when asking for defined disease, such as asthma, as many of the cases may not have been diagnosed in the population under study (Toren et al, 1993; de Marco et al, 1998; Huchon et al, 2002). It is notable that when different populations with differences in labelling of diseases and diagnostic practice are compared, the difference in diagnostic practice may be as great in magnitude as the real difference in morbidity.

In 1960s and 1970s, respiratory research was focused on chronic bronchitis, emphysema and airway obstruction. The first standardised respiratory questionnaire was developed by the British Medical Research Council (BMRC) and published in 1960. It was revised and expanded in 1965, 1966, and later (Medical Research Council, 1960; 1986; Holman et al, 1966). It was further used as a model for new questionnaires that were developed in the following years in Europe as the European Coal and Steel Community questionnaire (Brille, 1962), and in the USA, the National Heart and Lung Institute (NHLI) questionnaire (US Department of Health, 1971), the ATS and NHLI Division of Lung Diseases questionnaire (Ferris 1978), and the Tucson epidemiological study questionnaire (Lebowitz, 1975; 1976). The questions targeted mostly respiratory symptoms and risk factors, mainly tobacco smoke and occupational exposures, and were generally formulated to elicit information regarding diseases and risk factors to cover the lifetime of the population.

In the 1980s, the research in the field of respiratory epidemiology focused mainly on asthma and asthma-like symptoms. In this period three main questionnaires were developed: The International Union Against Tuberculosis and Lung Diseases IUATLD Bronchial Symptoms Questionnaire (Burney et al, 1987; 1989); European Community Health Survey ECHRS (Burney et al, 1994) and the International Study of Asthma and Allergies in Childhood ISAAC (Asher et al, 1995). The questions aimed mainly to screen for asthma and asthma-like symptoms, use of medicines, outdoor and indoor environmental exposures, dietary habits, genetic influences and quality of life, and they were formulated to elicit the information covering the last 12- months period of the subjects. A variety of methods have been used in epidemiological surveys to define asthma: self reports of physician-diagnosed asthma (Schwartz et al, 1990; Burney et al, 1989; Lundbäck et al, 1991), reports of asthma attacks (ECRHS, 1996), prevalence of asthma symptoms such as wheezing (Burney et al, 1989), combination of symptoms e.g. discriminate function predictors (Samet 1987; Burney et al, 1989), objective measurements like spirometry (Samet et al, 1988), use of methacholine or histamine for testing bronchial responsiveness (Hargreave et al, 1981; Burney et al, 1989; Venables et al, 1993) or a combination of bronchial hyper-responsiveness and symptoms (Enarson et al, 1987; Toelle et al, 1992; Lundbäck et al, 1992). In assessing asthma prevalence, the definition and classification of asthma remains controversial. The clinical diagnosis of asthma is established based on an overall assessment of the medical history, clinical signs and a documentation of bronchial variability (Sears, 1986). The diagnosis is arbitrary, and there are still no standardised and generally accepted methods for defining asthma in epidemiological studies (Pride et al, 1989). However, questionnaires remain as major instruments in identifying asthma in epidemiological studies (Samet 1987; Toren et al, 1993).

Starting in the 1990s, epidemiologists became more focused to the standardisation, terminology and definition criteria of COPD. During the 1990s several new national and international guidelines concerning diagnosis and management of COPD were published. Studies and analyses made by different criteria have shown that the prevalence of COPD depend on several of the criteria for airways obstruction (Viegi et al, 2000; Lindberg et al, 2005). In 2004, the ATS and ERS submitted a position paper on the standards for the diagnosis and treatment of patients with COPD, in which they adopted the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of 2000 (www.goldcopd.com; Celli & MacNee 2004). According to those criteria, the diagnosis of COPD requires spirometry, and COPD was defined as airway limitation with a FEV_1/FVC ratio of < 0.7 after bronchodilatation.

CHRONIC BRONCHITIS AND EMPHYSEMA

"Chronic bronchitis is a clinical disorder characterized by excessive mucous secretion in the bronchial tree. It is manifested by chronic or recurrent productive cough on most days for at least three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded" (ACCP and ATS, 1975; Fletcher et al, 1959).

Badham (Badham, 1808) and Laennec (Laennec 1827) made the classic description of chronic bronchitis and emphysema in the early 19th century. Developments in the 20th century include the widespread use of spirometry, recognition of airflow obstruction as a key factor in determining disability, and the improvement of pathological methods to

assess emphysema. In the second half of 20th century, three main hypotheses; the "British-", "Dutch-" and the "Fletcher" were developed.

The "British hypothesis" was an important starting point for the classification of obstructive lung diseases. British investigators at the 1959 CIBA Guest Symposium (CIBA, 1959) proposed definitions of chronic bronchitis and emphysema, incorporating the concept of airflow obstruction. Chronic bronchitis was defined as a specific disease on which impairment of lung function may develop dependent on host factors, but mainly dependent on exogenous factors and environmental influence such as smoking, air pollution and respiratory tract infections. Particularly respiratory tract infections were identified as an important cause of impaired lung function. The three main diseases, asthma, chronic bronchitis and emphysema as three different diseases with different clinical presentations, causes and prognosis were acknowledged.

The "Dutch hypothesis" by Orie et al (1961) and van der Lende et al (1969) suggested that special host characteristics determine the subject's response to different endogenous and exogenous exposures. Asthma, chronic bronchitis and emphysema were regarded as sub-groups of a single disease, and the term chronic non-specific lung disease (CNSLD) was suggested for the whole group of obstructive lung diseases. Various forms of obstructive airway diseases can potentially overlap in their clinical concept.

"Fletcher's hypothesis" (Flecher et al, 1976) was presented during 1970s and acknowledged that there were two different general manifestations of chronic bronchitis: one was simple chronic bronchitis without affecting lung function and without developing emphysema, and the other was chronic bronchitis with progressive obstructive lung function impairment and parenchyma damage. Fletcher further described the importance of smoking cessation, exemplified by the observation of more rapid decline in lung function in smokers compared to non-smokers.

ASTHMA

Asthma has been defined as follows: "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment" (GINA www.ginasthma.com, 2002).

Asthma is a Greek word meaning "breathless" or "to breathe with open mouth". Originally applied to shortness of breath of any cause, as in the description of the mode of death of metal by Agricola in 1556, it has come to be applied particularly to episodic breathlessness due to bronchial disease (Hoover et al, 1912). As with other common diseases, the concept of asthma has been modified as the knowledge of pathophysiology of the disease has increased.

In epidemiological studies, asthma has commonly been defined in two different ways: asthma-like symptoms (wheeze, whistling, dyspnoea etc) and self-reported asthma (physician-diagnosed or 'ever-diagnosed') (Liard et al, 2000); and the existence of BHR as assessed by a challenge to special stimuli (histamine, metacholine, cold air, exercise

test etc.) (Chinn et al, 2000). More recently, it has again been argued that a single definition of asthma is not applicable to all studies (Pekkanen et al, 1999). There are potential problems associated both with asthma-like symptoms rising from subjective symptom recognition and recall without complete agreement between asthma and BHR (Viegi et al, 2003).

The expression of asthma phenotype is due to the synergy between host and environmental factors. Major risk factors in this process are classified in the international guidelines (Sheffer, 1995) by predisposing, causal, contributing factors and factors aggravating asthma. Environmental risk factors include active smoking, environmental tobacco smoke, exposure to allergens, outdoor and indoor air pollution, work exposure, socioeconomic status, diet and alcohol consumption. Endogenous risk factors include sex, genetic factors, family history, ethnic groups, early risk factors, atopy, childhood and adulthood respiratory trouble (Viegi et al, 2003).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD has been defined as follows: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases" (www.goldcopd.com).

The original definition of COPD was provided in 1964 by Mitchell as "chronic airway obstruction of uncertain aetiology", emphasizing COPD as a diagnosis of exclusion (Mitchell et al, 1964). The early definitions of COPD did not specify whether asthma was included or not. The American Thoracic Society (ATS) statement of the definition of COPD explicitly excluded asthma (ATS, 1995). In the 1980s the term COPD was used among researchers and in the 1990s it became common among physicians in respiratory medicine. During the 1990s, several new national and international guidelines concerning diagnosis and management of COPD were published. The most well known are the American Thoracic Society's (ATS, 1995), the European Thoracic Society's (ERS) (Siafakas et al, 1995), the British Thoracic Society's (BTS, 1997), what has been developed to the British National Institute and Clinical Excellence (NICE, 2004). The first large international guideline for COPD was founded by US Heart Lung, and Blood Institute (the NHLBI) together with the WHO, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Powels et al, 2001).

Chronic bronchitis versus COPD

Chronic bronchitis is still defined as cough and excessive sputum production with or without chronic airways obstruction, the characteristic of COPD, but it is not necessarily a part of the disease. Symptoms of chronic bronchitis depend on chronic hyper-secretion of mucus in large airways. Chronic obstruction can occur with or without hyper-secretion. Cough and sputum production may precede the development of airflow limitation, and conversely, some patients develop significant airflow limitation without chronic cough and sputum production. Overlapping of the conditions may result in difficulties in diagnosing, however, once chronic obstruction exists, the diagnosis should be COPD.

Asthma versus COPD

Asthma and COPD are two distinct chronic disorders sharing one common functional feature: airflow limitation (GINA NHLBI/WHO, 1995, 1997; Powels et al, 2001).

Airflow limitation in asthma is by definition reversible either spontaneously or after treatment, whereas in COPD airflow limitation is not reversible or poorly reversible, and is usually progressive. Respiratory disease that includes symptoms associated with reversible airflow limitation, asthmatic airway inflammation and airway hyper-responsiveness may be diagnosed as asthma. The diagnosis COPD should be considered with chronic respiratory symptoms of dyspnoea and/or chronic cough, exposure of definite risk factors, particularly smoking, and not reversible. Wheezing is common in both asthma and COPD (Lindström et al, 2001; Lundbäck et al, 2003). Asthma and COPD may co-exist particularly among middle-aged and elderly.

SUMMARY OF THE FORMER SOVIET UNION CLASSIFICATION OF RESPIRATORY DISEASES BEFORE 1990

Principles of assessment and diagnosis of chronic bronchitis and emphysema

Classification and diagnosis of bronchitis has developed over time. For a long period the term chronic pneumonia was used as a nosologic form, reflecting an inflammatory process in the lung tissue. In 1972 in Tbilisi (Georgia), the classification for chronic bronchitis and chronic pneumonia was accepted by the Board of the Soviet Union Internal Medicine Scientific Society. The classification of chronic pneumonia did not exclude chronic bronchitis, asthma and emphysema, but instead chronic pneumonia could include these diseases. For the diagnosis of chronic pneumonia, it was important to note the following: stage (I, II, III); phase (exacerbation, remission); variables of clinical course (bronchiectasia, pneumosclerosis, festering etc); localisation (lobe, segment); pulmonary function; cardiac function. The classification of chronic pneumonia has been included in Appendix.

Chronic bronchitis during the Soviet era was defined as a diffuse, usually progressive damage of the bronchial tree caused by long-standing irritation of airways due to different exposures. This was characterised by changes in the secretory system of the mucosa, development of an inflammatory process and of sclerotic changes on deeper levels of the bronchial wall, accompanied by hyper-secretion of mucus, disturbance of bronchial clearance, factors which all may be expressed clinically as permanent or recurrent cough with sputum, and in case of damage of small bronchi and bronchiole accompanied with dyspnoea. The symptoms should not have been caused by other diseases (Ado, 1976; Kokosov, 1984).

In 1978 Fedosejev and Gerasin (Mjagkov, 1991) classified chronic bronchitis into four clinical groups according to duration: simple uncomplicated chronic bronchitis, purulent chronic bronchitis, obstructive chronic bronchitis, and purulent-obstructive chronic bronchitis, all similar to the BMRC definitions (Fletcher 1976). This classification did not designate the phase of disease, type of ventilatory insufficiency or pathogenesis of chronic bronchitis.

In 1980, Kokosov (Mjagkov, 1991) classified chronic bronchitis by seven characteristics: etiological, pathogenetical; respiratory system level, type of clinical process and sputum, functional, phase, and complication (please see Appendix). In 1987, Putov, Fedosejev and Homenko (Putov et al, 1987) characterized chronic bronchitis as diffuse, of long duration, irreversibility of bronchial tree involvement, characterised in most cases with hypersecretion and impaired drainage function of the respiratory system, leading mostly to malfunction of ‘diffusion’ (or gas exchange) and

genesis of cor pulmonale. They classified chronic bronchitis by the following: function (no obstructive, obstructive), sputum (catarrhal, purulent, purulent-obstructive, and asthmatic), phase (exacerbation, remission), and complications (respiratory insufficiency, cor pulmonale).

Principles of assessment and diagnosis of asthma

During the Soviet era, asthma was defined as an allergic disease including essential symptoms: bronchospasm, dyspnoea, hyper-secretion and swelling of bronchial mucosa (Jannus et al, 1975). Asthma as an allergic disease was thought to be either an atopic disease or an "infection allergy". Further, asthma was often considered to be a complication of, or a subgroup to, chronic bronchitis, or even to "chronic pneumonia" (Ado et al, 1976; Kokosov et al, 1984).

For a long period the definition and classification by Ado and Bulatov (1969) was used: "Asthma bronchiale– autonomous, chronic, recurring disease with infectious or without infectious (atopic) etiology, with a mandatory pathogenesis and a mechanism with hyper-sensibility and oedema of mucosa with clinical characteristics of shortness of breath and hyper-secretion".

In 1982, Fedosejev (Putov et al, 1984) amended the definition: "Main mandatory mechanisms for asthma are changed reactivity of bronchi, in addition specific immunological and/or non-immunological mechanisms, with clinically characteristic attacks of breathlessness, and/or status asthmaticus due to spasm of smooth muscules, hyper-secretion and oedema of mucosa". This classification is further described in Appendix. Chutschalin (1986) distinguishes clinical-pathogenetical forms of asthma: allergic, infection induced, prostaglandin (aspirin) induced, steroid-dependent, exercise induced and neurogenic asthma. Until the disintegrations of Soviet Union, in clinical practice the definition of asthma by Fedosejev and Chutschalin was used.

SUMMARY OF THE PREVALENCE OF RESPIRATORY DISEASES IN THE NORTHERN BALTIC AREA

Below, previously reported prevalence estimates of obstructive airway diseases from Estonia, Latvia and Lithuania will be compared with data from Finland and Sweden.

Chronic bronchitis

In Estonia the prevalence of chronic bronchitis in 1977 was reported to be 7.1% in Tallinn and 8.0% in Saaremaa, among subjects aged >18 years. In a Latvian population aged 20-70 years an 11.6% prevalence was reported, and in Lithuania it varied from 3.8% among women aged 25-29 years to 20.3% among men aged 55-59 years (Utkin et al, 1989). In Russia the prevalence varied between areas and in general it was stated to be 2% in the adult population (Putov 1991).

Higher prevalence estimates of chronic bronchitis have been reported from Finland (Huhti, 1965; Terho et el 1987). In a Finnish study representative for the whole population, the prevalence of chronic bronchitis and/or emphysema was found to be 22% among men and 7% among women (Von Hertzen et al, 2000). In the "FinEsS" Finland study in 1996, the prevalence of physician-diagnosed chronic bronchitis was lower than previously shown: 3.7% in Helsinki (Pallasaho et al, 1999) and 3.1% in Lapland (Kotaniemi et al, 2002).

In Sweden the prevalence of chronic bronchitis in 1970's and 1980's was estimated at approximately 4% (Kiviloog et al, 1974; Stjernberg et al, 1985; Lundbäck et al, 1991). Almost the same prevalence of physician-diagnosed chronic bronchitis was found in the "FinEsS" Sweden study 1996: 3.8% in Norrbotten (Lindström et al, 2001). The prevalence in Skåne was estimated at 4.6% (Montnemery et al, 1998).

Asthma

The 1990 prevalence of asthma in Estonia in the city of Tallinn and on the island of Saaremaa was found to be only 0.5% and 0.4%, respectively (Jannus-Pruljan et al, 1994). In 1994, the prevalence of asthma in Tartu, the second biggest city of Estonia, was estimated at 2.0% (Jõgi et al, 1996). Among children, the 1994 ISAAC study found a prevalence of 'ever' asthma among 13-14 year old schoolchildren to be 2.9% in Tallinn (Riikjärv et al, 1995).

Unfortunately there are no official or published data of estimates of asthma prevalence among adults in Latvia and Lithuania. In the ISAAC study the prevalence of 'ever' asthma among children aged 13-14 years was found to be 3.9% in the capital Riga, and 4.6% in rural Latvia (Björksten et al, 1998). In St Petersburg, Russia, the prevalence of adult asthma was 7.2% (Fedosejev et al, 2003), and in Moscow among children aged 13-14 years 2.4% (Björksten et al, 1998).

In Finland, the prevalence of asthma has been reported to be 4% in 1988 (Vesterinen et al, 1988). Haahtela published results in 1990 showing that the prevalence of asthma in Finnish conscripts aged 18-19 years had increased from 0.3% in 1966 to 1.8% in 1989 (Haahtela, 1990). In the"FinEsS" study in Helsinki in 1996, the prevalence of physician-diagnosed asthma was found to be 6.6% (Pallasaho et al, 1999). Among 13-14 year old children, the asthma prevalence was estimated at 7.4% in Helsinki, 4.6% in Kuopio and 6.6% in Lapland (Björksten et al, 1998).

The most recent studies in Sweden have shown the prevalence of physician-diagnosed asthma among adults to be 5-9% (Larsson et al, 1993; Rönmark et al, 1997; Lundbäck, 1998), among 13-14 year old children 10.8% in Stockholm and 10.0% Linköping (Björksten et al, 1998), and among 7-8 year old children 8.0% in northern Sweden (Rönmark et al, 1999).

COPD

Quite few reports have been published on the prevalence of COPD based on recently implemented disease diagnosis guidelines. An important factor when estimating the prevalence is the definition of COPD. The WHO official statistics demonstrates an increase in prevalence of COPD all over the world. Unfortunately, data and also official statistics about COPD in Estonia concerning prevalence and morbidity are missing.

According to the WHO official statistics, the prevalence of COPD was reported in Latvia to be 2.0% in 1990 and 1.7% in 1995; in Lithuania 2.4% in 1990 and 3.4% in 2002; in Russian Federation 1.9% in 1990 and 2.4% in 2002; in Finland 2.2% in 1990 and 3.9% in 2002. Official data for Sweden according to the WHO statistic base are not available (WHO CISID). In Finland the prevalence of COPD was found to be 3.7% in a population study (Hedman et al, 1999).

In Sweden, the prevalence of COPD in middle age and elderly (age > 45 y) according to the BTS criteria was found to be 8% and, according to the GOLD criteria, 14% in population studies in northern Sweden (Lundbäck et al, 2003).

Figure 1: Age-standardised death rates by diseases of respiratory system (per 100 000 European standard population). Females. (*Health in the Baltic Countries,1996)*

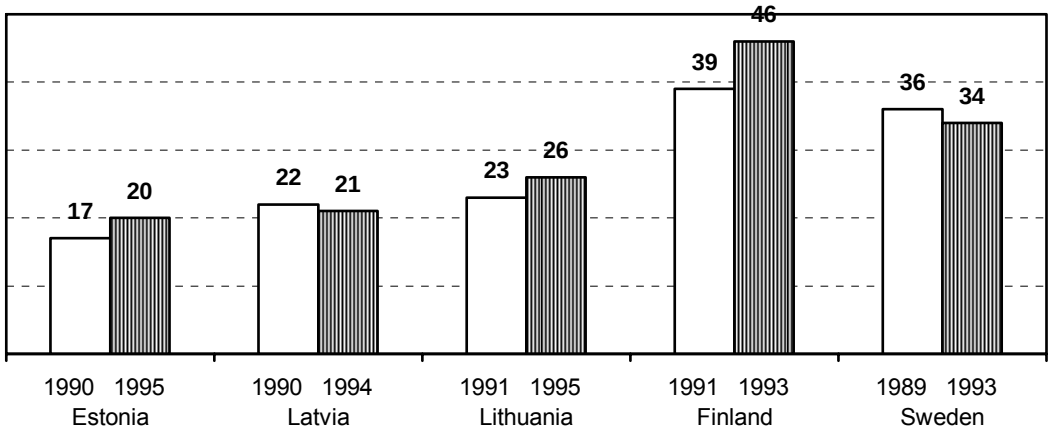
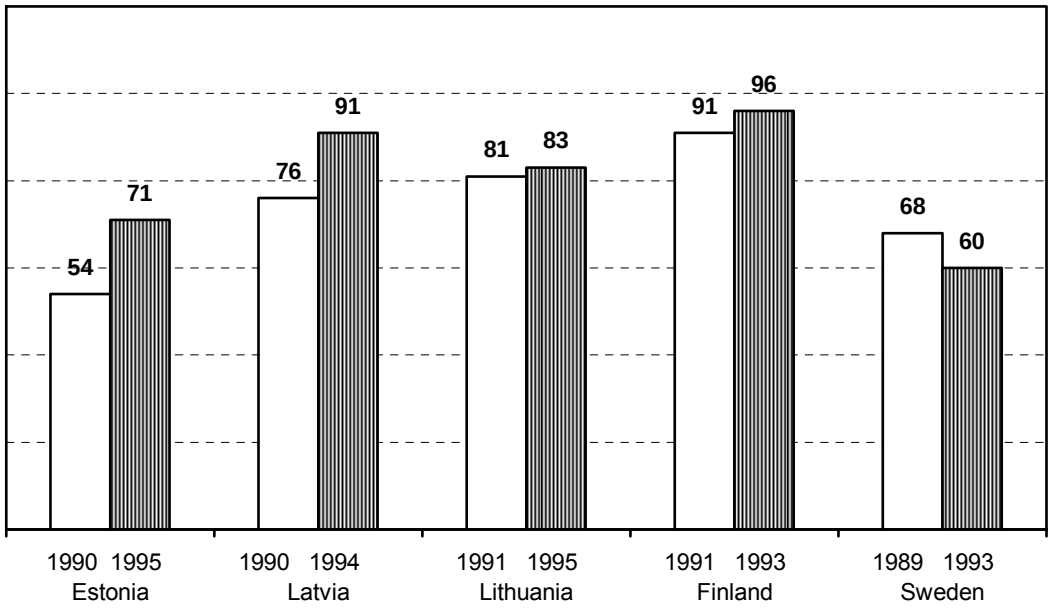


Figure 2: Age-standardised death rates by diseases of respiratory system (per 100000 European standardised population). Males. *(Health in the Baltic Countries, 1996)*



AIMS

1. To assess the prevalence of respiratory symptoms, asthma, chronic bronchitis and COPD in adults in Estonia by studying different parts of Estonia: Tallinn, the capital of the country, Saaremaa, an agricultural island in the Baltic Sea, and Narva, a heavily industrialised town located close to the Russian border.

2. To investigate the relationship of asthma, chronic bronchitis, COPD and respiratory symptoms with demographic data, living conditions, smoking habits, and other possible risk factors, and to compare prevalence of disease among native Estonians and non-Estonians living in Estonia.

3. To validate diagnoses based on postal self-administrated questionnaire and on structured interview with the results of functional and clinical tests.

4. To analyse differences and similarities in prevalence of respiratory symptoms and diseases between Estonia, Sweden and Finland including smoking habits.

5. To analyse differences in determinants of diseases in Estonia, Sweden and Finland.

MATERIAL AND METHODS

This thesis is based on original data from the "FinEsS" studies. The "FinEsS" studies started in 1995 with a multicentre cross-sectional study covering centres in Estonia, Finland and Sweden. The diseases under study include respiratory symptoms, chronic bronchitis, asthma, allergy, and COPD. The overall aim was to study prevalence and risk factors for obstructive airway diseases in Estonia, Finland and Sweden. In long-term perspective, the study aims to promote prevention and to estimate need for healthcare. The study includes eight centres from Estonia, Finland and Sweden, with totally 64,000 randomly selected subjects (Pallasaho et al, 1999; Lindström et al, 2001; Kotaniemi et al, 2001; Larsson M et al, 2001; Raukas-Kivioja et al, 2003; Jannus-Pruljan et al, 2004).

Study areas in Estonia

Estonia is the most northern of the three Baltic countries. The country is situated on the north-west part of the east European plain territory. The area of Estonia is 45,227 km^2. It had 1,446,000 inhabitants in 1996. The proportion of the urban population is around 70%. Major ethnic groups are Estonians (65%) and Russians (28%). The study covered Tallinn, the capital of the country, Saaremaa, an agricultural island in the Baltic Sea, and Narva, a heavily industrialised town located at the Russian border. The average daily temperature in February is -6^{o}C and in July +16^{o}C.

Study population

The study sample of "FinEsS" Estonia was randomly selected from the Estonian State Computing Centre based on data from July 1995. The sample consisted in total of 24,307 subjects aged 15-64 years, of which 12,494 were living in Tallinn, 6,013 in Narva, and 5,800 in Saaremaa. In order to achieve representative samples of the population allowing for comparison of results between the areas, the samples in each area were stratified according to age and gender. Randomisation was performed in each age group (15-24; 25-34; 35-44; 55-64) and included similar numbers of men and women, approximately 1200 in Tallinn, and 600 in Narva and Saaremaa respectively.
In a comparative assessment (Paper III) the age groups were adapted to those of other centres, and included subjects aged 20-64 years, in Tallinn 11,316, in Stockholm 7,453, and in Helsinki 7,484 subjects.

The sample for a clinical follow-up study (see below) was selected from subjects who had responded to the postal questionnaire. In Estonia the size was approximately 10% of the original study sample (Papers IV and V). It consisted of 2,676 invited subjects, who were randomly selected after stratification by age and gender. In Tallinn the sample consisted of 1,332 subjects, while Narva and Saaremaa contributed 672 subjects each.

Figure 3: Map of study area.

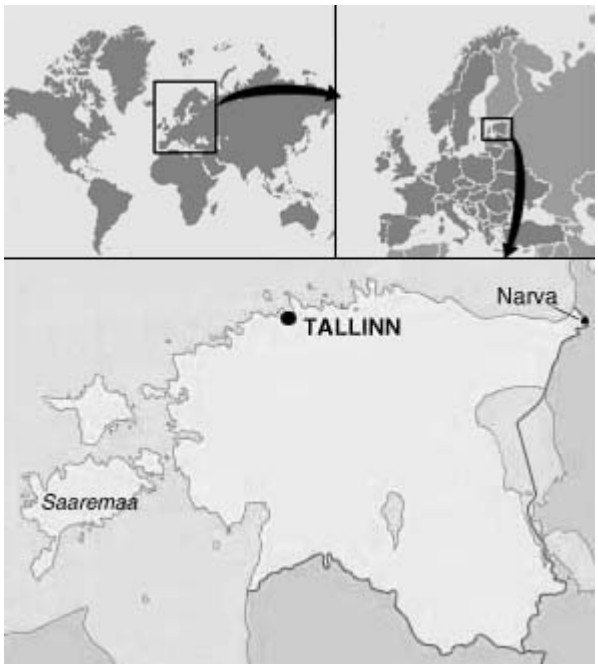


Table 1: Characteristics of the study areas (1996)

01.Jan. 1994	Tallinn	Narva	Saaremaa
Population	442 679	79 094	40 822
Territory in km²	158	85	2 992
Population density per km²	2 800	930	14
Type of settlement	Urban	Urban	Rural/urban 60/40%
Type of industry	Modern industrial	Power plants	Farming
	Commercial	Chemical plants	Fishing
	Administrative	Textile factories	Tourism
Ethnic composition	Estonians 50%	Estonians 6%	Estonians 98%
SO_2 (μg/m², annual means)	7.5	7.7	2.5
NO_2(μg/m², annual means)	21.7	16.2	3.5

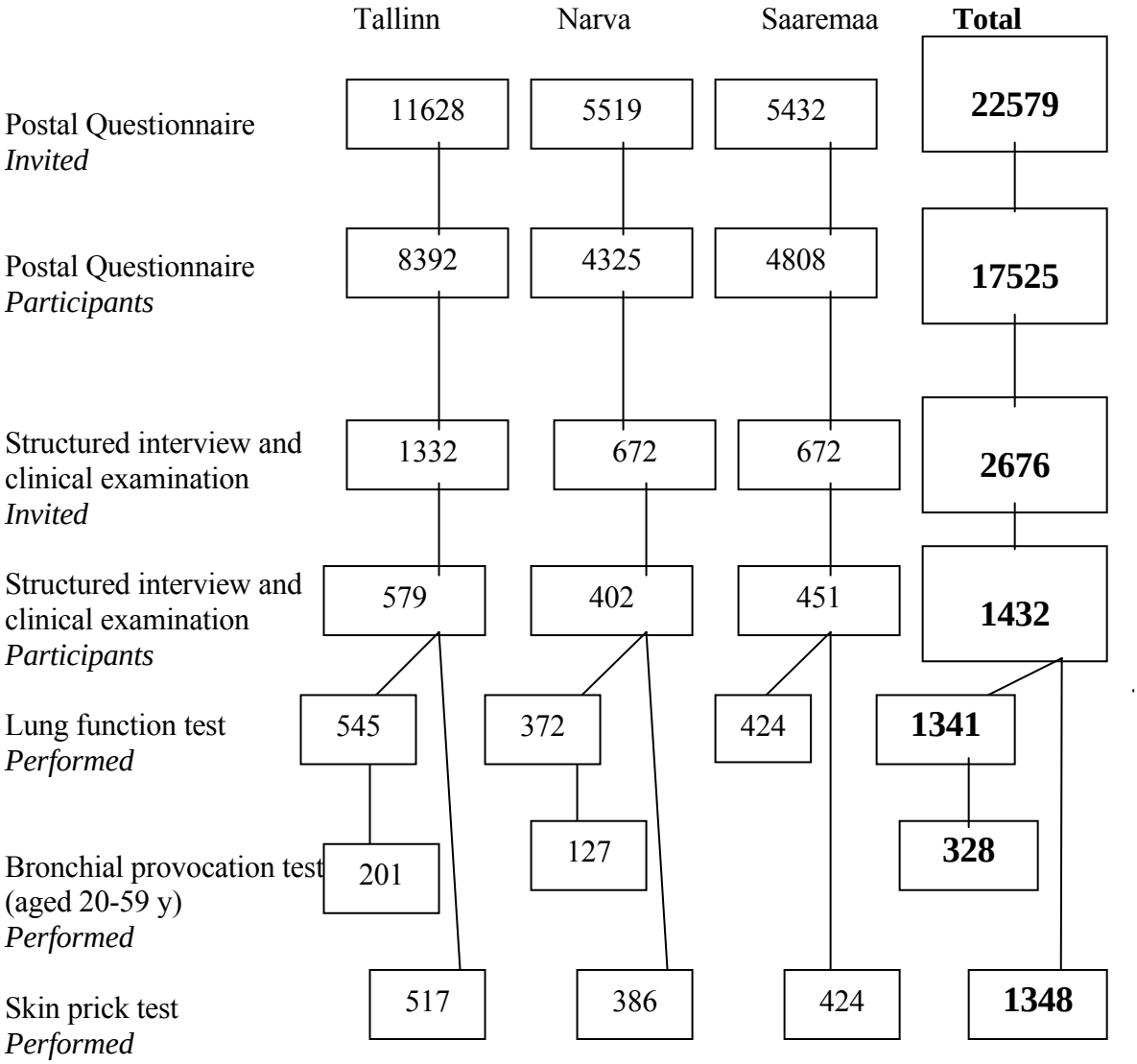
Study design

The study consisted of two phases; a postal questionnaire study, and a structured interview study with clinical examination, lung function tests and skin prick tests. The study design and participation is summarised in Figure 4.

The first phase, the postal questionnaire study (Paper I-III) was performed during the indoor heating season, from November 1995 to May 1996. To the 24,307 questionnaires, totally 19,253 answers were received. From the randomly selected subjects, 1,728, or 7.1% of the original study sample, were either dead, had moved abroad, or were living elsewhere having other addresses. It was remarkable that among the answers, 341 were received from subjects not included in the sample; for instance

other family members or persons living at the addresses but not included in the study sample, demonstrating interest and readiness for participation. After correction, 22,579 subjects constituted the adjusted study sample. After exclusion of all incorrect and unwanted answers, the remaining 17,525, or 77.6% of the real study sample, could be included in the study.

Figure 4: Study design and participation.



The Estonian version of the questionnaire was sent to the subjects with Estonian names and the Russian version to the subjects with non-Estonian names. In case of uncertain nationality, questionnaires in both languages were sent. To subjects who did not respond within two months, a reminder with a new questionnaire was sent. If necessary, a second reminder was sent two months later.

From the questionnaire responders randomly selected and stratified by age and gender, 2,676 subjects were invited to take part in clinical follow-up studies (Paper IV and V).

An invitation letter was sent to the study subjects, along with two reminders with specific timing and important information, including contact data. If possible, a phone call with an extra invitation was performed. Participation in the follow-up study was not as active as in the postal questionnaire study, and 1,432 subjects (response rate 53.1%) took part.

The clinical follow-up study was performed from 1997 to 2000 and included a structured interview, lung function test, reversibility and bronchial provocation tests, as well as measuring allergic sensitisation using skin prick tests. The examination was performed by a specially trained team; clinical examination was performed by pulmonologists. The clinical phase was performed in Tallinn at the Department of Pulmonology, Institute of Experimental and Clinical Medicine, which has been renamed as The National Institute for Health Development. In Saaremaa and in Narva the clinical phase was performed at the local county hospitals Kuressaare Hospital and Narva Hospital. After completing the questionnaire, advice and counselling for the future including advice to visit the family doctor was done individually as needed.

Clinical examination was performed in all participants. Likewise, lung function, reversibility and skin prick tests was planned to be performed in all participants. Skin prick test was performed in 1,348, and spirometry with an acceptable technique in 1,341 subjects. In Tallinn and Narva, bronchial provocation test was planned for 50% of the interview sample, 600 tests in Tallinn and 300 in Narva in subjects aged 20-59 years. Stratification was made by age group and gender before the interview. The bronchial provocation test was performed in 328 subjects.

METHODS

Postal Questionnaire

The "FinEsS" study questionnaires can be regarded as original questionnaires, though they have strong influences from previously validated questionnaires. As the study aimed to screen for respiratory symptoms, asthma, chronic bronchitis and COPD, a validated questionnaire covering these conditions, the Obstructive Lung Disease in Northern Sweden Studies (OLIN) questionnaire (Lundbäck, 1993; Rönmark, 1999; Larsson LG, 2001; Lindström, 2002; Lindberg, 2004), which is commonly used particularly in Sweden, was chosen for the postal as well as the interview study. The questionnaires had been developed from a Swedish modification (Mikaelsson et al, 1982; Stjernberg, 1985) of the BMRC Questionnaire (1960) and regarding questions about asthma with influences from the US Tucson and National Heart Lung and Blood Institute (NHLBI) questionnaires (Lebowitz et al, 1975; 1976), and the American Thoracic Society (ATS) questionnaire (Ferris, 1978).

In the current study, questions about wheezing were added from the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire (Burney et al, 1987, 1989), questions that also had been used in the European Community Respiratory Health Survey (ECRHS 1996).

The "FinEsS" study postal questionnaire include 28 questions about respiratory symptoms and diseases, diagnoses confirmed by physicians, symptoms in special circumstances or due to specific exposures, family history of airway diseases, use of medicines, smoking habits and profession. In Estonia specific questions regarding self-

estimated socio-demographic conditions and health status were added. The questions about symptoms and diagnoses required either "yes" or "no/don't know" answers.

The English version of the expanded OLIN questionnaire, i.e. the FinEsS questionnaire, was translated to Estonian, and additional questions were added. The questionnaire was further translated from English into Russian, and both the Estonian and Russian versions were translated back into English. The English version of the questionnaire is included in Appendix.

Interview questionnaire

The "FinEsS" study interview questionnaire consisted all together of 162 basic questions and 20 additional questions. The questions required either a "yes" or "no" answer, and some accrued also a "don't know" option.
The descriptive personal data were followed by the groups of questions: cough and phlegm, wheezing and whistling, breathlessness in general, attacks of shortness of breath and chest tightness, factors that provoke wheezing or whistling or attacks of shortness of breath with or without cough, asthma and chronic bronchitis, use of asthma medicine, use of antitussive or expectorative medicine, health care, other diseases than obstructive lung diseases, grown-up time, occupation/work, and smoking and nicotine use. Further, the Estonian questionnaire included questions about indoor climate, socioeconomic aspects of health status, educational level and diet.

The interviewers were trained together in order to diminish interobserver bias. Further, the interviewers were instructed frequently and a guideline was used. The interviews were performed by using the participant's native language.

Physical examination

Physical examination was performed by study physicians and included auscultation of lungs and heart and measuring the blood pressure. The physician made individual determinations for all subjects concerning need for exclusion from the following tests, i.e. skin prick test, lung function test, or metchacholine test based on pre-defined criteria.

Lung function tests

Spirometry
Lung function tests were performed using a volume spirometer (Mijnhardt Vicatest 5, The Netherlands). The spirometer was calibrated in a standardised manner at the start of every working day. The test procedure followed mainly the ATS recommendations (1987) and normal values were chosen according to the European Coal and Steel normal values.

Three slow expiratory vital capacity (EVC) measurements and three forced vital capacity (FVC) measurements including measures of the forced expiratory volume during the first second of the expiration (FEV_1) were performed, and the best FEV_1 and either FVC or EVC, respectively, were used for the analyses. The lung function tests were not performed in subjects having ischemic or other heart disease, untreated high blood pressure, pregnancy, cancer, or those who had difficulties in co-operation. All together lung function tests were not performed or not performed adequately in 91 subjects. The most common reasons for not performing lung function tests were high blood pressure mainly in older subjects, and problems with compliance during the test.

Reversibility test
Reversibility test was performed using metered dose inhalator (MDI) with Salbutamol 0.8 mg, administered using a Volumatic spacer. Spirometry was performed before and 15 minutes after inhalation of the bronchodilator. The post bronchodilator values were used when diagnosing COPD by the GOLD criteria.

Bronchial provocation test
The bronchial provocation test was performed with inhaled methacholine chloride according the method developed by Malmberg & Larsson (1991). Spirometry was performed using a volumetric spirometer (Vitalograph, Buckingham, UK). The highest of three reproducible measurements of FEV_1, was registered. FEV_1 after inhalation of isotonic saline was chosen as the basal value. Five minutes after the subject had inhaled diluent (isotonic saline), the metacholine testing started followed doubling concentrations of methacholine chloride starting at 0.03 mg/ml in the asthmatic subjects and 0.5 mg/ml in others. The test was continued until FEV_1 decreased by 20% or more compared to the value recorded after the saline provocation or after inhalation of 32 mg/ml. Three minutes after every provocation, one forced expiration was attempted. After the end of the test, the subjects inhaled via Volumatic 0.8 mg MDI Salbutamol, and fifteen minutes later FEV_1 and FVC were measured. The methacholine test was performed in subjects 20-60 years. The test was not performed in those with $FEV_1 <$ 65% of predicted, in subjects using beta-adreno-receptor antagonists, in subjects having ischemic or other heart disease, pregnancy, cancer, difficulties in co-operation, or had a respiratory infection within two weeks prior to the examination. In total there were 21 subjects in whom the methacholine test was not performed. The subjects were not allowed to smoke, drink coffee or tea 4 hours, to use short-acting ß-agonists 12 hours and long-acting ß-agonists 36 hours, chromolyn, theophyllin, anti-histamines and anti-cholinergics 24 hours before the provocation.

Allergic sensitisation
Allergic sensitisation was surveyed by using IgE and skin prick tests (SPT). In this thesis, the results of SPT are used.

Skin prick tests
SPTs were performed in duplicate on the volar aspects of the forearms with 15 allergen extracts that were labelled in histamine equivalent prick units (HEP), weight/volume (w/v), biologic units (BU), or index of reactivity (IR/ml). If not otherwise stated, the allergens were provided by ALK, Hörsholm, Denmark. The following allergen extracts were used: house dust mites *Dermatophagoides pteronyssinus* (10 HEP) and *Dermatophagoides farinae* (10 HEP); storage mites *Lepidoglyphus destructor* (10000 BU/ml) and *Acarus siro* (10000 BU/ml, Laboratorium Diephuis, Netherlands); four furry animals cat (10 HEP), dog (10 HEP), cow (1:100 w/v), and horse (10 HEP); pollen from birch (10 HEP), timothy (10 HEP), and mugwort (10 HEP); the molds *Alternaria alternata* (1:20 w/v) and *Cladosporium herbarum* (1:20 w/v); latex (100 IR/ml, Alyostal ST-IR, Stallergenes SA, France); and German cockroach (1:10 w/v, Bayer, Elkhart, IN, USA). Histamine dihydrochloride (10 mg/ml) was used as positive control and 50% glycerol as negative control. The skin prick tests were performed according to EAACI recommendations (Position paper 1993), and were carried out by two trained physicians (ER, ARK).

A SPT was interpreted as positive if the wheal was ≥ 3 mm, measured as the sum of the longest and the midpoint orthogonal diameters divided by two. The size of both

duplicated wheals was registered, and the larger wheal was included in analyses of the results. In total, 84 subjects were excluded from the skin prick testing due to acute asthma, upper or lower airways infection, unstable heart failure, cancer, pregnancy, or breastfeeding.

DEFINITIONS, DIAGNOSTIC CRITERIA, AND DETERMINANTS OF DISEASE

Definitions of respiratory symptoms

The diagnoses were based on the answers given by subjects to questions or combinations of questions about respiratory symptoms and diseases.

Longstanding cough: "Have you had longstanding cough during the last years?"

Sputum production: "Do you usually have phlegm when coughing, or do you have phlegm on your chest, which is difficult to bring up?"

Chronic productive cough: The criterion for sputum production fulfilled, and in addition a "yes" answer to the question "Have you had such periods on most days during at least three months at least two successive years?"

Any wheeze last 12 months: "Have you had wheezing or whistling in your chest at any time in the last 12 months?"

Recurrent wheeze: "Do you usually have wheezing, whistling, or a noisy sound in your chest when breathing?"

Attacks of shortness of breath (SOB) last 12 months: "Have you had asthma symptoms during the last 12 months (intermittent breathlessness or attacks of shortness of breath; the symptoms may exist simultaneously with or without cough or wheezing)?"

Specific exposure, provoking factors: Theses questions concerned factors that provoke wheezing or whistling, or attacks of shortness of breath with or without cough: physical effort, cold air, physical effort with cold air in winter, dusty places, tobacco smoke, car exhaust, strong smelling sents (perfumes, spices, printing ink, fumes, cleaners, strong smelling flowers etc), pollen exposure (leafing, grass, outdoor flower etc), furry animal (dog, cat, horse, rabbit etc).

Symptom combinations

The following symptom combinations were used in Paper IV and the first mentioned combination was used in Paper I and III. The symptom combinations were used as surrogates for a clinical diagnosis of asthma.

Wheezing with breathlessness apart from cold: "Have you had wheezing or whistling in your chest at any time in the last 12 months with breathlessness when you did not have a cold?"

Any wheeze + attacks of SOB

Any wheeze + attacks of SOB + at least 2 positive provoking factors

*Recurrent wheeze **or** WBAC + attacks of SOB*

*Recurrent wheeze **or** WBAC + attacks of SOB + at least 2 positive provoking factors*
.

Definitions of chronic bronchitis and emphysema

Chronic bronchitis and emphysema were defined by the questionnaires as follows.

Self-reported (ever) chronic bronchitis: Subjects answer „yes“ to the question "Have you now or have you had chronic bronchitis or emphysema?"

Physician-diagnosed chronic bronchitis: Subjects answer „yes“ to the question "Have you been diagnosed as having chronic bronchitis or emphysema by a physician?"

Definitions of asthma and use of medicines

Asthma was defined as follows both in the postal and interview questionnaires.

Self-reported (ever) asthma: Subjects answer „yes“ to the question "Have you now or have you had asthma?"

Physician-diagnosed asthma: Subjects answer „yes“ to the question "Have you been diagnosed as having asthma by a physician?"

Use of asthma medicines: Subjects answer „yes“ to the question “Do you currently use or have you earlier used asthma medicines regularly or as needed” and in the interview questionnaire at least one of the medicines enumerated.

Definitions of COPD

COPD was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (2001). The GOLD criteria define COPD as $FEV_1/FVC < 0.7$. We have used the values after broncho-dilatation test and the highest value of either VC or FVC.

The prevalence of COPD was also estimated by using the British Thoracic Society (BTS) criteria (1997). In addition to the ratio of FEV_1/FVC or $VC < 0.7$ the BTS criteria also include $FEV_1 < 80\%$ of predicted value. The BTS criteria state further that chronic or previous asthma with chronic airway obstruction may be included in COPD. Subjects with chronic obstruction, who had reported they had asthma, have been included in the analyses of COPD.

Determinants of disease

Age, smoking habits, gender, family history, area of domicile, nationality, and socioeconomic status by occupation have been used as determinants of disease. In Paper V, socioeconomic status was not used due to changes in socioeconomic status among the participants.

Smoking habits

Smokers were classified as subjects answering “yes” to the question “Do you smoke?” Subjects who had never smoked were classified as non-smokers. Those who currently smoked or had stopped smoking within the last 12 months prior to the study were classified as smokers. Subjects who had stopped smoking more than 12 months prior to the study were classified as ex-smokers. The subjects were asked how much they

smoked, how much they have smoked on average, how old they were when they started to smoke, and how often they had been exposed to tobacco smoke in the home environment and at work places. The smokers were also categorised by the number of cigarettes they smoked per day, less than 5, 5-14, and 15 or more. In the analyses of this thesis, pack-years were not used.

Family history
Family history of respiratory diseases was considered present if at least one of the questions about family history of asthma, chronic bronchitis or emphysema was answered in the affirmative (Paper I, IV, V).

In Paper III, family history of asthma and family history of chronic bronchitis or emphysema were used separately.

Socio-economic classification
Socio-economic group was based on occupation, and was analysed according to the Swedish classification (Statistics Sweden 1982). The subjects were divided into seven socio-economic groups based on occupation according to the Nordic Classification System of Occupations (The Nordic Classification, 1983).

In Estonia the postal questionnaire included also other socio-demographic data about the ethnical composition of the study:

"What is your mother tongue?"

"What is your nationality (ethnicity)?"

"If you were born outside of Estonia, since when do you live in Estonia?"

ANALYSES AND STATISTICAL METHODS

The data were computerised at the Department of Pulmonology, National Institute for Health Development, Tallinn. The statistician Tatjana Veideman was responsible for the project's data management. The statistical analyses were performed at the Department of Epidemiology, National Institute for Health Development and were assisted by the statisticians Tatjana Veideman and Aleks Baburin, and at the National Institute for Working Life, Umeå (Paper I, III, IV, V), where the statistician Elsy Jönsson, MSc, was the consultant to the study. In Tallinn statistical analyses were performed with the software packages Statistica, Stata 6.0 and SPSS. In Sweden statistical analyses were performed using the Statistical Package for Social Sciences (SPSS).

The following statistical methods were used: Student's t-test was used for comparison of means. Chi-square analyses were used for comparison of proportions, bi-variate analyses and test for trend. One way analysis of variance (ANOVA) was also used to test for trends. Multiple logistic regression models were used for analyses to assess the simultaneous influences of possible determinants of symptoms or diseases adjusted for possible confounders and effects of possible interaction. The independent variables included age, gender, family history of asthma or chronic bronchitis/emphysema, smoking habits, and area of domicile, which reflects air pollution and degree of urbanization as well. In paper V biological interaction was calculated according to the formulas using: the relative excess risk due to interaction $RERI = RR_{11} - RR_{10} - RR_{01} +$

1; attributable proportion due to interaction AP = RERI/RR_{11}; and the synergy index S = [RR_{11}-1]/[(RR_{10} -1) + (RR_{01}-1)] (Ahlbom & Alfredsson, 2005; Andersson et al, 2005). Generally, the 95% significance level, $p< 0.05$, was used to identify differences between observations.

RESULTS

PAPER I – ASTHMA, CHRONIC BRONCHITIS AND RESPIRATORY SYMPTOMS AMONG ADULTS IN ESTONIA ACCORDING TO A POSTAL QUESTIONNAIRE

The participation rate at the postal questionnaire study was 77.6% ranging from 72.9% (Tallinn) to 88.5% (Saaremaa). The participation was generally higher among women, 81.1%, than for men, 73.7% ($p< 0.001$). The proportion of smokers was 57.2% (!) in men and 28.1% in women, and was similar in the three study areas. In all centers, the highest proportions of smokers were found in the age group of 25-34 years. Among all men, 14.7% were ex-smokers (women 7.4%), while of men 28.0% were non-smokers (women 64.2%).

The most common symptom was sputum production, 29.5%, followed by longstanding cough 24.0%. The prevalence of any wheeze during the last 12 months was 21.7%, of recurrent wheeze 13.3%, and attacks of shortness of breath was reported by 12.5%. The prevalence of most respiratory symptoms increased with age, while no major gender differences were found, though the proportion of smokers among men was considerably higher than among women. All respiratory symptoms were most prevalent in Narva. The prevalence rates were in general lowest in Saaremaa. Respiratory symptoms and smoking were strongly correlated. Most symptoms increased significantly with the numbers of cigarettes smoked per day. The effect of smoking on the prevalence of respiratory symptoms seemed stronger in women than in men.

The prevalence of physician-diagnosed asthma was 2.0%, similar among men and women, and the lowest prevalence was found in Saaremaa, 1.6%. The prevalence did not change after standardisation to the whole population for ages 15-64 years.

The prevalences of physician-diagnosed and self-reported (ever) chronic bronchitis were 10.5% and 10.7%, respectively. Physician-diagnosed chronic bronchitis was reported by 15.3% in Narva, 10.4% in Tallinn, and by 6.4% in Saaremaa (test for trend: $p<0.001$). Both physician-diagnosed and self-reported chronic bronchitis were slightly though significantly more common among women, increased with age, and were related to smoking.

The risk for chronic productive cough increased nearly linearly with the number of smoked cigarettes. Smokers smoking > 15 cigarettes per day compared to non-smokers had an OR of 3.5. Other significant risk factors for chronic productive cough were increasing age and a family history of obstructive airway disease, OR 2.8, while gender had no influence. The main risk factor for asthma was family history of asthma, OR 4.3.

Living in Narva compared with living in Saaremaa was associated with an increased risk for most of the above-mentioned symptoms, yielding odds ratios from OR 1.3 (attacks of shortness of breath) to 2.9 (both chronic productive cough and recurrent wheeze). The odds ratios for living in Tallinn compared with living in Saaremaa were 1.6 for chronic productive cough, 1.4 for recurrent wheeze, and 1.5 for physician-diagnosed asthma.
Thus the OR for recurrent wheeze for current smokers living in Narva *vs* non-smokers living in Saaremaa was 9.9, and the comparison between corresponding citizens in

Tallinn *vs* Saaremaa was 4.7. The OR for current smokers *vs* non-smokers in the pooled data from all three areas was 3.4.

PAPER II - POSTAL SURVEY ON ASTHMA, CHRONIC BRONCHITIS AND RESPIRATORY SYMPTOMS AMONG ADULT ESTONIANS AND NON-ESTONIANS

For the postal questionnaire study, 53.4% of the answers were received from Estonians, 46.0% from non-Estonians while 0.6% had not indicated their nationality. The prevalence of current smokers was significantly lower ($p<0.001$) in Estonians than non-Estonians, 38.8% versus 43.6%. Non-Estonian men were more often smokers than Estonian men; 61.6% versus 53.6% ($p<0.001$). Overall, 40.8% of all participants were exposed to tobacco smoke in their living rooms (35.5% of Estonians; 47.0% of non-Estonians; $p< 0.001$).

The prevalence of physician-diagnosed asthma was similar in Estonians and non-Estonians (2.0%). The prevalence of physician-diagnosed chronic bronchitis was lower among Estonians, 7.9% vs. 13.5% among non-Estonians ($p<0.001$). This difference in prevalence was observed in all age groups.

The risk (OR) of chronic bronchitis for non-Estonians versus Estonians after correction for the influence of smoking habits, area of domicile, age, gender, and socioeconomic group was 1.30. A similar pattern of differences between Estonians and non-Estonians was observed for most respiratory symptoms. The reasons for this difference may in part be due to language, however, the consistent pattern suggests that language may not be an important explanation of the large difference. The difference may in part be due to differences in exposure from environmental tobacco smoke.

PAPER III - PREVALENCE AND RISK FACTORS FOR ASTHMA AND CHRONIC BRONCHITIS IN THREE CAPITALS, HELSINKI, STOCKHOLM, AND TALLINN

The response rate in the postal survey among subjects aged 20-64 years was 72% in Stockholm, 76% in Helsinki and 68% in Tallinn. Among men, the proportion of smokers was 32% in Stockholm, 38% in Helsinki, and 57% in Tallinn. Corresponding figures in women were 33%, 31% and 31% in Stockholm, Helsinki and Tallinn, respectively. These differences were highly significant in men ($p< 0.001$) while no statistically significant difference was found in women. Prevalence (%) of respiratory symptoms and physician diagnosed diseases is shown in table 2.

Table 2: Prevalence of some symptoms and diseases in Tallinn, Helsinki and Stockholm.

	Tallinn	**Helsinki**	**Stockholm**
Recurrent wheeze	12.5	7.0	8.3
Physician diagnosed asthma	2.3	6.2	7.6
Chronic productive cough	8.9	11.7	5.6
Physician diagnosed chronic bronchitis	10.6	3.4*	3.0*

* N.S. All others are significantly different from each other.

Although recurrent wheeze was most common in Tallinn, the prevalence of physician-diagnosed asthma was considerably lower in Tallinn than in Stockholm and Helsinki. The inverse was found for chronic bronchitis. Surprisingly, chronic productive cough was most common in Helsinki.

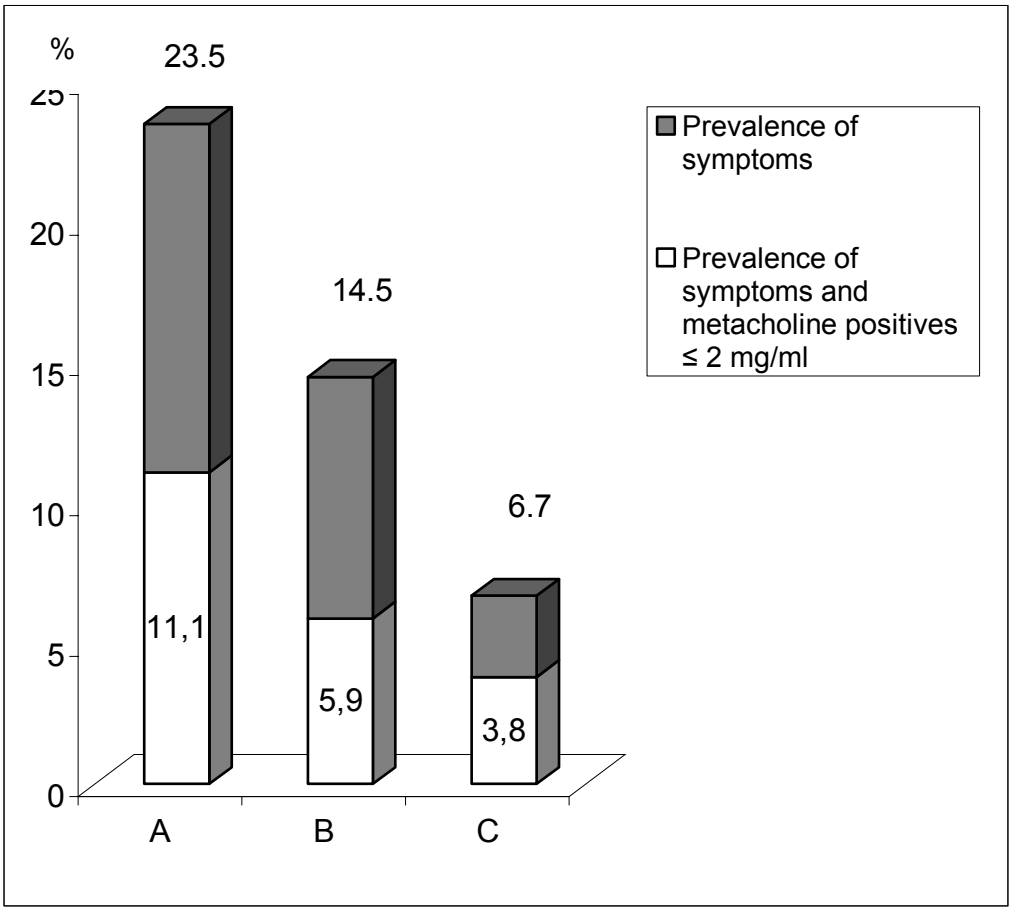
Risk factor analyses revealed a significantly increased risk of wheezing conditions for those living in Tallinn compared to Stockholm with odds ratios from 1.56 to 1.69, for longstanding cough, OR 1.92 (1.74-2.13), for attacks of shortness of breath during the previous 12 months, OR 1.35 (1.20-1.52), and for chronic productive cough, OR 1.49 (1.28-1.74). Subjects having symptoms common in asthma were more likely to have physician-diagnosed asthma in Stockholm and Helsinki than in Tallinn, while subjects having bronchitic symptoms had more often physician-diagnosed chronic bronchitis in Tallinn. Subjects having symptoms common in asthma reported often that they had chronic bronchitis. Although differences in prevalence between the cities were demonstrated, the risk factor pattern for diseases and symptoms in the cities showed no major differences.

PAPER IV - PREVALENCE OF ASTHMA IN ESTONIA USING DIFFERENT DIAGNOSTIC METHODS AND CRITERIA

The participation rate at the clinical follow-up study was 53.1%. It was lowest in Tallinn, 43.5%, while it was 59.8% in Narva and 67.1% in Saaremaa. The highest participation rate, 63.7%, was among women older than 45 years and the lowest, 41.3%, was among men younger than 30 years. No statistically significant differences in reported respiratory symptoms or diseases were found between all questionnaire survey responders and those participating at the clinical study. The proportion of current smoking was reported similarly in the postal questionnaire (PQ), 37.9%, as at the structured interview (SI) by the same subjects, 35.3%.

The prevalence of physician diagnosed asthma was 2.7% according to PQ, and 3.8% according to SI ($p=0.12$). Respiratory symptoms, except recurrent wheeze, were slightly more common in the SI than PQ. The prevalence of asthma defined by different symptom combinations varied from 5.4% to 8.2%. Of the combinations of symptoms we used when defining asthma, three resulted in almost identical estimates of prevalence: wheezing with breathlessness apart from cold, 6.7%; wheezing during the last 12 months, attacks of shortness of breath and asthma provoking factors, 6.6%; and recurrent wheeze, or wheezing with breathlessness apart from cold, and attacks of shortness of breath, 6.8%. These three symptoms seemed at the time to be relevant in defining asthma in epidemiological studies in Estonia. Among them, 53-60% demonstrated a bronchial hyper-reactivity defined as methacholine reactivity ≤ 2 mg/ml, 63-67% a methacholine reactivity ≤ 4 mg/ml, and up to 87% reacted to doses ≤ 8 mg/ml. The symptom combinations used as surrogate variables for asthma were strongly associated with a positive skin prick test.

Figure 5: Prevalence of symptoms and of a symptom combination common in asthma. Prevalence of the combination of hyper-reactivity and symptoms.



A	wheezing last 12 months
B	attacks of shortness of breath
C	wheezing with breathlessness apart from cold (WBAC)

PAPER V - CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN ESTONIA

Acceptable lung function tests were recorded for 1341 subjects, from 94.2% of invited men and from 93.2% of invited women. Of those examined, 38.3% were younger than 40 years, 35.4% middle aged (40-55 years) and 26.3% 56 years or older. The age distribution was 16-69 years, and 629 (47%) were non-smokers, 226 (17%) ex-smokers, and 486 (36%) current smokers. The prevalence of COPD in Estonia was 7.8%, among men 12.2% and women 4.1% according to the GOLD criteria. Prevalence among non-smokers was 4.6%, ex-smokers 10.6% and smokers 10.8%. The prevalence in Tallinn was 6.2%, Narva 8.1% and Saaremaa 9.7%, but these differences were not statistically significant. The prevalence of COPD was highly smoking-dependent among men, and of smoking men aged > 60 years, 44% had COPD (GOLD). Unexpectedly, in contrast to symptoms (Paper I), smoking seemed not to significantly influence the prevalence of COPD among women. However, the proportion of smokers among elderly women was very small.

Increasing age, male gender and smoking among men appeared as the predominant risk factors for COPD. Also, family history of obstructive airway disease was a significant risk factor for COPD. After standardisation of the results for the Estonian population aged, 15-64 years the adjusted prevalence of COPD was calculated at 7.0% in total; among men 9.8% and among women 3.9%. By smoking habits, the adjusted COPD prevalence was 4.2% among non-smokers, 9.0% among ex-smokers and 9.3% among smokers.

Table 3: Proportion of symptoms and physician diagnosed diseases among subjects with COPD according to the GOLD criteria.

Reported symptoms or diseases	**%**
Cough	73
Sputum production	66
Chronic productive cough	28
Wheeze	66
Breathlessness	59
Physician diagnosed chronic bronchitis or emphysema	31
Physician diagnosed asthma	11

DISCUSSION OF METHODOLOGY

Even if epidemiological studies of respiratory diseases have been performed for many years and been well validated, different types of bias can still occur during the process. This study started ten years ago in the fall of 1995. There was a strong need for epidemiological data of respiratory diseases in Estonia. Estonia was a young independent country, still having influences from the previous Soviet time.

STUDY DESIGN AND BIAS IN STUDY DESIGN

In designing a study, epidemiologists attempt to reduce two main types of errors, randomly occurring errors and systematic errors. A study can be affected by bias because of the way in which the subjects have been selected (selection bias), the way the study variables have been measured (information bias), or some other confounding factors (Rothman, 2002).

The current study was cross-sectional, aiming at estimating prevalence and risk factors. We conclude that the prevalence estimates are valid with the exception of physician-diagnosed asthma in Estonia, which according to Papers III and IV seems to considerably underestimate a true asthma prevalence in Estonia due to classification of disease and to observation. Risk factors calculated in cross-sectional studies must be judged carefully. They express associations of uncertain causality, and may express cause, consequence, or parallel phenomena.

Study areas were chosen in order to adequately give a cross-sectional picture of Estonia– urban and rural, and likewise two main ethnical group – Estonians and non-Estonians, mainly Russian-speaking population groups. Thus, the results of this thesis should thus be reasonably valid for Estonia in the relevant ages.

Study sample
The calculation of the study size was based on following estimates:

- Response rate at 75%
- Prevalence of disease between 4-8%
- Difference between men and women in the different centres of ≥ 1% unit to be statistically significant
- Significance level at $p<0.05$

The required sample size for the "FinEsS" study was estimated to be 8,000 subjects with a response rate of 75%. As we had no real prediction of the response rate in Estonia, the sample sizes of 12,000 in Tallinn and 6,000 in both Narva and Saaremaa were chosen.

The sample size was as large or larger than for other similar European studies (Burney et al, 1994; Bakke et al, 1991; Lundbäck et al, 1991; Larsson L, 1995; Hedman et al, 1999).

Stratification could create bias. Since the study aimed to make comparisons between areas, the study sample was stratified by age and gender. Stratification was performed within each age group (15-24 years; 25-34 years; 35-44 years; 55-64 years) and included similar numbers of randomly selected men and women in each stratum in each study

area. Stratification was performed because of uncertainty of participation in different ages. Stratification was also performed in Örebro, Sweden, but not in the other FinEsS centres.

The Questionnaire used is well validated (Lundbäck 1993; Larsson L, 1995; Lundbäck et al 2001). The questionnaire has been used in several surveys within the OLIN studies and other studies in Sweden (Larsson L et al, 1993; Montnemery et al, 1998; Hasselgren et al, 2001). A few questions were added. Still some bias may occur due to differences in language during translation or interpretation. In this context, it has become increasingly evident, that using descriptors of breathlessness can assist in understanding the language of dyspnea. Subjects can distinguish different sensations of breathlessness caused by a variety of conditions including cardiopulmonary diseases (Simon et al, 1990). In the language of dyspnea, ethnic/racial cultural differences exist and are important to consider in a study (Hardie et al, 2000).

The translation of the questionnaire was double-checked, and some small errors were identified that had no influence on the study results. The translation of the questions regarding profession and work were not correct and created problems when standardising socio-economic status. This process was time consuming but still resolvable.

A non-responder study was performed in Tallinn with a randomly selected sample of 200 non-responding subjects using 54 phone calls and 146 postal letters (response rate 40%). Main reasons for not responding were: not having received the questionnaire due to wrong address (36%), lack of time (19%), no interest to participate (16%), and forgotten to mail the questionnaire back (12%). The non-responders study was performed similarly to others of its type, in which non-response did not create any significant bias (Rönmark et al, 1999; Kotaniemi et al, 2001). All analyses about non-response have shown that the non-participants did not have had any major impact on the results in the Nordic countries, mainly due to the very high participation rate in nearly all surveys. However, the papers by Rönmark and Kotaniemi show that smokers and young manual workers were slightly, but significantly, underrepresented in surveys in both Finland and Sweden, although prevalence of symptoms and diseases were not notably affected due to the high participation rates in the original surveys.

LUNG FUNCTION TESTS

Spirometry
Lung function tests were performed and analysed in Paper IV and V. The same spirometer was used in all Estonian centres. A limited number of well-trained nurses and doctors performed the spirometry tests to minimise inter-observer bias and possible cooperation differences in performing spirometric measures. The test procedure followed the ATS recommendations (ATS 1987; 1991).

Due to different contra-indications, though not mandatory, such as un-treated heart disease, lung function tests were not performed or were not performed with acceptable technique in 91 subjects (6%) who participated in the follow-up study. The proportion of the non-performed or non-acceptable tests was similar in all areas and occurred mostly in the elderly. The reversibility test was performed in all subjects who performed spirometry by using 0.8 mg salbutamol via metered dose inhaler.

Bronchial hyper-responsiveness

Since 1970's, many different methods and modifications of methods for provocation challenges have been developed. In epidemiological studies bronchial hyper-responsiveness (BHR) has been used since 1980s. Ann Woolcock defined asthma in epidemiology almost three decades ago as "past or present breathlessness symptoms accompanied by bronchial hyper-responsiveness" (Woolcock et al, 1987). Later, this definition was developed further by Toelle, Woolcock and co-workers (Toelle et al, 1992). Still, there is an overlap with regard to bronchial responsiveness between asthmatic and non-asthmatic subjects, and also asymptomatic individuals may have increased responsiveness to metacholine (Lundbäck et al, 1992; Ehrs et al, 2005). Using the same Malmberg & Larsson (1991) method, Ehrs et al (2005) found that almost all patients with a clinically relevant asthma, though mild, reacted on methacholine doses ≤ 2 mg/ml. Thus a responsiveness below this cut-off level using the Malmberg & Larsson method can be regarded as hyper-reactivity.

In our study, the bronchial provocation test was performed according to Malmberg & Larsson (1991) by use of a dry simple device aiming to increase the deposition of nebulized metacholine in lower airways. The device controlled the inspiratory flow and volume. The method has a high sensitivity, and has demonstrated that the bronchial responsiveness to methacholine in many healthy subjects is nearly similar to what is found in mild asthma (Ehrs et al, 2005).

ALLERGIC SENSITISATION

Skin prick tests

The tests were performed by two researchers. The result of a skin prick test is dependent on the potency of the allergen extracts, the cut off limits, and the technique used (Haahtela, 1993). The impact of different allergens on allergic sensitisation and allergic diseases vary by country. In fact, there are today more than 300 allergenic substances for testing (Baldacci et al, 2000). In Estonia, the only study of allergic sensitisation in a general adult population performed prior to our study was carried out in the city of Tartu among subjects ages 20-44 years (Jõgi et al, 1995).

DISCUSSION OF MAIN RESULTS

The present study is the first large-scale epidemiological survey in Estonian adults of respiratory symptoms and diseases including COPD in relevant ages. The „FinEsS“ study was allowed to use a previously validated study design to find and compare prevalence and to identify risk factors of obstructive airway diseases in Estonia, Finland and Sweden. Specific aims were to estimate and compare the prevalence of respiratory symptoms, asthma, chronic bronchitis, COPD and type-1-allergy, in the different centers, to investigate if there are differences in prevalence between urbanised and rural areas, and to investigate the relationship of native and immigrant populations. Previously respiratory epidemiology of young adults and children has been studied within the framework of the European Community Respiratory Health Survey (ECRHS) in the Estonian city of Tartu in 1994. The prevalence of respiratory symptoms, asthma and allergic rhinitis among young adults aged 20–44 was studied (Jõgi, 2001). The International Study of Asthma and Allergy in Childhood (ISAAC) investigated children aged 10-12 years in 1992-1993 (Riikjärv et al, 1995). A cross-sectional study on the prevalence of allergic diseases and respiratory symptoms in Estonian pre-school and school-children was also performed in 1992–94 (Vasar, 1998).

PARTICIPATION

The response rate in the postal questionnaire study was 78%, and was slightly lower than in Sweden and Finland (Pallasaho et al, 2005). It was similar or slightly lower compared with other recent studies in the Nordic countries (Rönmark et al, 1997; Bakke et al, 2000; Eagan et al, 2002) and the local ECRHS (Jõgi et al, 1996), but higher or similar as the ECHRS in France (Neukirch et al, 1995) and in most European countries.

The participation at the clinical follow-up study was 53%, lower than in the local ECRHS (Jõgi et al, 1998), but similar to the “FinEsS”study centres in Helsinki and Stockholm, though lower than in Northern Finland (Kotaniemi et al, 2005). The low participation may partly have been due by the possibility that persons having economical difficulties were not motivated to participate in studies. Also, communication with the subjects and agreement on the time for examination was complex. For instance, phone contacts were difficult because of lack of the traditional phones, since not all subjects had any type of telephone, whereas in other locations, telephone-based methodology has been proved to facilitate participation in population studies (de Monchy et al, 2004). Despite the low participation rate, the analysis performed to investigate the representativity of the study sample of the clinical follow-up study showed no difference in prevalence of symptoms in the PQ answers between all participants in the PQ survey and those who participated in the follow-up study (Paper IV).

SMOKING HABITS

The prevalence of male smokers, 57%, was approximately twice as high as among women, 28% (Paper I). The same proportion of smoking men, 58%, was found in the ECRHS survey in Tartu, while 34% of women in Tartu smoked (Jõgi et al, 1996). The ECRHS study in Tartu covered the age of 20-44 years. The smoking habits among men

were twice as high as compared with the results from the „FinEsS“ studies in Finland and Sweden, while the prevalence of female smokers was similar to the levels in the other Nordic countries (Pallasaho et al, 1999; Lindström et al, 2000; Kotaniemi et al, 2001). Among Estonian men, 24% were heavy smokers consuming 15 cigarettes or more per day. The proportion of current smokers decreased gradually after the age of 40 both among men and women. The same trend has been observed in Sweden although the overall prevalence of smoking was lower in Sweden already during the 1970's and 1980's (Kiviloog et al, 1974; Stjernberg et al, 1985; Lundbäck et al, 1991). The different trends in smoking habits deserve to be summarised. When comparing the three capitals (Tallinn, Helsinki and Stockholm), both current smoking, and smoking more than 14 cigarettes daily were most common in Tallinn among men of all ages. In women older than 40 years, current smoking was most common in Stockholm, while younger women most often were current smokers in Tallinn. In contrast to Helsinki and Tallinn, current smoking was more common among women than men younger than 50 years in Stockholm (Paper III).

Smoking was the major risk factor for respiratory symptoms with no consistent influence of gender. Bronchial reactivity to cigarette smoke is a tobacco smoke specific bronchial response being important for symptoms and prognosis in chronic bronchitis and COPD (Jensen et al, 1998). Association between smoking and airflow limitation has been found to be stronger than the association with alcohol consumption, educational level and income (Lange et al, 1989). For ex-smokers, after smoking cessation, the decline rate of FEV_1 levels off but without a return of FEV_1 to the basal level (Fletcher et al, 1976). Smoking cessation protects people with mild COPD from additional loss of lung function (Kanner et al, 2001). Our finding that a large proportion of elderly smokers develop COPD has support in other studies (Sobradillo et al, 1999; Mannino et al, 2000; Lundbäck et al, 2003; Kotaniemi et al, 2005). As in other studies, the prevalence of COPD was strongly dependent on smoking habits, however, in our study among men only. The difference in prevalence of COPD between non-smokers and smokers was not as large as found in Sweden and Finland (Lundbäck et al, 2003; Kotaniemi et al, 2005).

In Estonia the environmental tobacco smoke (ETS) exposure at home was also high, in women 31% than in men 19%. In contrast, exposure outside the home was more common in men (53%) than in women (37%), and 23% of men reported more than one hour of ETS exposure outside of the home compared to 16% of women (Larsson M et al, 2003). Exposure from ETS may contribute to the high prevalence of respiratory symptoms among non-smokers, in particular non-smoking women. In Estonia, compared to the Nordic countries, many families have small apartments and live in overcrowded conditions. For example, this may mean that if the father in a family smokes, the other non-smoking family members are at risk for considerable ETS exposure. In east-west comparative studies, ETS at home during infancy has been detected to be a risk factor for atopic disease especially in Eastern Europe (Bråbäck et al, 1995). The effects of ETS in women may be more serious than in men, since women may be more susceptible to tobacco smoke (Becklake et al, 1994). A considerable number of studies have evaluated the effects of ETS on asthma in childhood (Jaakkola, 2000).

PREVALENCE OF RESPIRATORY SYMPTOMS AND DISEASES

Respiratory symptoms

The prevalence of at least one respiratory symptom was 45% among the Estonian adults, which is slightly higher than the results found in Finland and Sweden when using the same questionnaire (Lindström et al, 2001). We found a higher prevalence of bronchial hyper-responsiveness and allergic sensitisation (Raukas-Kivioja et al, 2003) than has been reported previously in Eastern Europe (ECRHS, 1996; von Mutius et al, 1994; Jõgi et al, 1996).

Starting from the time of the breakup of the Berlin Wall and the fall of communism, the ‚East-West' lifestyle disparity started to diminish, and this has provided an opportunity to investigate life-standard and environmental influence on respiratory disease. Comparative studies between developed affluent market economies and previous social countries detected low prevalence of allergies and asthma both among children (Bråback et al, 1994; 1995; von Mutius et al, 1992; 1998; Schafer et al, 1996; Duhme et al, 1998; Björksten B et al, 1998; Weiland et al, 1998) and adults (von Mutius et al, 1994; Nowak et al, 1996; Nicolai et al, 1997; Jõgi et al, 1998). A majority of studies have shown asthma to be more common in ‚West', although many studies have found no major differences in prevalence of respiratory symptoms (Bråback et al, 1994; 1995), or found prevalence rates higher in the ‚East' (von Mutius et al, 1992; 1994; Bråback et al, 1994; Jõgi et al, 1996).

Asthma

Today, respiratory allergic disorders and asthma constitute a hudge health problem in Europe, and the impact may be increasing since the prevalence is highest among young people. The overall weighted prevalence of respiratory allergic disorders in Europe has been estimated at 24.4%, varying from 11.7% in Spain to 33.6% in Italy (Dahl et al, 2004). Even wide geographical variations of atopy have been observed in the ECHRS study (Sunyer et al, 2004). Among children, lifestyle may affect the atopy-related disorders. The hypothesis that „western lifestyle" is associated with a high prevalence of childhood allergy has been supported by comparative studies of Scandinavia and Eastern Europe. The prevalence of atopy-related disorders has been found higher in Scandinavia than in Estonia, Latvia and Poland (Björksten et al, 1998). A recent investigation in Estonian children born before and after the regaining of the Estonian independence has shown a similar increase of allergic diseases indicating that influence of „Western" lifestyle may be operative throughout childhood (Annus et al, 2005).

The prevalence of symptoms common in asthma, such as attacks of shortness of breath, recurrent wheeze, any wheeze during the last 12 months, and combination of such symptoms, was found in Estonia to be similar or even higher than reported in studies in the Nordic countries and the ECHRS in Estonia. At the same time, the prevalence of physician-diagnosed asthma was reported by the PQ study to be only 2%, which is much lower than the prevalence found in studies in the neighbouring countries Sweden and Finland, where the prevalence was 6-9% (Lundbäck, 1998; Pallasaho et al, 1999; Kotaniemi et al, 2001). The contradiction of the results, that is, where only 23.1% of the subjects living in Tallinn who had "wheezing with shortness of breath without cold" had been diagnosed as having asthma, while the corresponding figures in Stockholm and Helsinki were 48.0% and 43.8%, respectively, probably refers to an underdiagnosis of asthma in Estonia (Paper III).

When defining operational criteria for asthma in our study, we examined a number of combinations of symptoms common in asthma. Three of them resulted in almost identical estimates of prevalence: wheezing with breathlessness breath apart from cold, 6.7%; wheezing during the last twelve months, attacks of shortness of breath and asthma provoking factors, 6.6%; and recurrent wheeze or wheezing with breathlessness apart from cold and attacks of shortness of breath, 6.8%.

These three above mentioned combinations of symptoms showed also a similar pattern with BHR. Further, all symptoms and combinations of symptoms used were significantly related to skin prick test positivity. Of the subjects fulfilling these three symptom criteria, 53-60% were hyper-reactive to methacholine doses ≤ 2 mg/ml, 63-67% were reactive to doses ≤ 4 mg/ml, and up to 87% reacted to doses ≤ 8 mg/ml. In contrast, only 67% of subjects reporting physician-diagnosed asthma reacted to doses ≤ 8 mg/ml. Of patients with clinically relevant asthma, almost all have reacted on doses ≤ 2 mg/ml using the same Malmberg & Larsson (1991) method (Ehrs et al, 2005).

Our results can be contrasted to results found among Estonian children. A comparative study of Swedish and Estonian schoolchildren suggested that although wheezing symptoms were equally common in Estonia and Sweden; they were less severe in Estonia. More frequent symptoms and a high rate of atopy, BHR and anti-asthmatic medication characterized wheezing children in Sweden. In contrast, BHR, atopy and medication were less common among wheezing children in Estonia (Annus et al, 2001). BHR was also determined among Estonian schoolchildren by several methods, but none of the methods were very useful for the identification of wheezing or asthmatic children. In contrast to the results of studies in Western Europe, most children with bronchial hyper-reactivity in Estonia were not atopic in early 1990s (Vasar et al, 1996).

Ann Woolcock defined asthma in epidemiology almost three decades ago as past or present breathlessness symptoms accompanied by bronchial hyper-responsiveness (Woolcock et al, 1987). Later on, this definition was developed further by Toelle, Woolcock and co-workers (1992). When interpreting our results using the above method for defining asthma, the prevalence in Estonia would be even higher than observed using our operational asthma criteria. The prevalence of wheezing during the last 12 months was 23.5% at interview in our study. As 47% among them reacted to methacholine doses ≤ 2 mg/ml, the prevalence of asthma using the Woolcock criteria would have been 11%. Since almost a half of the subjects reporting symptoms common in asthma, such as wheezing (prevalence 23.5%) and attacks of shortness of breath (prevalence 14.5%), were hyper-reactive as defined as PC_{20} ≤ 2 mg/ml methacholine, the prevalence of asthma would be within the range of 6-11% using the criteria suggested by Woolcock and co-workers (Woolcock et al, 1987; Toelle at al, 1992). When using the symptom combinations having a prevalence of 5-8% instead of "past or present breathlessness symptoms" together with hyper-reactivity as a definition of asthma, 3-5% would have been classified as having asthma in Estonia. Such definition includes probably very few false positives or non-asthmatic subjects classified as having asthma, while many subjects with mild intermittent asthma might not have been identified (i.e. high positive predicted value and high specificity but low sensitivity).

The relatively lower proportion**,** 67%, of subjects with physician-diagnosed asthma who were reactive on doses ≤ 8 mg/ml methacholine reflects a low positive predictive value, and the low prevalence of physician diagnosed asthma itself reflects a low sensitivity when the symptom combinations were used as surrogates for a clinically relevant asthma. Using the question "ever having asthma" as test yielded similar results. Instead, use of asthma medicines as test for asthma resulted in somewhat higher sensitivity and positive predictive value. If one assumes that the symptom combinations are reasonable as a measure of a true or clinically relevant asthma prevalence, then use of asthma medicines was a better instrument than physician-diagnosed asthma when estimating asthma prevalence in Estonia in the late 1990's.

Use of asthma medication was reported in the PQ to be 2.4%. The time difference from the PQ survey to the SI study was only 1-4 years. The prevalence of physician-diagnosed asthma had increased to 3.8% and use of asthma medicines to 5.4% illustrating the changes and development of clinical practice. Positive changes in the community and awareness enhance people's ability to evaluate their health and go to the doctors in earlier stages of diseases. Influence of the large western pharmaceutical companies and their marketing may also have effected this process. Also the ECRHS follow-up study found an increase in the proportion of subjects treated for asthma but not in the prevalence of those reporting symptoms common in asthma (Toren et al, 2004). Either increased use of effective treatment has resulted in decreased morbidity among asthmatic subjects, or those with mild disease have become more likely to label themselves as asthmatic (Chinn et al, 2004). The changes in asthma prevalence in adults may result from increased awareness of symptoms, and/or an increased willingness to report them, and/or from an increased willingness of physicians to make the diagnosis and prescribe treatment, but probably not mainly from increased disease prevalence (Lundbäck et al, 2001; Barraclough et al, 2002). Despite a changed environment, no changes in the prevalence of asthma, allergic rhinitis, respiratory symptoms and atopic sensitisation over 4 years in 10-11 year old schoolchildren in Estonia were found (Riikjärv et al, 2000).

In summary, when using criteria for asthma based on combinations of symptoms, a probable prevalence of asthma among adults in Estonia would have been 5-8% in the late 1990s. When using more strict criteria for asthma, as suggested by Woolcock et al (1987), the prevalence of asthma in Estonia would have been even higher. The prevalence seems higher than has been supposed and found in previous studies based on patient self-reporting of asthma and on physician-diagnosed asthma. The use of a report of asthma or a report of physician-diagnosed asthma as measures of asthma prevalence results in a large underestimation of asthma in the general population of Estonia. Since asthma-related symptoms are common in Estonia, the results indicate a low awareness of asthma in the general population, underdiagnosis of the disease, and use of different diagnostic criteria for asthma in the clinical praxis compared with Nordic and Western European countries.

Chronic bronchitis and COPD

Our study assessing different respiratory symptoms showed a consistent pattern that Estonian subjects yielded a high prevalence of symptoms, with a high proportion being diagnosed with chronic bronchitis, even among subjects aged 20 to 30 years. When comparing our findings with the results of studies performed up to 30 years ago in the Baltic countries, the prevalence of chronic bronchitis had not markedly changed (Utkin et al, 1989). The prevalence of diagnosed chronic bronchitis in Estonia was considerably higher than in Scandinavian countries (Kiviloog et al, 1974; Stjernberg et al, 1985;

Lundbäck et al, 1991), but similar to that in United Kingdom, where chronic bronchitis was found to affect 17% of men and 7% of women (Littlejohns et al, 1989). Also studies in Denmark have indicated a high prevalence of chronic bronchitis (Iversen et al, 1988). Despite the higher prevalence of smokers among men than women in our study, the prevalence of chronic bronchitis was found to be higher in women. Further, in all different smoking categories, and in all study areas, physician-diagnosed chronic bronchitis was more common among women.

In contrast to other studies in Europe (Huhti et al, 1965; Kiviloog et al, 1974; Gulsvik et al, 1979; Stjernberg et al, 1985; Terho et al, 1987; Littlejohns et al, 1989; Lundbäck et al, 1991; Larsson L et al, 1993; Pallasaho et al, 1999), the prevalence of chronic productive cough was lower than the prevalence of physician-diagnosed chronic bronchitis, which became apparent especially among non-smokers, a finding that may be a result of different diagnostic labelling influenced by the criteria used in former Soviet Union (Kokosov et al, 1984). There was no minimum time limit for the symptomatic period, that is, three months a year during at least two successive years (ATS, 1962), to make the diagnosis of chronic bronchitis according to the Soviet definition of chronic bronchitis.

Nevertheless, the large differences between Estonia and the neighbouring Nordic countries in prevalence of disease level, and the more limited differences on symptom level, is probably a result of differences in diagnostic labelling of disease. Until the end of 1980`s, the definitions of chronic non-specific respiratory diseases officially accepted in the Soviet Union were used in Estonia. Our study was performed before major changes had taken place in socio-economic status, social life, or life-style in Estonia. Further, the traditional diagnostic practices still existed with chronic bronchitis as a large disease entity within the group of diseases labelled chronic pneumonia with asthma as a subgroup within chronic bronchitis (Ado et al, 1976; Kokosov et al, 1984).

Chronic bronchitis and chronic mucus hyper-secretion are not only disturbing symptoms, but they are also associated with a faster decline in lung function (Vestbo et al, 1996; Lindberg et al, 2005). Although generally accepted criteria for chronic bronchitis have existed for decades, our study suggests that comparisons of prevalence of chronic bronchitis between countries can preferably be made on symptom level, i.e., chronic productive cough, as has been suggested by the Swedish OLIN- studies (Lundbäck et al, 1994) and as has been done in the ECRHS (Cerveri et al, 2001).

Data on COPD in Estonia based on epidemiological studies were missing before the FinEsS study. We had expected the prevalence of COPD in Estonia to be considerably higher than in the neighbouring Nordic countries. The prevalence of COPD for those aged 16-69 years was found to be 7-8% according to the GOLD criteria, similar or somewhat higher than in comparable ages in the neighbouring Nordic countries (Bakke et al, 1991; Kotaniemi et al, 2005). Some of the risk factors for COPD are well known and include smoking, air pollution, occupational exposures, but also poverty, passive smoking, age, sex, familiar and genetic factors (Doll et al, 1994; Siafakas et al, 1995; Buist 1996; Sobradillo et al 1999; Viegi et al, 2001; Mannino 2002; Lundbäck et al, 2003; Vestbo 2004). As Estonian men smoke two times more than women, it was expected that COPD among men would be more frequent than among women. At the same time, the non-smoking elderly women had a similar prevalence as elderly smoking women, a result that has been discussed previously. Historically, male gender was considered a risk factor for COPD (Davis et al, 1989). Recently has been suggested that women may be more susceptible to develop COPD, which is always interpreted in the

context of the relatively recent increase in cigarette smoking among women (Gold et al, 1996; Silverman et al, 2000), but there is also a possible risk factor in the environmental tobacco smoke.

We have found that the prevalence of COPD in Estonia is similar as has been estimated in several community studies, 4-8% in adult population samples, with a considerable increase by age and smoking. One must keep in mind that there were study limitations where those age 70 years and older were not included in our study. Manual workers in industry with exposure to dust, gas and fumes are at risk for COPD, and a family history of obstructive airway disease is related with COPD, the later confirming results by others (Eagan et al, 2004; Lundbäck et al, 2003).

REGIONAL AND SOCIO-DEMOGRAPHIC DIFFERENCES IN PREVALENCE OF RESPIRATORY DISEASES AND SYMPTOMS WITHIN ESTONIA

Respiratory disorders constitute a huge health problem over the world. Allergic disorders are increasing in younger and chronic bronchitis and COPD in older people. Asthma is reported to be most common in Australia and New Zealand, followed by the UK and areas in the US and Canada, all of which are "western" and predominantly English speaking countries (Woolcock, 1991; ECRHS 1996; D'Souza et al, 1999; ISAAC 1998; Arif et al, 2003). Although asthma is least common in rural areas in developing countries, for instance in Africa (Dagoye et al, 2003) and in the interior of China (Cheng-Yeung et al, 2002), the prevalence is high in large cities in developing countries (Brogger et al, 2003). Furthermore, asthma is generally more common in urban compared with rural areas (Braun-Fahrlander et al, 1999; Kilpelainen et al, 2002). Though dominated by urban living, Eastern but also Central Europe have been reported to have a relatively low prevalence of asthma (Jõgi et al, 1996; Robertson et al, 1993).

The selection of the areas aimed to give a cross-sectional picture of Estonia, including the rural area of the island Saaremaa, the capital Tallinn, and the heavily industrialised town Narva. The choice of the study regions was based on the ethnic composition and the level of air pollution in Estonia aiming to reflect a representative sample of the whole Estonian population. The ethnical composition of the population necessitated the use of questionnaires both in the Estonian and the Russian languages. As far as we know the use of questionnaires in different languages created no adverse problems.

The proportion of smokers was similar in the three study areas also by gender and age. The prevalence of respiratory symptoms increased with age, while no major gender differences were found, though the proportion of smokers among men were considerably higher than among women. All respiratory symptoms were most prevalent in Narva. The prevalence rates were in general lowest in Saaremaa, likewise the prevalence of asthma and physician-diagnosed chronic bronchitis. In agreement with others (Bråbäck, 1995; Wieringa et al, 1997), an urban factor was also found for asthma, and living in Tallinn or Narva, compared with Saaremaa, yielded a slightly increased risk of being diagnosed as having asthma or symptoms common in asthma.

Notably, there was a trend of higher prevalence of COPD (although attributed to mild COPD) found in the rural island of Saaremaa, especially in older men and women, and also in non-smoking subjects. These findings differ from findings in certain studies, showing that living in urban areas is associated with a higher risk of chronic respiratory symptoms compared to living in rural areas and being exposed to airborne polluting

agents (Dockery et al, 1993; Viegi et al, 1991; Bakke et al, 1991). However, there are also studies showing high prevalence of bronchitic symptoms in rural areas (Iversen et al, 1988).

There was no difference between the areas according to the proportion of participation in lung function tests. Difference in smoking habits does not seem to explain most of this trend in variation, since these differences were small in magnitude and, moreover, the area with the highest prevalence was the area with the highest percentage of those who had never smoked. Several studies have also suggested that COPD may be present in specific families, and some genetic alterations have been related with a higher risk of developing COPD (Sandford et al, 1997). The island Saaremaa has been a closed area before 1991 because of military policy of Soviet Union and has had a relatively constant population. We cannot exclude the possible influence of biological or genetic differences in the risk of obstructive lung disease. Further investigation is needed in the future to exclude different forms of possible bias.

Effects of ethnical differences and migration have been investigated throughout the world (Ballin et al, 1998; Rosenberg et al, 1999; Ledogar et al, 2000; Tobias et al, 2001; Valery et al, 2001; Arif et al, 2003). In all our three investigated areas, the prevalence of smokers among Estonians compared to non-Estonians was lower (Paper II). All respiratory symptoms examined were significantly more common among non-Estonians and remained so after correcting for possible confounders including smoking. This was true particularly for chronic bronchitis and bronchitic symptoms, while the differences in symptoms common in asthma were less pronounced. Symptoms common in asthma were slightly more common among non-Estonians than Estonians, and remained so after correction for age, gender, family history of the disease, smoking habits and area. The prevalence of chronic bronchitis in non-Estonians was almost twice as high than in Estonians. Especially high was the prevalence in non-Estonians compared to Estonians in the age group of 60–64 years, 24% vs. 9%, respectively. This difference is partly related to the higher prevalence of smokers and smoking in living rooms among non-Estonians, and probably also to living in highly polluted areas, particularly in Narva, in which non-Estonians comprise a large majority. Narva is situated in the vicinity of two major air pollution sources in Estonia, the Baltic and Estonian Thermal Power Plants. Therefore, the pollution level has been continuously high (Kallaste et al, 1992). However, also after correcting for age, gender, area, smoking habits, and socioeconomic group, being non-Estonian was associated with a notably higher risk for chronic bronchitis, as well as for bronchitis symptoms, such as chronic productive cough, sputum production, longstanding cough, and also recurrent wheeze.

SUMMARY OF RISK FACTORS

The risk of having asthma, chronic bronchitis, respiratory symptoms and COPD was calculated both by using bi-variate analyses and multiple logistic regression analysis. Risk factor analyses revealed that heavy smoking was the major risk factor for respiratory symptoms with no consistent influence of gender. Age and family history of obstructive lung diseases influence also respiratory symptoms and diseases. Living in the polluted area of Narva was associated with the highest risk for mainly bronchitic symptoms, even after taking into consideration the effects of smoking, age, gender, and family history of obstructive airway diseases. In addition to general air pollution, the industrial setting of the Narva region may also contribute to occupational airborne exposure of importance. Living in the rural Saaremaa was associated with the lowest

risk for all symptoms. For smokers living in Narva vs non-smokers living in Saaremaa the ORs were 8 - 10 for having either one or other of these two conditions.

Increasing age, male gender and smoking (in men only) appeared as the strongest risk factors for COPD. After taking into consideration age, gender, and family history, living in the polluted area of Narva was not associated with a higher risk compared with living in the rural less polluted island of Saaremaa. In contrast to the pattern of bronchitis symptoms, COPD tended to be most common in Saaremaa. However, this trend was attributed only to GOLD stage 1. As found by others, family history of obstructive airway disease was significantly associated with COPD (Sobradillo et al, 1999; Lundbäck et al 2003; Kotaniemi et al, 2005).

SUMMARY OF COMPARISON WITH FINLAND AND SWEDEN

This study showed an obvious difference in diagnostic practices regarding obstructive airway diseases between Finland and Sweden versus Estonia. A markedly higher proportion of subjects with asthma-related symptoms had physician-diagnosed asthma in Sweden and Finland than in Estonia, whereas Estonian physicians favoured the diagnosis of chronic bronchitis.

Our study showed a consistent pattern where Estonian subjects had a high prevalence of symptoms and a high proportion being diagnosed with chronic bronchitis, whereas the proportion of diagnosed asthma was lower than among Finnish and Swedish subjects (Kotaniemi et al, 2001; 2002; Pallasaho et al, 1999; 2004; 2005; Lindström et al 2001; Larsson M et al, 2001). Even attacks of shortness of breath, which was the strongest predictive symptom for asthma, was most common in Estonia. Similar results were reported by the ECRHS: prevalence of wheezing was higher in Estonia, 26.5%, than in Sweden, 19.0%, whereas the proportion of subjects classified as having asthma based on the two questions “having suffered from an asthma attack” or “currently using asthma medication” was only 2.0% in Estonia compared to 5.9% in Sweden (Jõgi et al, 1996). This difference may reflect a different meaning of the term asthma according to the general opinion in Estonia compared with that in Sweden and Finland in addition to the differences in diagnostic traditions.

Although the symptoms were generally most common in Estonia, their prevalence did not differ greatly between the three countries. Interestingly, the total proportion of diagnosed airway diseases, either asthma or chronic bronchitis, was at the same level in all countries, which also suggests a difference in diagnostic practices. Thus, in Estonia the very low prevalence of physician-diagnosed asthma on one hand, and the high prevalence of chronic bronchitis on the other hand, may to a great extent be explained by different diagnostic traditions and not only by differences in true prevalence. Irrespectively of what symptom was present, the diagnosis of chronic bronchitis was preferred in Estonia.

Most respiratory symptoms, both symptoms associated with asthma or chronic bronchitis, were more common in Estonia. A higher likelihood for the diagnosis of asthma and a lower likelihood for the diagnosis of chronic bronchitis appeared in Sweden and Finland than in Estonia. Asthma is probably under-diagnosed in Estonia, whereas chronic bronchitis may be under-diagnosed in Sweden and Finland. Further studies combining symptom questionnaires with lung function measurements, hyper-reactivity and atopy testing will provide a more detailed picture of diagnostic differences between the countries.

CONCLUSIONS

1. The prevalence of respiratory symptoms was high in Estonia. It was most common in Narva, followed by Tallinn and Saaremaa. The most common symptoms were sputum production (prevalence 30%), longstanding cough (24%) and wheezing during the last 12 months (22%). The prevalence of physician-diagnosed chronic bronchitis was 11% (15% in Narva, 10% in Tallinn and 6% in Saaremaa). The prevalence of physician-diagnosed asthma according to postal questionnaire was 2.0%, and at interview a few years later it was 3.8% (4.3% in Tallinn, 4.2% in Narva and 2.7% in Saaremaa). The prevalence of COPD was 7.8% with no statistically significant differences between the three areas. After adjusting for the age and gender distribution in each area and for smoking habits in the population, the prevalence was slightly lower.

2. Smoking and having a family history of obstructive airway diseases were risk factors for all respiratory symptoms, while increasing age was a risk factor for bronchitic symptoms. Living in Narva compared with living in Saaremaa and living in Tallinn compared with the Nordic capitals Stockholm and Helsinki was associated with an increased risk for most symptoms. Family history of asthma was the major risk factor for asthma. Increasing age, male sex and smoking (in men only) were dominating risk factors for COPD. When comparing Estonians and non-Estonians living in Estonia, physician-diagnosed chronic bronchitis was significantly more prevalent in non-Estonians than in Estonians. Similar significant differences were found in prevalence of all respiratory symptoms, especially those common in chronic bronchitis. The prevalence of physician-diagnosed asthma in native Estonians and non-Estonians was similar.

3. Measuring prevalence of asthma based on postal self-administrated questionnaire and structured interview compared with results of functional and clinical data, it can be concluded that physician-diagnosed asthma in Estonia reflects probably a considerable under-diagnosis. Disease criteria for asthma based on symptom combinations yielded a prevalence of 5-8%, which is similar to the prevalence of asthma among adults in neighbouring Nordic countries.

4. In Estonia, the prevalence of chronic bronchitis was found to be much higher, of physician-diagnosed asthma much lower, and of COPD nearly similar compared with Sweden and Finland. The considerable differences in prevalence of physician-diagnosed asthma between Estonia, Finland and Sweden could at least partly be explained by differences in diagnostic practices. Diagnostic criteria based on the Soviet-time definitions is discussed as a possible explanation to the low prevalence of physician-diagnosed asthma and the high prevalence of chronic bronchitis in Estonia compared with other Nordic countries. Asthma in Estonia and chronic bronchitis in Sweden and Finland seemed to be under-diagnosed.

5. Despite differences in prevalence of symptoms and diseases, the risk factor pattern was similar in the three countries.

PERSPECTIVES

In spite of large number of respiratory epidemiological studies, the reasons for the increasing prevalence of many respiratory diseases are still largely unknown. In our modern world, changes in, environment, lifestyle and living standards evoke consideration of possible new determinants and risk factors for respiratory disease, helping to bring about changes in understanding and treatment of diseases.

Our study was started before the relatively recent large changes in economy and life style occurred in Estonia. There is a strong need for follow-up studies to help bring knowledge of health effects of these accelerating changes in the community. Large cohorts are required to ensure that associations may be explained by risks, rather than by chance. More longitudinal studies in relevant populations are needed. Further co-operation between different disciplines, medical and non-medical, in the field of public health deserves increased attention and support in order to facilitate such studies.

ACKNOWLEDGEMENTS

The writing of these papers and this thesis has been an ongoing process, to which many people have contributed, and therefore I want to express my sincere gratitude for their time and assistance. Thanks to the help of my colleagues and their contributions, it has been possible for me to be concurrently a scientist, practicing doctor and a mother for my children.

My greatest gratitude goes to my supervisor **Bo Lundbäck**, for encouraging me to pursue the interesting, yet pothole-filled road of a scientist; for guiding me and showing me the key to writing scientific articles, for being there for me and for answering my questions. Also I would like to thank his whole family for warm-hearty reception and unforgettable visits in Umeå.

From the bottom of my heart I want to thank my teacher and guide, co-supervisor **Lii Jannus-Pruljan**, whose open heart, wisdom, grace has helped me find balance in numerous instances.

Deep thanks to **Eva Rönmark**, my co-supervisor, for all her relevant advice, comments and support.

My respect and gratitude also goes to **Kjell Larsson**, my co-supervisor, for his advice, his never ending wisdom and suggestions.

I am grateful to **Jaak Kiviloog** in Örebro – without you I would never have begun this work.

My gratitude goes to all colleagues in the department of pulmonology in The Institute for Health Development – the head **Helle-Mai Loit** and scientific secretary of the Institute **Jaak Põlluste,** for their never ending energy. **Elvi Lillak, Evi Raukas, Ingrid Täht, Aet Raukas-Kivioja, Ave Nagelman** and study nurse **Lea Laht**. Thank you for such pleasant cooperation and teamwork. Also I would like to thank the Department of Epidemiology, especially **Mati Rahu**, who never seems to run out of useful advice, **Mall Leinsalu** for sociodemographic data and help, and **Tatjana Veideman**, the statisticians, who always conducted her data processing precisely and fast.

I thank you – all of "FinEsS" international team, for being a happy family, especially **Elsy Jönsson** in Umea for statistical data processing; **Britt-Marie Sundblad** in Stockholm for your support and advise; **Mai Lindström** in Lulea – I thank you for your compelling enthusiasm and energy; **Jyrki Kotaniemi** in Kemi for your interesting discussions; **Paula Pallasaho** in Helsinki – thank you for you cooperation and partnership; **Matz Larsson** and **Margot Frisk** in Örebro for frutful co-work.

Thanks to **Rain Jõgi**, the Chief of the Tartu University Lung Clinic for cooperation and long lasting friendship.

I want to thank my teacher **Ritva Tammivaara** in Turku, for teaching me first skills in communicating with the Western medical world.

My thanks go to all my friends at the Karolinska Institute Environmental Intstitute for your understanding and acceptance, especially secretaries **Ulla Sundberg** and **Evi Werendel** for great help in navigating the bureaucracy.

Special thanks to **Michael Haney** for linguistic revision of papers and this thesis.

I highly value all the efforts of my colleagues in Tallinn Diagnostic Center and Estonian Ministry of Social Affairs, whose helpful attitude made it possible for me to keep on fighting on many fronts.

The Swedish Heart-Lung Foundation, the Estonian Scientific Foundation (grants number 3630 and 3636), and the Swedish Committee for Eastern European Affairs, are acknowledged for financial support.

My dear family, I thank you for understanding and supporting me always. My daughters **Triinu, Ülle Helena** and **Teele**, if you hadn't been brave, hard working and resourceful, it would have been so much more difficult to complete my theses. My husband **Tiit**, thank you for being my first and primary advisor, assistant and critic; I thank you for those prolific conversations.

My sisters, especially **Juta**, whom I can always count on. If you hadn't taken the time to protect the back front, things wouldn't have gone so smoothly.

My parents, I thank you for instilling the values that you did in me.

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APPENDIX

The FinEsS questionnaire (postal)

	Yes	No, don't know
1. Have any of your parents, brothers or sisters had:		
a) Asthma	( )	( )
b) Allergic eye-/ nose catarrh (hay-fever)	( )	( )
c) Chronic bronchitis or emphysema	( )	( )
2. Have you now or have you had any of the following diseases:		
a) Asthma	( )	( )
b) Allergic eye-/nose catarrh (hay-fever)	( )	( )
c) Chronic bronchitis or emphysema	( )	( )
d) Any other lung or airways diseases	( )	( )
If „yes", which: ……		
3. Have you been diagnosed as having asthma by a doctor?	( )	( )
4. Have you been diagnosed as having chronic bronchitis or emphysema by a doctor?	( )	( )
5. Do you currently use asthma medicines permanently or as needed?	( )	( )
6. Have you now or have you had asthma symptoms during the last 10 years (intermittent breathlessness) or attacks of shortness of breath. The symptoms may exist simultaneously with or without cough or wheezing?	( )	( )
If „yes":		
a) Have you had these symptoms during the last year (the last 12 months)?	( )	( )
7. Have you had longstanding cough during the last years?	( )	( )
8. Do you usually have phlegm when coughing, or do you have phlegm on your chest, which is difficult to bring up?	( )	( )
If „yes":		
a) Do you bring up phlegm on most days during periods of at least three months?	( )	( )
b) Have you had such periods during at least two successive years?	( )	( )
9. Have you wheezing, whistling or a noisy sound in your chest when breathing?	( )	( )
10. Have you had wheezing or whistling in your chest at any time in the last 12 months?	( )	( )
If "no" go to question 11, if "yes":		
a) Have you been at all breathless when the wheezing noise was present?	( )	( )
b) Have you had this wheezing or whistling when you did not have a cold?	( )	( )

11. Have you awakened up with a feeling of tightness in your chest at any time in the last 12 months?	( )	( )
12. Have you been woken by attack of shortness of breath at any time in the last 12 months?	( )	( )
13. Do you usually have breathlessness, wheeze or severe cough:		
a) on effort	( )	( )
b) in cold weather	( )	( )
c) on effort in cold weather during winter	( )	( )
d) in dusty places	( )	( )
e) from cigarette- or tobacco smoke	( )	( )
f) from car exhaust fumes	( )	( )
g) from strong smelling scents (perfumes, spices, printing ink, cleaner)	( )	( )
h) from pollen	( )	( )
i) from animals with fur (cat, dog, cow, horse etc)	( )	( )
14. Do you smoke? (smokers also include those who smoke a few cigarettes or pipe fills a week, and those who have stopped smoking during the last 12 months)?	( )	( )
If „yes“:		
a) How many cigarettes do you smoke per day?		
Less than 5	( )	( )
5-14	( )	( )
15 or more	( )	( )
If „no“	( )	( )
b) Have you been a smoker but have stopped smoking more than one year ago?	( )	( )

Following questions were also included in the Estonian questionnaire:

15. Do you or somebody of members of your family smoke at home in living rooms? ( ) ( )

16. How many hours per day do you spend in rooms outside of home where you are exposed to tobacco smoke? ( ) ( )

1. > 5 hours	( )	( )
2. 1-5 hours	( )	( )
3. < 1 hour a day	( )	( )
4. nearly never	( )	( )
5. I don't leave home		

17. How do you estimate your health?

1.excellent	( )	( )
2. quite good	( )	( )
3. medium	( )	( )
4. quite bad	( )	( )
5. very bad	( )	( )

18. What is your main occupation?.....
19. How many years have you been working in this occupation?.....years
20. Are you

1. working	( )	( )
2. studying	( )	( )
3. retired	( )	( )
4. not working	( )	( )
5.disabled	( )	( )

21. What is your first language? ……

22. What is your ethnic origin?.....

23. If you are born outside of Estonia, since when do you live in Estonia?

24. What is your date of birth? Day…. Month …. Year ….

25 Are you a man or a woman? M ( ) W ( )

26. What is your personal status?

1. single	( )	( )
2. married	( )	( )
3. unregistered marriage	( )	( )
4. widow (er)	( )	( )
5. divorced	( )	( )
6. living separately	( )	( )

Thank you for your participation

SUMMARY OF SOME SOVIET DISEASE CRITERIAE

I. Classification of chronic pneumonia (in Tbilisi 1972).

Stadium	Characteristics	Activity of process and character of exacerbation	Main variety of clinical process	Roentgenological changes	Functional status	
					Pulmonary	Haemodynamic
I	a) Protracted pneumonia, duration more than 8 weeks. b) Recurrent pneumonia with chronic bronchitis. Process is limited and reversible only by absence of bronchitis deformans.	Established or slow process, mostly infiltrative or peribronchial.	Bronchospastic syndrome exists or not.	Infiltrative changes in lungs, peribronchial and perivascular infiltration. Deformative focal bronchitis.	Due to exacerbation and bronchospasm impaired ventilation and deficiency of permeability.	Due to exacerbation, impared blood flowin lung circulation.
II	Frequent recidives. a) Localised process (purulent condition, pneumosclerosis). b) Extensive diffuse bronchitis.	Established or slow process, mostly infiltrative or peribronchial. Can go into remission.	Bronchospastic syndrome exists or not. Bronchi-ectasia exist or not.	(Relating to clinical events.)	a) Same as phase I, but more established. Possible arterial hypoxemia. In case of exacerbation, pulmonary insufficiency I-II. b) Obstructive, restrictive or combined ventilatory disorder. Possible changes in blood gas and acid-alkali balance. Pulmonary insufficiency I-II.	a) Same as phase I. b) Permanent hemodynamic disorder, development of cor pulmonale, possible transitory right ventricle type circulatory insufficiency. Heart insufficiency I-II.
III	Continuous active process. Diffuse impairment of lung tissue, diffuse bronchitis (pneumosclerosis, emphysema, purulent condition).	Established or slow process, mostly infiltrative or peribronchial.	Bronchospastic syndrome exists or not. Bronchi-ectasia exists or not	(Relating of clinical events	Combined lung function disorder with arterial hypoxaemia, hyperkapnia and changes in acid-alkali balance. Lung function insufficiency II-III.	Permanent hemodynamic disorder. Decompensated cor pulmonale. Heart insufficiency II-III.

II. Classification of chronic bronchitis by Fedosejev and Gerasin 1978
(Fedosejev and Gerasin, 1978; Mjagkov, 1991)

1. Simple no complicated chronic bronchitis with sputum excretion without impaired ventilatory function.

2. Purulent chronic bronchitis with excretion of purulent sputum continuously or during exacerbations.

3. Obstructive chronic bronchitis with persistent impaired ventilatory function.

4. Purulent-obstructive chronic bronchitis.

III.Classificaion of chronic bronchitis by Kokosov 1980
(Kokosov et al, 1980; Mjagkov, 1991)

1. Etiological: bronchitis, induced by chemical and physical factors; dusty bronchitis; infectious bronchitis; allergic bronchitis; unspecified bronchitis.

2. Pathogenetical: primary chronic bronchitis; secondary chronic bronchitis (as a result of long-lasting bronchitis or caused by diseases of other organs).

3. Respiratory system level: proximal bronchitis (impairment of large bronchi), distal bronchitis (impairment of small bronchi).

4. Type of clinical process and sputum: dry acute bronchitis; muco-purulent bronchitis; purulent bronchitis.

5. Functional: obstructive bronchitis, non-obstructive bronchitis.

6. Phase: exacerbation; remission.

7. Complication: hemoptysis; asthmatic syndrome (pre-asthma); emphysema; cor pulmonale; respiratory and heart (right ventricle) failure.

IV. Classification of asthma by Fedosejev G.B (1982).

I .Phases of development

1. Pre-asthma. Conditions at risk for developing asthma: acute and chronic asthma, acute and chronic pneumonia with bronchospasm, vasomotor rhinitis, urticaria, vasomotor oedema, migraine, neurodermitis with eosinophilia, and high level of eosinophils in sputum with immunological or no immunological pathogenetic mechanism.
2. Asthma bronchiale. After first attack or status of asthma.

II. Forms of asthma.

1. Immunological form.
2. Non-immunological form.

III. Clinical-pathogenetical variables of asthma.

1. Atopic. Allergen induced.
2. Infection-addicted (infection-allergic).
3. Autoimmune.
4. Dyshormonal. Caused by dysfunction of endocrine system.
5. Neuro-psychical
6. Adrenergic dysbalance.
7. Primary changes of reactive bronchi, could be congenital, come up in connection with chemical, physical, and mechanical irritants and infections and characterised with attack of breathlessness in connection with physical activity, cold air, medicine etc. (excluding aspirin asthma and exercise induced asthma).
8. Cholinergic.

IV. Severity of asthma.

1. Mild.
2. Persistent.
3. Severe.

V. Phase asthma.

1. Exacerbation of asthma.
2. Stabilising of exacerbation.
3. Remission.

VI. Complications.

1. Pulmonary: emphysema, respiratory insufficiency, atelectasis, pneumothorax etc.
2. Non-pulmonary: myocardial dystrophy, cor pulmonale, heart insufficiency etc.