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ASTHMA, CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RESPIRATORY SYMPTOMS AMONG ADULTS: PREVALENCE AND RISK FACTORS - The FinEsS Study in Northern Finland

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Academic dissertation

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To my family

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1. FOREWORD

Epidemiological studies can provide important information about diseases and symptoms in a population. Although results of epidemiological studies cannot be predicted from the results of clinical or physiological studies, clinical and physiological methods are often useful as instruments for epidemiological studies. ”The mechanism of a disease is unlikely to be discovered before its cause, and at a time of apparently dwindling resources investment in the epidemiology [of asthma] should pay good dividends.” (Burney 1988).

Because asthma and other obstructive lung diseases are influenced by both genetic and environmental factors there is an obvious need for epidemiological studies in different populations and environments. These studies can shed light on several important questions concerning respiratory diseases, including:

- How prevalent are the obstructive respiratory diseases?
- Which are the important determinants associated with these diseases?
- Can effective preventive measures be found?
- Is the management of diseases effective?
- How does the natural history of these diseases in different environments and populations develop?

This thesis begins with an overview of epidemiological studies performed particularly in the neighbouring Nordic countries, and in Finland. The intention has been to contribute a summary of results from the most important studies. Several other studies would also deserve mention. After the review of the literature, the specific aims and outcomes are presented and discussed.

2. ABBREVIATIONS

ANOVA = analysis of variance
ATS = American Thoracic Society
BHR = bronchial hyperreactivity
BTS = British Thoracic Society
CCHS = Copenhagen City Heart Study
CIBA = Ciba Foundation Guest Symposium
COLD = chronic obstructive lung disease
COPD = chronic obstructive pulmonary disease
DZ = dizygotic
ECRHS = European Community Respiratory Health Survey
ERS = European Respiratory Society
ETS = environmental tobacco smoke
FEV_1 = forced expiratory volume in one second
FFI = FinEsS study interview
FFQ = FinEsS study questionnaire
FinEsS = Finnish, Estonian and Swedish respiratory survey
FVC = forced vital capacity
GINA = Global Initiative for Asthma
GOLD = Global Initiative for Chronic Obstructive Lung Disease
ISAAC = International Study of Asthma and allergies in Childhood
IUATLD = International Union Against Tuberculosis and Lung Disease
MDI = metered dose inhaler
MEF_{50} = maximal expiratory flow at 50% of FVC
MRC = Medical Research Council
MZ = monozygotic
NHANES = National Health and Nutrition Examination Survey (USA)
NHLBI = National Heart Lung and Blood Institute (USA)
NICE = National Institute for Health and Clinical Excellence (UK)
OAD = obstructive airway disease
OLIN = Obstructive Lung Disease in Northern Sweden Study
OPE = obstructive pulmonary emphysema

OQ = OLIN questionnaire

OR = odds ratio

RHINE = Respiratory Health in the Northern Europe Study

RR = relative risk

SOB = shortness of breath

SPSS = Statistical Package for the Social Sciences

SPT = skin prick testing

WHO = World Health Organisation

3. ABSTRACT

3.1 BACKGROUND AND AIMS

Former epidemiolgical surveys during had indicated a lower prevalence of asthma and a higher prevalence of chronic bronchitis in Finland than in Sweden and other Nordic countries. In this study we aimed to assess with internationally comparable study methods, firstly, the prevalence of obstructive respiratory conditions, secondly, the effect of cold climate on respiratory symptoms and conditions, and thirdly, the prevalence of chronic obstructive pulmonary disease (COPD) among adults in northern Finland.

3.2 METHODS

Studies I to V analysed data from a population-based postal questionnaire survey among a random sample of 8,005 adults of ages 20 to 69 in southwestern and central Lapland. Study I was designed to assess the prevalence of obstructive lung diseases and the risk factors for these conditions, while Study II evaluated whether non-response bias has any significant effect on the results found in Study I. In Study III we analysed whether a cold climate influences risk for asthma, chronic bronchitis or respiratory symptoms. Study IV compared the results with simultaneously collected data from southern Finland, to find out whether north-south differences existed in Finland in the prevalence of obstructive lung conditions. In Study V we compared the influence of smoking habits on prevalence of respiratory symptoms and chronic bronchitis in northern Finland and northern Sweden. In Study VI, a random sample of 959 postal survey respondents was invited to join a clinical study including a structured interview, skin-prick test, and pulmonary function measurements.

3.3 RESULTS

In the study population the prevalence of physician-diagnosed asthma was 6.0%, in men 5.9% and in women 6.1% (with non-response correction the prevalence was 5.4%, in men 5.3% and in women 5.5%). The prevalence of self-reported chronic bronchitis was 4.4%, in men 4.7% and in women 4.0% and rose with increasing age and smoking. Significant risk factors for asthma were age, family history of asthma, and family history of obstructive airway disease (OAD). Among outdoor workers, the risk for chronic bronchitis was higher than among indoor workers. Skiers had no significantly increased risk for asthma or respiratory symptoms.

No significant difference appeared in physician-diagnosed asthma or chronic bronchitis between southern and northern Finland. The prevalence of physician-diagnosed chronic bronchitis was slightly but significantly higher in Norrbotten than in Lapland. However, living in Finland was associated with a greater risk for chronic productive cough, sputum production, and dyspnoea.

The overall prevalence of COPD in northern Finland was 5.4% by British Thoracic Society (BTS) criteria and 9.4% by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, but among those with a smoking history of more than 40 pack-years the respective prevalence was 53% and 66%. A family history of OAD was associated with a significantly higher risk for COPD. A significant increase in risk for COPD occurred with earlier start of smoking.

3.4 CONCLUSIONS

1. In comparison to the epidemiological studies published during the 1960ies and 1970ies, our results from the mid-1990ies revealed that the prevalence of asthma in Finland has risen and has also come closer to the level found in Sweden.
2. Non-response may influence the results in a postal questionnaire study.
3. Living or working in a cold environment may cause an increase in respiratory symptoms but does not affect asthma prevalence.
4. Prevalence of asthma and chronic bronchitis in northern and southern Finland was similar.
5. Bronchitic symptoms were more prevalent in Finland than in Sweden.
6. Among lifelong heavy smokers COPD prevalence was more than 50%. Earlier age at start of smoking significantly elevates the risk for COPD.

4. ORIGINAL PUBLICATIONS

I. Kotaniemi J-T, Lundbäck B, Nieminen MM, Sovijärvi ARA, Laitinen LA. Increase of asthma in adults in northern Finland? A report from the FinEsS study. Allergy 2001;56:169-174.

II. Kotaniemi J-T, Hassi J, Kataja M, Jönsson E, Laitinen L-A, Sovijärvi ARA, Lundbäck B. Does non-responder bias have a significant effect on the results in a postal questionnaire study? Eur J Epidemiol 2002;17:809-817.

III. Kotaniemi JT, Latvala J, Lundbäck B, Sovijärvi A, Hassi J, Larsson K. Does living in a cold climate or recreational skiing increase the risk for obstructive respiratory diseases or symptoms? Int J Circumpolar Health 2003 May;62(2):142-157.

IV. Kotaniemi J-T, Pallasaho P, Sovijärvi ARA, Laitinen LA, Lundbäck B. Respiratory symptoms and asthma in relation to cold climate, inhaled allergens and irritants. J Asthma 2002;39(7):649-658.

V. Lindström M, Kotaniemi J, Jönsson E, Lundbäck B. Smoking, respiratory symptoms, and diseases. A comparative study between northern Sweden and northern Finland: report from the FinEsS study. Chest 2001;119:852-861.

VI. Kotaniemi J-T, Anssi Sovijärvi A, Lundbäck B: Chronic Obstructive Pulmonary Disease in Finland: prevalence and risk factors. COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 3:331-339.

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5. INTRODUCTION

In Finland three pioneer studies on respiratory epidemiology were published between the years 1960 and 1970 (Järvinen et al 1960a, Huhti 1965, Alanko 1970). According to them the prevalence of asthma was lower, but the prevalence of chronic bronchitis much higher in Finland than in Sweden and Norway during the 1960ies (Julin and Wilhelmsen 1967, Irnell and Kiviloog 1968) or in the 1970ies (Kiviloog et al 1974, Gulsvik 1979a and b). Since the year 1970, much data on asthma epidemiology has accumulated internationally. Results from Europe are in line with those of other western countries: The prevalence of asthma has risen (Sly 1999). The same trend has occurred in the Nordic countries among both children (Åberg et al 1995, Nystad et al 1997) and adults (Åberg 1989, Björnsson et al 1994). In Sweden, the prevalence of asthma was markedly higher in the northern part than in central or southern Sweden (Åberg 1989, Larsson L et al 1994, Lundbäck 1998).

During the 20th century the tobacco epidemic changed the disease pattern in respiratory epidemiology. The burden of COPD has been recognised word-wide (Murray and Lopez 1996, Gulsvik 1999, Halbert et al 2003): COPD became the most important respiratory disease among the middle-aged and elderly, and as a cause of mortality far more important than asthma. On the other hand, asthma and allergic conditions are the most prevalent chronic diseases among young adults and children (ECRHS 1996, ISAAC 1998).

Is the situation in Finland still different from that of the other Nordic countries? How prevalent are asthma and COPD in Finland? What factors are associated with asthma and COPD? To obtain more accurate and more comparable results, during the 1990ies new international co-operative surveys in the field of respiratory epidemiology began of adults (ECRHS 1996) and children (ISAAC 1995, Asher et al 1995). In the same manner, the **FinEsS** (**Fin**land, **Es**tonia, **S**weden) co-operation began in 1995 between Finnish, Estonian, and Swedish researchers. As a part of this co-operation, the present study - **The FinEsS Study in Northern Finland –** aimed to seek answers to the questions presented above.

6. DEFINITIONS

This section briefly summarises important terms and definitions used in this thesis. COPD has been defined in international guidelines (ATS/ERS, BTS/NICE, GOLD, all updated in 2004), as also was the definition of asthma by the Global Initiative for Asthma (GINA), (Global Strategy for Asthma Management and Prevention, updated 2004).

The following section provides generally accepted international definitions for pulmonary diseases. Operational detailed definitions used in this study are given in the methods section and in the published studies I to VI. Therefore they are not repeated here.

6.1 ASTHMA

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 hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. The episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. (GINA, Global Strategy for Asthma Management and Prevention, updated 2004).

6.2 CHRONIC BRONCHITIS

Chronic bronchitis is defined by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of 3 months a year, for at least 2 successive years, and cannot be attributed to other causes. This hypersecretion can occur in the absence of airflow limitation, ERS – consensus statement 1995 (Siafakas et al 1995).

6.3 EMPHYSEMA

Emphysema is defined anatomically by permanent, destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis, ERS – consensus statement 1995 (Siafakas et al 1995).

6.4 COPD

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. (GOLD guidelines, NHLBI/WHO, updated 2004).

7. REVIEW OF THE LITERATURE, OBSTRUCTIVE LUNG DISEASES IN ADULTS

This background section gives an overview of the epidemiology of obstructive pulmonary conditions, especially comparing Finland with its neighbouring Nordic countries.

7.1 OVERVIEW

7.1.1 Development of methodology

Since 1959 the meaning of diagnostic terms such as asthma, chronic bronchitis, and emphysema has become more clearly defined (Fletcher 1978). Internationally accepted definitions and diagnostic standards of asthma and chronic obstructive lung diseases (CIBA 1959, WHO 1961, ATS 1962), and the development of epidemiological survey methods (MRCC 1960, Fletcher and Tinker 1961, Lebowitz et al 1975, Lebowitz and Burrows 1976, Ferris 1978) have benefited studies in respiratory epidemiology.

The term "chronic obstructive pulmonary disease" (COPD) was first used in 1964 (Mitchell and Filley 1964), and has been in common use since the early 1980ies. According to general opinion, 80 to 90% of COPD is associated with smoking, but only 10% to 20% of smokers develop the disease (MacNee 2000). Its prevalence was estimated as 4% to 6% among adults in western countries (Gulsvik 1999). Since 1995 the burden of this disease has been generally recognised (Hurd 2000), and new guidelines and criteria for diagnosis adapted: ATS 1995, ERS 1995, BTS 1997, GOLD 2001, updated 2004, BTS/NICE 2004, and ATS/ERS 2004.

7.1.2 Nordic pioneer studies

Epidemiological studies during the 1960ies and 1970ies in the Nordic countries showed prevalence for asthma of 1.1% to 2.8% and for chronic bronchitis of 1.5% to 4.6% in the general adult population. In Finland, the prevalence of asthma was similar or lower, but the prevalence of chronic bronchitis or obstructive pulmonary disease seemed to be much higher than in other Nordic countries, Table 1.

Table 1. Prevalence (%) of obstructive lung diseases in Nordic countries 1960-1979.

author	age	asthma		chronic bronchitis or COLD or OPE	
		men	women	men	women
Julin et al (1967)	16 to 64	1.1	2.8	2.1	1.8
Irnell et al (1968)	30 to 64	2.3	2.3	2.7	1.5
Kiviloog et al (1974)	35 to 54	2.8	2.5	4.3	3.7
Gulsvik (1979)	16 to 69	1.6	1.2	3.7	4.6
Järvinen et al (1960)	> 15	-	-	8.7	3.7
Huhti (1965)	40 to 64	0.5	1.6	28.2	5.8
Alanko (1970)	10 to 59	1.2	1.6	-	-

COLD = chronic obstructive lung disease (Gulsvik 1979)
OPE = obstructive pulmonary emphysema (Järvinen et al 1960)

7.1.3 International trend toward an increase in asthma

According to studies published in the western countries during the 1980ies and 1990ies, the prevalence of asthma and other obstructive lung diseases has increased rapidly. In England and Wales the prevalence of current asthma increased from 1970 to 1981 from 1.16% to 2.05% in men and 0.88% to 1.59% in women in all age groups (Fleming and Crombie 1987). In Aberdeen, Scotland, among schoolchildren aged 8 to 13 years, the prevalence rose from 4.1% in 1964 to 10.2% in 1989 (Ninan and Russell 1992). According to another UK study, 17% of men and 7% of women had chronic bronchitis at ages 40 to 70 (Littlejohns et al 1989). In a further UK study for ages 65 to 96 years, 58.4% had at least one respiratory symptom, and 21.6% had morning phlegm (Dow et al 1991). An increase in the prevalence of asthma between 1973 and 1988 from 5.5% to 12% in 12-year-old children was found in Wales (Burr et al 1989). In Manitoba, Canada, the prevalence of physician-diagnosed asthma increased in all age groups among both men and women between 1980 and 1990 (Manfreda et al 1993).

7.1.4 End of the asthma epidemic?

According to the most recent reports, the increase of asthma in schoolchildren and adolescents in some western countries may be levelling off. In Melbourne, Australia, schoolchildren ages 6 and 7 were studied with the ISAAC questionnaire; 2,843 participated in the year 1993 and 2,968 in 2002 (Robertson et al 2004), revealing a significant reduction in the prevalence of reported asthma in Melbourne schoolchildren.

In Aberdeen, Scotland, children mainly aged 9 to 12 years were studied in 1999 by questionnaires in the schools that had also participated in the 1964, 1989, and 1994 studies (Devenny et al 2004). The results revealed that the rate of rise in the prevalence of childhood asthma had slowed.

7.1.5 Development in other Nordic countries

In Norway, the prevalence of asthma in adults studied from 1985 to 88 was 2.4% in the general population at ages 18 to 73 (Bakke et al 1991a). Several Swedish studies have reported an obvious increase in the prevalence of asthma in adults (Lundbäck 1998, Montnemery et al 1998), as well as among children (Åberg et al 1995) and conscripts (Åberg 1989). Asthma prevalence was higher in northern than in southern Sweden (Åberg 1989, Lundbäck et al 1993a, and Lundbäck 1998).

7.1.6 Asthma in Finland

Vesterinen et al reported (1988) the prevalence of asthma in an adult population in Finland to be 1.35% in 1975 and 1.80% in 1981. Haahtela et al (1990) found that the prevalence of asthma in Finnish conscripts aged 18 to 19 years had risen from 0.29% in 1966 to 1.79% in 1989. Several papers published in Finland between 1985 and 1995—mostly on selected population samples—agree with the findings of an international trend toward an increasing prevalence of asthma. The overall impression demonstrates an increasing prevalence of asthma in Finland.

7.1.7 COPD in Finland

Although Finland was among the first countries to initiate a national COPD program (Laitinen and Koskela 1999), the epidemiology of COPD in Finland has been studied less extensively than for asthma during the last two decades. Keistinen et al (1996 and 1998) published register studies showing a trend toward increasing burden of COPD. Isoaho et al (1994a) reported the prevalence of COPD at age 65 years or older among men to be 12.5% and among women 3.0%.

In a population-based study in adults (von Hertzen et al 2000) a clinically relevant airflow obstruction ($FEV_1/FVC \leq 0.69$) was found in 11% of men and in 5% of women.

7.2 ASTHMA, CHRONIC BRONCHITIS AND COPD: LARGE-SCALE INTERNATIONAL STUDIES

7.2.1 European Community Respiratory Health Survey

Probably the most important international comparative study of asthma and allergy among adults is the European Community Respiratory Health Survey (ECRHS), started in 1994. Based on analysis from 34 centres in 14 countries, a wide geographical variation in the prevalence of physician-diagnosed asthma was clear. In the Nordic countries: Sweden, Norway, Denmark, and Iceland participated in the ECRHS, producing a large number of publications based on pooled data and on data from single countries. Asthma prevalence was highest in New Zealand and Australia (11% to 13%) and lowest in the eastern part of Germany (1.2%) and Spain (1.5%-3.0%). Use of asthma medicines also varied considerably between countries but also within countries (Janson et al 1997). The prevalence of allergic sensitisation and the dominating allergens also varied considerably between countries.

The ECRHS aimed also at identifying risk factors for asthma. With all its limitations, the cross-sectional design provides interesting results. This is not an attempt to describe the entire ECRHS: Several excellent original and review articles cover different fields of the study. Rather, some results of general interest and some related data shall be reviewed.
In addition to parental asthma and sensitisation to perennial and seasonal allergens, significant risk factors for asthma in Spain based on the Spanish ECRHS data included also having fewer than three older siblings (Sunyer et al 1997). Other ECRHS analyses point in the same direction (Svanes et al 1999), thus supporting the hygiene hypothesis as a cause of the increase in asthma (Strachan 2000). Although the data may point in this direction, the very low risk ratios (significant due to the large study) can scarcely explain the increase in asthma prevalence.
The ECRHS verified the urban-rural differences. An urban-suburban comparison study in Belgium indicated that house-dust mite allergy is a major determinant of asthma, whereas no factors that contributed to a higher urban prevalence of present asthma symptoms could be identified (Wieringa et al 1997). Though the number of cats in a society was positively related to prevalence of asthma, childhood exposure to pets was associated with a lower prevalence and sensitisation to cats in adulthood (Roost et al 1999).

In Italy of the 6,031 who had returned the ECRHS questionnaire, 1,850 subjects were invited to a clinical study including a standardised interview, lung function test, methacholine challenge, IgE, and skin-prick tests (de Marco et al 1998). When results from the 811 subjects with complete data were analysed, among those with a clinical diagnosis of asthma (n=105), 69% reported current wheezing and 68% asthma. The conclusion was that the question on ever-asthma gives prevalence estimates close to those obtained by clinical judgement and that in Italy asthma was underdiagnosed.

A postal questionnaire study with the ECRHS questionnaire was conducted in three areas of Sweden (Björnsson et al 1994). The population sample in each area was 1,800 men and 1,800 women, 20 to 44 years of age, of whom 7.4% had asthmatic symptoms and 6.1% an asthma-related disorder. Of the subjects, 12.9% had bronchitis symptoms, and prevalence was higher among current smokers, 21.6%, than among ex- or non-smokers, 8.1% and 7.8%. When a non-response study was conducted among the 1,080 non-respondents by telephone, 89 subjects among the non-respondents agreed to answer the questionnaire. No significant differences appeared in symptom prevalence from those of the respondents. Another ECRHS study in Italy (de Marco et al 1994) did observe a non-response bias. According to its linear regression model, symptom prevalence rates appeared to be overestimated by 4% to 10%, slightly inflating prevalence estimates. Calculations revealed that the bias increases steeply at nonresponse rates higher than 30%, a situation quite common in asthma surveys. Reliable comparisons of international data when response rates differ seems to require a correction of the observed prevalence.

7.2.2 The International Study of Asthma and Allergies in Childhood (ISAAC)

Even though the scope of this thesis covers respiratory epidemiology among adults, the ISAAC studies deserve a mention. Worldwide, ISAAC co-operative studies have involved children aged 6 to 7 (91 centres) and 13 to 14 (155 centres), and follow-up studies are in progress. Although adults were not studied, some observations are as follows: wide variations appeared in the prevalence of asthma among the study centres. In the older age group, the prevalence of self-reported asthma was 1.6% to 4.6% in countries in eastern Europe, but was very high in Australia and New Zealand: 20.2% to 30.4% (The ISAAC Steering Committee 1998). Respiratory symptoms and allergies in 5- to 8- and 12- to15-year-old children were compared in a questionnaire study between western and eastern Germany (Duhme et al 1998). The reported prevalence rates of asthma, hay fever, and eczema were lower in the east. Surprisingly, according to Pekkanen et al (1997), the prevalence on childhood asthma in Finland seemed to be lower than in other European countries.

7.2.3 Other studies on increase in asthma prevalence in western countries

A large number of studies in Western Europe, North America, and Australia-New Zealand verify an increase in asthma prevalence over the last 40 to 50 years. Very high prevalence rates have been reported, especially among children, whereas the increase among adults has been lower. In comparison with prevalence, mortality from asthma is low, and does not reflect the epidemic.

7.2.3.1 Asthma among schoolchildren and young adults

In England and Wales, in the 5- to 34-year age group, asthma mortality rose annually by an average 4.7% from 1974 to 1984 (Burney 1986). During the last two decades asthma mortality in England and Wales, as in other western European countries, has been low, although the prevalence has increased. A longitudinal survey in England indicated a true increase in asthma morbidity among primary schoolchildren (Burney et al 1990). Within age groups, trends in successive annual cohorts showed an increasing prevalence of asthma (boys 6.9%, girls 12.8%) for each annual birth cohort. The prevalence of asthma and allergic disorders among children in Munich, western Germany, and Leipzig, eastern Germany, were compared in a study on schoolchildren aged 9 to 11 (von Mutius et al 1992). Cumulative lifetime prevalence of physician-diagnosed asthma was 7.3% in Leipzig and 9.3% in Munich, but cumulative bronchitis prevalence was higher in Leipzig than in Munich. According to the authors, the lower prevalence of allergic disorders in Leipzig could point toward aetiological factors associated with a Western lifestyle and living conditions.

A longitudinal study from birth to age 33 in England, Scotland, and Wales reported a cumulative incidence of wheezing illness of 18% by age 7, 24% by age 16, and 43% by age 33. Atopy and active cigarette smoking were major influences on the incidence and recurrence of wheezing during adulthood (Strachan et al 1996). According to a register study in the Province of Saskatchewan, Canada, asthma prevalence increased in children and adults from 1981 to 1990 (Senthilselvan 1998): In 1990, asthma prevalence was 5.1% in children ≤ 4 years old, 4.4% in children 5 to 14, 2.2% in young adults 15 to 34, and 1.9% in adults 35 to 64.

A retrospective analysis of available data from the Belgian Armed Forces for the period 1978-91 revealed that among conscripts the prevalence of reported asthma rose from 2.4% in 1978 to 7.2% in 1991, while the proportion of asthmatics with airway hyperresponsiveness remained similar at 48.4% in 1978 and at 51.4% in 1991 (Dubois et al 1998). The authors concluded that these observations provide support for the fact that the increase in asthma symptoms was not simply due to reporting bias.

7.2.3.2 Asthma among adults and the elderly

In 1979 a study from south Wales reported cumulative lifetime prevalence of asthma to be 6.5% in subjects aged ≥ 70 years (Burr et al 1979), while another UK study conducted during the period October 1992 to May 1993 revealed asthma prevalence to be 4.5% in subjects aged > 65 years (Parameswaran et al 1998). A two-part questionnaire survey was conducted with a random sample (n=24,398) of persons aged 16 to 50 yrs registered at one of the 41 general practices in Greenwich, near London (Marks et al 1997). The prevalence of wheeze and asthma in the previous 12 months was 26% and 14%. In 1993, the prevalence of asthma among adults in Greenwich was higher than in a similar survey in 1986.

The reported prevalence of asthma in France is lower than in the UK. A study of the general population aged 20 to 44 of three French urban areas showed a prevalence of asthma attacks in the previous 12 months to be 2.7% of the study subjects in Grenoble, 3.5% in Montpellier, and in 4.0% in Paris (Neukirch et al 1995). For nasal allergies, the prevalence rates were 28.0%, 34.3%, and 30.8%. The authors concluded that these results are consistent with the hypothesis of a recent increase in asthma and allergies.
In Western Australia in the age group 18 to 55, a random sample of 553 subjects in 1981 and another sample of 1028 subjects in 1990 were studied with a questionnaire, histamine challenge test, and skin prick test. Recent wheeze increased from 17.5% to 28.8% and diagnosed asthma from 9.0% to 16.3%, with the largest increase in subjects aged less than 30 (Peat et al 1992). Results from Manitoba, Canada, revealed that the prevalence of physician-diagnosed asthma increased for all age groups in both male and female subjects between 1980 and 1990 (Manfreda et al 1993).

7.2.4 Prevalence of COPD and bronchitis symptoms in association with smoking habits

The word-wide smoking epidemic has resulted in an increasing prevalence of COPD and increasing mortality from respiratory conditions (Murray and Lopez 1996). Thus, along with prevalence studies, some mortality data are also included in this section.

7.2.4.1 Development of terminology and definition of the disease

Prior to the term “COPD”, the term was “chronic bronchitis and emphysema”. During two decades, from the 1960ies to the 1980ies, the obstructive form of chronic bronchitis became more and more

to be considered as a single disease entity with or without emphysema. During the 1980ies and 1990ies the term COPD successively replaced this combination term. Lundbäck has thoroughly reviewed the development of COPD terminology in his 1993 thesis. Despite agreement on how to define and describe the disease, no general agreement on how to operationally define COPD existed until the mid-1990ies. And when these criteria came along, the operational criteria by the ATS, BTS, and ERS were diverging from those of GOLD. The divergences affect specificity for disease; GOLD had the lowest and BTS probably the highest.

The former ERS criteria, which were based on each population's own normal values, were the most physiologically correct criteria, taking into account even the fact that subjects with a normal forced expiratory volume (FEV_1) can be classified as having COPD. However, during 2004, ERS and ATS have adopted the GOLD guidelines with small modifications. The ATS/ERS standards define obstruction $FEV_1/FVC \leq 0.70$. The new BTS guidelines – published as the National Institute for Health and Clinical Excellence (NICE) guideline No. 12. – define obstruction as FEV1/FVC < 0.70, and do not require lung function measurement after a reversibility test. Mild COPD by GOLD criteria ($FEV_1 > 80\%$ of predicted) is still not included in COPD based on the BTS guidelines.

7.2.4.2 Cornerstone findings

The epidemiology of COPD in terms of prevalence and risk factors has been reviewed by several authors, among them Gulsvik (1999) and Hurd (2000a). Usually the prevalence has been estimated at 4 to 10%, though the estimates vary greatly, depending on the criteria used. Large studies include the US NHANES III (Mannino et al 2000, Petty 2000) and the European IBERPOC studies performed in Spain (Pena et al 2000). Both have produced similar prevalence estimates of 6% to 10% with a very high prevalence particularly among elderly smokers. Nordic studies have yielded similar results (Bakke et al 1991a, Lindström et al 2002, Lundbäck et al 2003b). When estimating the prevalence of COPD, use of physician-diagnosed disease is not very useful, as the proportion of underdiagnosis is large (Lindström et al 2002, Lundbäck et al 2003a, Stang et al 2000). Further, the results from a longitudinal population-based study suggest that physician bias may result in labelling male patients as emphysematous and female patients as asthmatic or bronchitic (Dodge et al 1986). Measurement of lung function is essential for diagnosing COPD (Chapman et al 2001, Zielinski et al 2001).

7.2.4.3 Smoking-associated mortality

In a prospective cohort study in Great Britain of a nationally representative sample, 1,532 British men and women aged between 40 and 64 were interviewed in 1958 by use of a questionnaire which formed the basis of the Medical Research Council's questionnaire on respiratory symptoms (Carpenter et al 1989). By the end of 1985, 889 deaths had been reported, including 51 in men due to chronic bronchitis. An extensive 50-year prospective study in the UK studied the effect of the smoking epidemic on mortality among British doctors, revealing that among men born around 1920, cigarette smoking tripled age-specific mortality rates. On average, according to Doll et al (2004), cigarette smokers die about 10 years younger than non-smokers. In current heavy smokers (≥ 25 cigarettes/day), mortality from respiratory and cardiovascular causes was twice that in non-smokers, and represented two-thirds of the excess mortality in current smokers.

Age-adjusted COPD mortality rate in 1993 in the USA increased 47.3%, from 52.6 in 1979 to 77.5 per 100,000 (Mannino et al 1997). When data from NHANES I to III was analysed to assess the impact of COPD in the USA (Mannino et al 2002) during 2000, an estimated 10 million US adults reported physician-diagnosed COPD. However, data from NHANES III showed that approximately 24 million US adults had impaired lung function, indicating that COPD is underdiagnosed. During 2000, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths. In 2000, the number of US women dying from COPD was higher than the number of men (59,936 vs. 59,118).

7.2.4.4 Other international results

A population-based cross-sectional survey in an urban area of southern Brazil classified 12.7% of the interviewed subjects as having chronic bronchitis (Menezes et al 1994). Low family income, poor schooling, smoking, and childhood respiratory illnesses were significantly associated with chronic bronchitis. A Canadian register study in 1999 calculated that 750,000 Canadians had chronic bronchitis or emphysema diagnosed by a health professional. Prevalence rates were as follows: ages 55 to 64 years, 4.6%; 65 to 74 years, 5.0%; ≥ 75 years, 6.8%. From 1980 to 1995, the total number of deaths from COPD increased from 4,438 to 8,583 (Lacasse et al 1999).
A retrospective cohort of British patients with COPD was constructed from a large automated database of UK general practice data (Soriano et al 2000). From 1990 to 1997 the annual prevalence rates of physician-diagnosed COPD in women rose continuously from 0.80% to 1.36% ($p < 0.01$), rising to the rate observed in men in 1990.

The population-based, multicenter study in Spain, IBERPOC, reported the prevalence of COPD in ever-smoking men in the age group 40 to 49 years to be 8.6% and in the group 60 to 69 years 30.6%; the corresponding prevalence rates in ever-smoking women were 4.3% and 6.1%. The vast majority of COPD cases had not been diagnosed previously. The prevalence of COPD, estimated in the USA and Europe by use of age-specific and smoking-specific rates of COPD (Stang et al 2000), suggest that only 14% to 46% of all COPD cases have been diagnosed in the US. When the impact of COPD in eight countries in North America and Europe was studied in 2000 (Rennard et al 2002), results revealed frequent work loss and frequent use of health services.

In adults aged ≥ 50 years, asthma, chronic bronchitis, or emphysema commonly co-exist (Soriano 2003). This might offer an explanation for the high proportion of undiagnosed COPD. In a register study, international variations in smoking among men and women aged 20 to 44 and 45 to 74 were assessed in12 European countries (Cavelaars et al 2000). In the 45- to 74-year age group, higher rates of current and ever-smoking among lower-educated subjects were found in some countries. In the 20- to 44-year age group, educational differences in smoking were generally greater than in the older age group, and smoking rates were higher among less-educated people in most countries. The age patterns observed suggest that socioeconomic differences in diseases related to smoking will increase in the coming decades in many European countries.

7.3 ASTHMA, CHRONIC BRONCHITIS AND COPD IN THE NORDIC COUNTRIES

7.3.1 Denmark

7.3.1.1 The Copenhagen City Heart Study (CCHS)

The relation of ventilatory impairment and of chronic mucus hypersecretion to death from all causes and death from obstructive lung disease (chronic bronchitis, emphysema, or asthma) was studied in 13,756 subjects randomly selected from the general population of the City of Copenhagen (Lange et al 1990). During the 10-year follow-up, 2,288 subjects died. In 237 subjects, obstructive lung disease was considered an underlying or a contributory cause of death. Chronic mucus hypersecretion was associated with only a slightly higher risk of death from all causes (RR = 1.1 for women, 1.3 for men).

The annual decline in lung function in subjects with self-reported asthma was analysed in the Copenhagen City Heart Study (Ulrik and Lange 1994), in a sample comprising 10,952 subjects aged 20 to 90, randomly selected from the city of Copenhagen and followed over a 5-year period. The overall prevalence of asthma was 3.7% in men and 3.6% in women. Multiple regression analysis showed a higher decline in forced expiratory volume in one second (FEV_1) in subjects with new asthma. The excess decline was, on average, 39 ml/year in men and 11 ml/year in women, compared with that in non-asthmatic subjects.

Data from the CCHS on 5,354 women and 4,081 men aged 30 to 79 allowed assessment of the association between chronic mucus hypersecretion and FEV_1 decline and hospitalization from COPD (Vestbo et al 1996). Chronic mucus hypersecretion was significantly and consistently associated with both an excess FEV_1 decline (23 ml/year in men, 13 ml/year in women) and an increased risk for subsequent hospitalization for COPD. Mortality was studied in women and men in relation to smoking habits (Prescott et al 1998) in a population of 30,917 subjects, indicating that women may be more sensitive than men to some of the deleterious effects of smoking.

The relationship between smoking cessation and development of asthma was investigated in the CCHS (Godtfredsen et al 2001), in 10,200 subjects who provided information on self-reported asthma and smoking habits from the first two examinations (baseline and 5-year follow-up), and the 6,814 subjects who also attended the third and last examination (10-yr follow-up). Ex-smokers had a higher incidence of self-reported asthma than did never-smokers. The authors concluded that subjects perceive chronic obstructive pulmonary disease as asthma; hence a relationship between smoking cessation and asthma may be due to misclassification rather than causality.

7.3.1.2 Other Danish studies

An epidemiological study performed with a self-administered questionnaire in a representative sample of 1685 Danish farmers (Iversen et al 1988) produced a response rate of 73.3%. The prevalence of asthma was 7.7% and of chronic bronchitis 23.6%. The prevalence of asthma and of chronic bronchitis, respectively, increased from 3.6% and 17.9% in 31- to 50-year-old farmers to 11.8% and 33.0% in 51- to 70-year-old farmers, and from 5.5% and 17.5% in dairy farmers to 10.9% and 32.0% in pig farmers. A logistic regression analysis with correction for age and smoking habits confirmed that pig farming was a risk factor for asthma (OR 2.03), chronic bronchitis (OR 1.53), and wheezing during work (OR 3.33).

A 7-year follow-up on FEV_1, forced vital capacity (FVC), bronchial reactivity, and respiratory symptoms for 181 Danish farmers (Iversen and Dahl 2000) had a participation rate of 76.3%. Farmers who worked exclusively with pigs in the follow-up had an accelerated decline in FEV_1 but not in FVC, when compared with figures for dairy farmers, whose decline in FEV_1 was close to the expected. The authors concluded that working in a pig house causes an accelerated decline in FEV_1 but not in FVC. The mean decline was approximately 0.5 L during a working life, and some farmers may develop clinically significant airway obstruction due to work in a pig house.

7.3.2 Norway

7.3.2.1 Bergen and Hordaland studies

Most studies of respiratory epidemiology in Norway have their origin in the Department of Respiratory Medicine headed by Professor Amund Gulsvik at the University of Bergen (Haukeland University Hospital). This department has produced about 20 PhD theses since 1992, most of them focused on respiratory epidemiology. During 2004 alone, four PhD theses about respiratory epidemiology were finalised based on data from several cohorts. The oldest cohort has been followed since 1985. Much interest has been paid to validity aspects including studies of non-response, with several studies of non-response published.

Pioneer studies on respiratory epidemiology in Norway grew out of the Oslo Asthma Cohort Study in 1979 (Gulsvik 1979 a and b). The postal study was conducted in Oslo from 1972 to 1974, with a questionnaire being mailed to a random sample of 19,998 individuals aged 15 to 70 years. Information came back from 17,692 subjects (88.7% of those in the sample still alive).

Crude prevalence rates of the symptoms were: morning cough 24%, breathlessness on climbing two flights of stairs 11%, and wheezing 17%. Only 27% of the men and 46% of the women in the survey population were non-smokers. The prevalence of respiratory symptoms was closely related to the amount smoked. The main results of the clinical study (Gulsvik 1979a) have been mentioned. The study was followed up from 1998 to 1999 (Brögger et al 2003), with the same self-completed postal questionnaire and exactly the same questions and survey methods as in the 1972 study. The crude prevalence of ever having had a doctor's diagnosis of asthma rose from 3.4% to 9.3%. After controlling for smoking, the risk for asthma among those aged < 40 years had tripled, with the increase in asthma 50% greater in females than in males. The increase in asthma prevalence and asthma-like symptoms in adults was large, but less pronounced among those aged > 40.

Non-response to a questionnaire was examined in 1985 in The Hordaland County Cohort Study (Bakke et al 1990b). The study population was a random sample of 4,992 subjects from the general population aged 15 to 70 years in Hordaland County, Norway. The overall response rate was 90%, with a 63% response to the initial letter and 56% and 36% to the first and second reminder letters. Smokers were late respondents, and subjects with respiratory disorders tended to be early respondents. Using only the initial mailing would have changed the estimated prevalence of smokers from 39% to 35%. The prevalence rate of asthma was 3.5%, emphysema 0.5%, and bronchitis 18.1%. The main reasons for non-response were an incorrect mailing address and a feeling of lack of personal benefit from responding.
The first survey of the Hordaland County Cohort Study from 1985 was also followed by a clinical examination and studies of risk factors, mainly focused on occupational airborne exposures (Bakke et al 1991b). The relationship between such exposure and respiratory symptoms and asthma was examined by a self-administered questionnaire for a cross-sectional survey of a random sample (n = 4,992) of the general population aged 15 to 70 yrs. A history of occupational dust or gas exposure was associated with morning cough, chronic cough, phlegm when coughing, breathlessness on exercise, occasional wheezing, and a physician's diagnosis of asthma after adjustment for sex, age, smoking habits, and urban-rural area of residence. The population-attributable risk for occupational dust or gas exposure for the respiratory disorders ranged from 11% to 19%. Prevalence of COPD was studied in the same cohort and has been mentioned (Bakke et al 1991a).
This study was followed up in 1996, in order to establish incidence rates for a wide range of respiratory symptoms and asthma, and to relate them to sex, age, and smoking habits. Of the initial cohort of 3,786 subjects, a total of 2,819 replied to postal questionnaires at both baseline and follow-up. The 11-year cumulative incidence of asthma was 4.0% in males and 3.5% in females.

For respiratory symptoms, the cumulative incidences for both sexes ranged from 2.0% (dyspnoea grade 4) to 25.8% (wheezing), being higher in females for most symptoms (Eagan et al 2002). The authors of that study summarised the findings of major population studies on adult asthma incidence in a review (Eagan et al 2005). The pooled estimate of adult asthma incidence was 4.6 per 1,000 person-years in women and 3.6 in men. The estimate among only general-population cohort studies was higher, a respective 5.9 and 4.4 per 1,000 person-years in women and men. In the few studies that allowed the incidence of asthma to be estimated among those aged > 50, a trend appeared towards higher incidence with age. It is likely that this is at least partly explained by misclassification of COPD.

Effects mainly of quartz exposure but also other occupational exposures were studied in Bergen. A random sample of 1,933 men aged 22 to 54 were invited to the survey. Smoking habits and measurements of FEV_1 were recorded at the initial survey in 1965-1970 (n = 1,591) and at follow-up in 1988-1990 (n = 951). An accelerated decline in FEV_1 was evident in subjects exposed to sulphur dioxide gas and to metal fumes. The adjusted decline in FEV_1 increased progressively in subjects exposed to increasing numbers of occupational agents. In this community follow-up survey in men, smoking and occupational exposures to sulphur dioxide gas, metal fumes and the numbers of specific agents were important predictors for an accelerated decline in FEV_1 (Humerfelt et al 1993). Occupational quartz exposure was reported by 13% (n = 3,445) of participants, with a mean duration of 7 years. Multiple linear regression analyses showed that the difference in FEV_1 associated with each year of quartz exposure was -4.3 ml compared with the -6.9 ml from smoking 20 cigarettes per day for one year (Humerfelt et al 1998).

Association of skin-prick test positive allergy with a reduced FEV_1 in adults was studied in a stratified random sample of 1,239 adults aged 18 to 73 (Omenaas et al 1995). Subjects with house-dust-mite antibodies showed lower sex-, age-, and height-standardized residuals of FEV_1 ($SFEV_1$) than did those without any specific IgE antibody. This relationship did not differ significantly by sex, age, smoking habit, total serum IgE level, or season, and remained significant after exclusion of subjects with obstructive lung disease. In a multiple linear regression analysis, the presence of house-dust-mite antibodies was the only significant predictor of reduced $SFEV_1$.

A cross-sectional, population-based study (n = 25,000) of lung disease was performed in 1998-1999 in two regions of Norway: Oslo and Bergen-Hordaland (Brögger et al 2002). A 1% random sample (n = 171) of previous postal responders were resurveyed by telephone contact. The response rate

was 67% for the telephone interview. Fewer incomplete answers and more complete information were provided by telephone than by mail, with a lower prevalence by telephone survey for morning cough and exposure to passive smoking at work or home. The authors concluded that comparability between these postal and the telephone survey modes was good. The survey mode may thus have an effect on study results, depending on the specific questions asked.

The extent of COPD misdiagnosis was examined in the Bergen Study of the Elderly, 1996-1998 using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition in healthy, never-smoker, asymptomatic adults aged >70 years (Hardie et al 2002). Approximately 35% of them had an FEV_1/FVC of < 0.70 and would be classified as having at least stage I COPD according to the GOLD criteria. This percentage increased with age, and in those >80 yrs approximately 50% would be classified as having COPD and approximately one-third would have an FEV_1 of < 80% predicted (stage II COPD). The authors concluded that the GOLD criteria probably leads to a significant degree of over-diagnosis of chronic obstructive pulmonary disease in those aged >70. Bergen is also involved in the ECRHS and its follow-up in the Respiratory Health in the Northern Europe Study (RHINE), which will be discussed elsewhere in this thesis.

7.3.2.2 Other Norwegian studies

The prevalence of asthma was evaluated among young elite cross-country skiers in Trøndelag, Norway, and Jämtland, Sweden (Sue-Chu et al 1996). These two regions in central Scandinavia have different climates during the winter season, with a coastal type in Trøndelag, whereas a colder, drier climate in Jämtland. The study population comprised 171 skiers (118 from Norway, 53 from Sweden). The prevalence of self-reported asthma-related symptoms was 46% in Norway and 51% in Sweden. In Norway, 14% of the skiers were hyper-responsive to methacholine (a test for bronchial hyperreactivity, BHR) compared to 43% in Sweden; estimated prevalence of clinically diagnosed asthma was 12% in Norway and 42% in Sweden. The self-reported frequency of respiratory allergy was lower in Norway (11%) than in Sweden (32%). However, on an individual basis, self-reported allergy did not predict occurrence of asthma or BHR.

Some studies have indicated that females are more vulnerable to the deleterious effect of tobacco smoking (Prescott et al 1998). Within the Nord-Trondelag Health Study, to investigate the associations between tobacco smoking and reported respiratory symptoms and lung function (Langhammer et al 2003), 65,225 subjects aged ≥ 20 years were screened. Among these, 10,941

subjects selected randomly or because of reported asthma or asthma-related symptoms participated in a study consisting of spirometry and a personal interview. Tobacco smoking was associated with increased prevalence of respiratory symptoms, reduced lung function, and lower score for global self-rated health. Further, smoking burden was associated with a larger relative reduction in expiratory lung function in females. Females reported more symptoms and lower self-rated health, than did males with a similar smoking burden. Even though smoking in females was associated with a larger reduction in percentage of predicted lung function than in males, this does not fully explain the higher symptom prevalence in females.

7.3.3 Sweden

This section focuses on The Obstructive Lung Disease in Northern Sweden (OLIN) Study, which comprises one of the largest surveys in the field of respiratory epidemiology with its approximately 40,000 study subjects. The methods used in the Finland-Estonia-Sweden (FinEsS) study were developed mainly from the OLIN study, and the FinEsS studies can be seen as an expansion and continuation of the OLIN Studies in Finland, Estonia, and Sweden.

7.3.3.1 The OLIN studies

The OLIN studies began in 1985 with a cross-sectional survey of asthma, chronic bronchitis, and respiratory symptoms among adults (Lundbäck 1993), to study prevalence and risk factors for these diseases. The first survey was performed in three steps: a postal questionnaire survey followed by structured interviews and lung function tests; the third step was a validation study of the results of the two first steps. Later, the OLIN studies have expanded into a large program of measures involving prevalence, incidence, and remission of diseases and conditions and their determinants. Of these, the focus has been mainly on modifiable risk factors. Dominant methods today include longitudinal studies with repeated cross-sectional surveys of their cohorts; to study trends in prevalence and burden of disease, new cohorts have been recruited at certain time intervals. Case-reference studies have also been based on both prevalent and incident cases of asthma. Today, five large cohorts of the general population are under study, including schoolchildren, adults, and the elderly, and beyond that, cohorts of asthmatics recruited for case-referent studies. The OLIN studies have also resulted in a large number of publications, six PhD theses, and a number of master's theses, and PhD students from many countries are doing research within the OLIN studies and related studies.

The first OLIN Study was a prevalence study among 6,610 adults (3,372 men and 3,238 women) aged 35 to 36, 50 to 51, and 65 to 66 years living in eight selected areas of Norrbotten; 86% completed a postal questionnaire satisfactorily (Lundbäck et al 1991), of whom 22% reported sputum production, and 14% reported recurrent (or frequent) wheeze. Ever having asthma was reported by 6%, whilst 4% stated that they had or had had chronic bronchitis or emphysema. These results indicate that the prevalence of asthma in the middle of the 1980ies could have been higher in northern Sweden than that reported from other parts of Sweden.
This postal survey was followed up, and a stratified sample of 1,506 (91% of those invited) including symptomatics and healthy controls underwent structured interviews and lung function tests (Lundbäck 1993). Asthma prevalence remained at a similar level, while it was considered that the postal survey had under-estimated the prevalence of chronic bronchitis, with elderly smokers having under-reported their bronchitic symptoms. The adjusted prevalence of chronic bronchitis was estimated to be of the order of 9%. The follow-up study also assessed the role of respiratory symptoms as indicators of impairment of lung function, and defined risk factors for respiratory symptoms and lung function impairment (Lundbäck et al 1994). Persistent wheeze, followed by chronic productive cough, was the symptom that predicted the greatest proportion of cases of impaired lung function.

An important element of the validation study within the first OLIN study was methacholine-testing of mild asthmatics (n=98), symptomatics without a diagnosis of asthma, and controls, in total 284 subjects (Lundbäck et al 1993b). Of the mild asthmatics, 79% reacted to methacholine doses < 8 mg/ml, while the corresponding figure in the symptomatic but non-asthma group was 34%. These results indicate that a carefully performed structured interview accurately diagnoses asthma in epidemiologic studies and that a bronchial provocation test adds very little on the group level but may be of importance on the individual level in characterising the individuals under study.
Another important step in validation was a study of non-response (Rönmark et al 1999a). The non-respondents were slightly more symptomatic; a greater proportion were smokers and belonged to lower socio-economic classes. Due to high participation rates (80-90%) the non-response caused no major bias.
By defining strict baseline characteristics and by combining classical epidemiological methods with clinical measures in a structured and well-defined manner, the first OLIN study created a firm basis for longitudinal studies. The first OLIN cohort has been followed for 20 years with three large postal surveys and several clinical surveys in sub-samples, including lung function.

Among the approximately 30 original articles based on this cohort, a number have contributed new knowledge at an international level. The OLIN studies were among the first clarifying the fact that half of all smokers sooner or later develop COPD (Lundbäck et al 2003b). At ages > 45 years, the prevalence of COPD according to the BTS guidelines was 8%, but 14% according to the GOLD criteria. The large majority of subjects fulfilling the criteria for COPD were symptomatic, while the proportion of those diagnosed as having COPD or similar diagnoses was small.
The large under-diagnosis of COPD has been recognised from the OLIN study (Lindström et al 2002) as well as from other studies (Lundbäck et al 2003a). Register studies in Sweden suggest that COPD contributes only one percent of Sweden's total costs for illness (Jacobson et al 2000), also underestimate the societal costs of COPD that is demonstrated by the OLIN studies (Jansson et al 2002). Recently, data on incidence of COPD have appeared (Lindberg et al 2005a).

Regarding asthma, several publications report incidence or remission, which in adults is very rare (Rönmark et al 1997, 1999, Lundbäck et al 2001). One important message is that increased diagnostic activity and, in reality, changing diagnostic criteria over the last 10 to 20 years have contributed considerably to the rapidly increased figures for the prevalence of asthma, and that the increase in asthma is a sum of these changes and shows a real increase in prevalence. The adjusted incidence was estimated at 2 to 3/1000/year, whereas a crude incidence of self-reported physician-diagnosed asthma was 2 to 3 times as high. Of risk factors, a family history of asthma applied at all ages, and smoking seems to be related also to incident asthma as verified by methacholine tests. Further, high BMI is related to incident asthma irrespective of gender and allergic status (Rönmark et al 2005).

Obstructive sleep apnoea has also been covered within the OLIN studies. Prevalence of obstructive sleep apnoea (OSA) among subjects with bronchitis was assessed in the OLIN cohort 1 with sleep investigations after screening by questionnaire (Larsson LG et al 2001). The prevalence of obstructive sleep apnoea with an apnoea/hypopnoea index (AHI) of 10 as the cut-off point and concomitant daytime symptoms such as daytime sleepiness or liability to nodding off during breaks in activities in the daytime was 5.4% for subjects with bronchitis and 2.3% for respiratorily healthy subjects. When a random sample aged 20 to 69 was used to study the prevalence of apnoeas and snoring in the general population (Larsson LG et al 2003), snoring as a problem or relatives´ concern about witnessed sleep apnoea was reported by 18% of men and 7% of women.

The OLIN paediatric study deserves mention, as it annually follows > 3500 children in three towns, comprising 60% of all children in Norrbotten aged 7 and 8 years at study start in 1996 (Rönmark thesis 1999c). As in the studies of adults, this study continuously provides new data. Interesting results include incidence and remission of asthma and allergy in relation to a number of determinants, among which has been documented an interesting pet-protective effect against asthma and allergy (Perzanowski et al 2002). The incidence of allergic sensitisation, which is the most important risk factor for asthma developing during school age, was estimated at 14% from age 7 to 11 (Rönmark et al 2003).

7.3.3.2 Other Swedish studies

This review includes only those Swedish studies relevant to this thesis. Swedish data from the ECRHS has already been mentioned. Beyond that, information on allergy deserves mention. The Swedish part of the ECRHS has also contributed with data about allergic sensitisation among young adults in three areas of Sweden (Plaschke et al 1996). The methods included skin prick testing (SPT), analyses of total and specific IgE antibodies in serum, and a questionnaire. SPT was performed for 1,572 subjects and analyses of specific IgE for 1,470. One or more positive SPT were found in 35.6%, and one or more positive specific IgE in 31.7%, similarly in the three areas: Uppsala, Gothenburg, and south Västerbotten (i.e., Umeå and inland). Birch, grass, cat, and dog were the most frequent sensitising agents and occurred at a similar prevalence, around 15%, in the three areas. The SPT to mite was positive in 14.1% in Gothenburg, 7.4% in Uppsala, and 7.9% in Västerbotten. Heredity, male sex, and low age were independently associated with atopy. Being born in the Scandinavian countries was independently associated with sensitization to cat, whereas birth in other countries was associated with sensitization to mite.

Of older Swedish epidemiological surveys, the study of Julin and Wilhelmsen (1967) has been mentioned. A random sample of 1,054 men and 1,113 women 16 to 64 years of age from a Swedish urban population was studied in 1964-1965. Prevalence of asthma was 2.0% and of chronic bronchitis 1.9%. Kiviloog et al examined in 1974 the distribution of subjects with airway diseases. Of 24,834 subjects in the age group 35 to 54, 296 subjects fulfilled screening diagnosis of asthma or chronic bronchitis. A representative sample of these, comprising 185 subjects, revealed in 86 bronchial asthma (without chronic bronchitis), in 69 chronic bronchitis (without asthma), and in 30 both chronic bronchitis and asthma; the prevalence estimates for men and women are in Table 1. The prevalence estimate of asthma (without chronic bronchitis) was 2.0% and that of chronic

bronchitis (without asthma) 3.4%, and the combination of asthma and bronchitis 0.6%. Subjects with asthma (n=86) had a mean FEV_1 91% of predicted, those with chronic bronchitis (n=69) 89%, and subjects with both asthma and chronic bronchitis 77% (Kiviloog et al 1975).

Computer records of Swedish conscript examinations in 1971 and 1981 were analysed regarding prevalence of asthma and allergic rhinitis (Åberg 1989). During the 10-year period, among the approximately 55,000 males age 18 in each cohort, the prevalence of asthma increased from 1.9 to 2.8% and of allergic rhinitis from 4.4 to 8.4%. Prevalence of allergic rhinitis was already higher in the northern than in the southern part of the country in 1971, and the increase in both diseases was higher in the northern parts of Sweden, doubling the prevalence in the north over that of the south in 1981. The distribution of prevalence was similar to the national temperature pattern, the higher prevalence being associated with a colder outdoor climate. Both diseases were also more prevalent in urban than in rural areas.

The prevalence of asthma-associated symptoms in the county of Jämtland where there is high asthma-drug use, and the county of Gävleborg where it is lower, was assessed in 1990 by a postal questionnaire – a variant of the OLIN questionnaire – answered by 11,300 subjects (Larsson L et al 1994). Three age groups were included: all 16-year-olds, 13% of those aged 30 to 39, and 13% of those 60 to 69. A total of 2,100 subjects reporting airway symptoms in a questionnaire and 450 asymptomatic controls were further investigated at an interview with lung function tests and, in 500 cases, with a methacholine challenge. The prevalence of current asthma was close to 8% in all age groups in Jämtland and significantly lower (close to 6%) in all age groups in the warmer, more industrialised, and more densely populated county of Gävleborg. The questionnaire, which was validated, was found useful for estimating asthma prevalence. No risk factors other than smoking were calculated in detail.

The cross-sectional questionnaire study was repeated in 1993 (Larsson L 1995). The incidence of asthma was calculated for the 2,308 individuals who answered the questionnaire in both surveys and who were found not to have asthma in 1990. The yearly incidence of asthma based on self-reported disease, physician-diagnosed asthma, asthma-drug use, or asthma-associated symptoms was between 0.8% and 1.3%, depending on criteria. All criteria resulted in a higher incidence in female subjects. Smoking and female sex were risk factors for asthma. The incidence of asthma was close to the incidence of new drug use for asthma.

The prevalence of bronchial asthma, chronic bronchitis/emphysema, respiratory symptoms, smoking habits, and medication in a random sample of 12,071 adults aged 20 to 59 was assessed in southern Sweden in a postal survey with a slightly modified OLIN questionnaire (Montnemery et al

1998). The prevalence of physician-diagnosed asthma was almost on the same level as in the OLIN studies. In never-smokers with no family history of asthma, the prevalence of physician-diagnosed asthma in subjects reporting childhood ETS exposure was 6.8% vs. 3.8% in non-exposed subjects.

Recently, also the Nordic-Baltic part of the ECRHS II (the RHINE study) has measured the incidence of asthma. Incidence was similar to that reported by the OLIN studies and close to 2/1000 per year (Toren et al 2004). No significant differences existed between the three Swedish centres (Umeå, Uppsala, Gothenburg), whereas the incidence was significantly higher in Iceland and Bergen, Norway, and very low in Tartu, Estonia. The very low incidence in Tartu was neither discussed nor questioned.

7.3.4 Finland

The most important Finnish studies on respiratory epidemiology in adults will be discussed here in detail mainly in chronological order, divided into three sections:

1. Early studies from 1960 to 1979
2. Studies published from 1980 to 1995,
3. Recent studies from 1996 to 2004

Most have been register studies or descriptive, cross-sectional studies, based on questionnaire and lung function measurements. Only a few used other methods as measurement of bronchial reactivity (Alanko 1970, Helenius et al 1998, Kilpeläinen et al 2001a and 2002) or skin prick tests (Terho et al 1987, Reijula et al 1990), while a strong feature in several Finnish studies has been use of longitudinal data (Huhti et al 1977, Terho et al 1987 and 1995, Vesterinen et al 1988, Haahtela et al 1990, Nieminen et al 1991, Keistinen et al 1993, 1996 and 1998, Rimpelä et al 1995, Kujala et al 1996, Huovinen et al 1999 and 2001, Karjalainen et al 2001, Jaakkola et al 2003).

On the other hand, only a few large-scale population-based studies of the general adult population have been performed in Finland (Järvinen et al 1960, Huhti 1965, Alanko 1970, von Hertzen et al 2000, Hedman et al 1999); among these, only Alanko and von Hertzen et al studied more than 5,000 subjects. Further, comparison of these with international results is difficult, because of divergences in methods: the methods in early studies by Järvinen (1960), Huhti (1965), and Alanko (1970) diverged somewhat from international studies of that time. Although some later surveys followed the methods of many international studies, divergent methods have been used also in some more recent Finnish studies (Isoaho et al 1994a, Hedman et al 1999). International comparability of these Finnish findings may thus be slightly hampered by these methodological divergences, especially results dealing with asthma and chronic bronchitis.

7.3.4.1 Early studies 1960-1979

Three pioneer surveys were performed according to high scientific standards. Even if the methods of that time included some deviations from today's, these studies offer a solid basis for assessing changes and developments in the field of respiratory epidemiology in Finland.
Järvinen et al published 1960 data on obstructive pulmonary emphysema in Finland. The study population was 4,500 adults (≥ 15 years) in a small town on the Finnish west coast; 3,375 subjects participated. The clinical study consisted of a questionnaire, pulmonary radiographs, and "a flow meter test for bronchiolar obstruction". According to the study criteria, 137 men (8.7%) and 67 women (3.7%) had obstructive pulmonary emphysema. The role of smoking habits was presented separately (Järvinen et al 1960b).

Huhti examined the 40- to 64-year-old population in another small rural community in western Finland (1965). His study procedure consisted of a questionnaire, lung function tests, chest x-ray examination, and when necessary, a complete medical examination. The participation rate was very high; 730 men (95.9%) and 890 women (96.2%). Prevalence rates were: asthma 0.5% in men and 1.6% in women, emphysema 10.0% and 2.3%, and chronic bronchitis 28.2% and 5.8%. The definition of emphysema is close to that of the present GOLD criteria for COPD. The prevalence of pulmonary tuberculosis was 5.5% in men and 4.3% in women. This population-based study provided results from a very well-conducted clinical examination in a randomized group of adults with a very high participation rate.
Although the author's wording in the title was "…in a Finnish ***rural*** population…" a proportion of the study population was working in a copper smelting plant, a chemical plant, woodworking factory or in other industries. The reader should also bear in mind that many of the men in the study group had participated in the Second World War (the Winter War of 1939-1941 and the Continuation War of 1942-1944). Wartime conditions with the exceptionally cold winter of 1939-1940 may have affected respiratory health among some of these subjects. A problem may also be the wording in the study questionnaire concerning chronic phlegm; in the Finnish version, this question differed from the original English one (MRC questionnaire). These three facts may have had an effect on results, especially on the high prevalence of chronic cough and chronic bronchitis.

In 1970 Alanko published results on the prevalence of asthma from the same community examined by Huhti. The study population comprised 5,862 subjects 10 to 59 years of age, and 5,287 (90.2%) of them participated in the questionnaire study. Of the male subjects, 1.2% had physician-diagnosed asthma, vs. 1.6% of females. Current asthma was diagnosed as a combination of bronchial

hyperreactivity and wheezing or hyperreactivity and dyspnoea. In young adults (20-24) the prevalence of current asthma was 0.19%, in subjects 55 to 59 it was 3.28%, and for the whole study population (5,287 subjects 10-59 years) 1.21%, indicating a lower prevalence of asthma in Finland than in other Nordic countries in the 1960ies and 1970ies.
A population sample comprising 653 men and 823 women aged 40 to 64 years was surveyed in 1961 to determine the prevalence of chronic respiratory disease (Huhti 1965). In a follow-up study, Huhti analysed the 10-year mortality of his study population. In men without lung disease, the smokers´ mortality was 1.8-fold greater than for non-smokers. In female smokers, the risk of death was roughly twice that of female non-smokers (Huhti et al 1977).

7.3.4.2 Studies published in Finland between 1980 and 1995.

These studies reported the increasing prevalence of asthma, as well as the burden of COPD in Finland, and analysed associations of atopy and smoking in asthma and chronic bronchitis. Haahtela et al (1990) found an apparent real increase in asthma based on reports and statistics from the Finnish defence forces. Roughly 900,000 men – 98% of the men of conscription age – were examined from 1966 to 1989, and a comparable number examined from 1926 to 61. During the 1926 to 1961 period, the prevalence of asthma recorded at call-up examinations remained steady at between 0.02% and 0.08%. Between 1961 and 1966, however, a continuous, linear rise began, with the prevalence increasing from 0.29% in 1966 to 1.79% in 1989 – that is, representing a 6-fold increase. It seems unlikely that a change of that magnitude could have been entirely due to change in diagnostic techniques or other confounding factors. Reijula et al (1990) evaluated the prevalence of respiratory symptoms in relation to occupation and smoking habits in 211 randomly selected male reindeer herders in northern Finland. No significant differences could be determined in respiratory symptoms, smoking habits or ventilatory function between full-time reindeer herders and their controls. Positive skin prick test reactions to common allergens in reindeer herders were to some extent lower than expected. Only one test subject was positive to reindeer epithelium. Prevalence of chronic bronchitis was 10% in non-smokers and 28% in regular smokers. Dyspnoea caused by cold air was reported by 14% of subjects.

Terho et al (1987) analysed relations between atopy, smoking, and chronic bronchitis among farmers in cross-sectional and longitudinal studies. The first cross-sectional study comprised 9,017 farmers; those 6,899 without chronic bronchitis at study beginning and who continued farming were followed for 3 years. The prevalence of chronic bronchitis was 4.1% in non-atopic non-smokers,

10.1% in atopic non-smokers, 10.6% in non-atopic smokers, and 25.7% in atopic smokers. The relative risk for chronic bronchitis, calculated from the incidence data adjusted for the effects of age, sex, smoking or atopy by logistic regression analysis, was 2.2 for atopy and 2.3 for smoking. Atopy and smoking had independent and additive effects on the occurrence of chronic bronchitis.

In the second study, the cross-sectional sample comprised 18,351 subjects, including 1,025 prevalent cases, and the follow-up sample comprised 17,134 subjects, 553 of whom were incident cases of chronic bronchitis (Terho et al 1995). Chronic bronchitis was associated with atopy (relative risk 1.41) and smoking (2.43). In the follow-up data, chronic bronchitis was related to atopy (1.28), smoking (2.31), and farming (1.45). These results give more support to the "Dutch hypothesis" (Orie et al 1960), according to which atopy is a predisposing factor in the aetiology of chronic bronchitis, than to the British one (Fletcher and Peto 1977), which considers smoking to be the causal factor leading to chronic bronchitis and irreversible obstructive changes in airways.

Nieminen et al (1991) evaluated aggregation of cases of bronchial asthma in adult twin pairs in the nationwide Finnish twin cohort consisting of 13,888 adult monozygotic (MZ) and same-sex dizygotic (DZ) pairs. A diagnosis of bronchial asthma in one or more of these registers was obtained for 525 (236 men and 289 women) of 27,776 twin individuals. Among MZ pairs, ten concordant and 138 discordant pairs were identified, and among DZ pairs, 12 concordant and 343 discordant pairs. The authors reported the correlation with liability to asthma to be 0.425 in MZ twins and 0.247 in DZ twins, with a heritability estimate of 35.6 percent. The age-adjusted cumulative incidence of asthma in these groups was between 1.7% and 2.2%.
A nationwide sample of 12-, 14-, 16-, and 18-year-olds was studied in cross-sectional surveys by postal questionnaire in 1977, 1979, and 1991 in Finland to assess whether asthma and allergic rhinitis had increased from 1977 to 1991 (Rimpelä et al 1995). Prevalence of asthma was 1.0% from 1977 to 1979 and 2.8% in 1991, that of allergic rhinitis 5.0% and 14.9%. Physician-diagnosed asthma and allergic rhinitis increased 3-fold among Finnish adolescents from 1977 to 1991. The authors considered the major part of this increase probably to be real.

In a register study Keistinen et al reported asthma related hospital treatment in Finland from 1972 to 1986. In 1972 in Finland, 277 such hospital treatment periods were registered per 100,000 inhabitants and 406 per 100,000 in 1986. The most pronounced change occurred for those aged ≥ 65 years. Although the number of asthma-related treatment periods increased, the number of new patients with asthma did not. The increase in asthma-related hospital treatment periods seemed

attributable to frequent treatment of the same patients. Co-morbidity, e.g., COPD and cardiac diseases, might also explain the increase in hospital treatments among the elderly with asthma. (Keistinen et al 1993). In another study hospital admission figures for patients with COPD collected from hospital discharge registers in Finland from 1972 to 1992 showed an average of 17.0 admissions per 1,000 individuals per year for men and 2.1 for women. The annual increase in the number of such periods, relative to population, was +1.5% for men and +5.1% for women. The mean number of hospitalisation days increased among women but tended to decrease among men from the late 1980ies onwards (Keistinen et al 1996).

Isoaho et al analysed the prevalence of COPD and asthma in the population aged ≥ 64 by a cross-sectional epidemiological survey in a rural community in southwestern Finland (Isoaho et al 1994a, b), with 488 men and 708 women (93% of those eligible) participating. Methods included a nurse's interview and spirometry with a bronchodilator test; the cut-off point for obstruction was a FEV_1/FVC ratio < 0.66. The prevalence of COPD was 12.5% for the men and 3.0% for the women. In both sexes only about 2% of those who had never smoked suffered from COPD, but among the current smokers, prevalence was 35% for men and 13% for women. The prevalence of current asthma was 2.9% in the men and 3.8% in the women and accounted for about 40% of the lifetime cumulative prevalence of self-reported asthma.

7.3.4.3. Recent studies since 1995

The trend toward increasing asthma prevalence in Finland is further supported by recent results, and the prevalence rates seem to be to close those found in the other Nordic countries, whereas the prevalence of COPD in Finland remains to be assessed by internationally accepted criteria. Several risk factors connected to asthma and COPD were evaluated in these publications.

As also reported by others such as Larsson K et al (1993), Helenius et al (1997) found an association between the type of training for competitive sports and the risk for asthma. Physician-diagnosed asthma occurred in 18 of 107 long-distance runners (17%), in 9 of 106 speed and power athletes (8%) and in 4 of 124 controls (3%). Prevalence of physician-diagnosed asthma in elite athletes is high and an association with the competitive event is suggested, with long-distance runners being at greater risk for developing asthma than are speed and power athletes.

Some 58 elite runners, 79% of them belonging to Finnish national teams, participated in a study on exercise-induced bronchospasm (Helenius et al 1998). This included a questionnaire on respiratory symptoms, skin prick tests, and spirometry at rest and after an exercise-challenge test at subzero temperature in winter and after a similar exercise challenge test in summer at the end of the birch-pollen season. Exercise-induced broncho-spasm (a post-exercise reduction of 10% or more in FEV_1) was observable in 5 (9%) of the 58 runners, and 15 (26%) of the runners had probable exercise-induced bronchospasm in either the winter or the pollen season.
However, Kujala et al (1996) showed in a case-control study that lifetime occurrence of asthma or other pulmonary diseases in former international level elite athletes who represented Finland between 1920 and1965 was not increased, indicating that exercise alone, even in a cold environment, did not lead to increase the prevalence of asthma, at least up to the mid 1980ies. Between 1936 and 1985, two controls but none of the athletes died of asthma.

A farm environment in childhood may protect against sensitization, allergic rhinitis, and asthma. (von Ehrenstein et al 2000). Kilpeläinen et al (2002) studied two random samples selected from 1631 subjects responding to a questionnaire survey: subjects with asthma or wheezing, and subjects without asthmatic symptoms. A total of 296 (72%) participated. Skin prick tests, measurements of IgE-antibodies, methacholine challenge, and bronchodilation tests were performed. Current asthma was found in 3.1% of subjects from a childhood farm environment, and in 12.4% from a non-farm environment. Sensitization to cat was less common in subjects from childhood farm environments. Thus, a farm environment in childhood may protect against adult asthma and sensitization – especially to cat – the most important asthma-related allergen. In contrast, in childhood-farm subjects, sensitization to house-dust mite was more common.
In a questionnaire survey of 10,667 Finnish first-year university students aged 18 to 25 years, Kilpeläinen et al (2001) evaluated the association between home dampness and current physician-diagnosed asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, common colds, and bacterial respiratory infections. Of dampness categories analysed, visible mould or damp stains or water damage was reported by 15.0%. The strongest association was between exposure to visible mould and asthma and common colds. Risk for current asthma in damp homes was highest among subjects with atopic heredity.

Hedman et al (1999) studied the prevalence and relation to asthma of aspirin intolerance, nasal polyposis, allergic rhinitis, and smoking habits. A postal questionnaire surveyed a population-based random sample (4,300) of adult women and men aged 18 to 65 years in southern Finland. The

prevalence of aspirin intolerance causing shortness of breath or attacks of asthma was 1.2%, higher in patients with doctor-diagnosed asthma (8.8% versus 0.8%, relative risk = 11.4). The non-response adjusted prevalence of doctor-diagnosed asthma was 4.4% and that of COPD 3.7%. However, the method to detect COPD does not conform to recommendations: those who answered *yes* to the question "Has a doctor diagnosed any of the following diseases in you: chronic bronchitis? or emphysema?" were labelled as COPD cases.

Von Hertzen et al (2000) examined the severity of airway obstruction and the occurrence of respiratory symptoms in a large, nationally representative population sample. The study population comprised 7217 randomly selected subjects (aged 30 years and older) who participated in a comprehensive health examination survey. Survey methods comprised questionnaires, interviews, physical measurements including spirometry, and clinical examinations. In the whole study population, the age-adjusted prevalence of chronic bronchitis or emphysema or both was 22% among men and 7% among women, whilst clinically relevant airway obstruction (FEV1/FVC% ≤ 69) was present in 11% of men and in 5% of women. Prevalence of COPD was however, not reported.

Jaakkola et al (2003) assessed relations between occupation and risk for asthma in adulthood in a 1997 to 2000 population-based incident case-control study of 521 cases and 932 controls in south Finland. Occupations were classified according to potential exposure to asthma-causing inhalants. Asthma risk was consistently higher for both men and women in the chemical, rubber and plastic, and wood and paper industries. Of the predominantly male occupations, metal and forestry work were the strongest determinants of asthma. For women, asthma risk was higher for waiters, cleaners, and dental workers. Results suggest an increased asthma risk both in traditional industries and in forestry and in several nonindustrial occupations.

In another study evaluating occupational risks for asthma, Karjalainen et al (2001) found that although occupational asthma accounted for only 5% of all cases, 29% of the male asthma cases and 17% of the female cases were associated with occupation. Risk was higher in agricultural, manufacturing, and service occupations. The results indicate that the impact of occupational factors in the inception of adult-onset persistent asthma, and consequently the potential for prevention, is much larger and more widespread than generally assumed.

Huovinen et al (2001) identified 262 twin pairs discordant for incident asthma from the Finnish twin cohort during a 17-year follow-up. According to the results of a co-twin case-control study, the atopic twin had a higher risk for asthma than did the non-atopic co-twin (RR 2.91). The more educated twin had a lower risk for asthma than did his/her twin sibling with less education (RR 0.45), and the twin who participated in conditioning exercise had a lower risk for asthma than did the more sedentary co-twin (RR 0.55). The authors concluded that in addition to allergic diseases, educational level and physical activity are associated with adult-onset asthma, which indicates a role for factors associated with life-style.

In another register study based on the Finnish Twin cohort, Huovinen et al (1999) examined among adult twins the prevalence of asthma and hay fever, and the incidence and temporal relationships of asthma, hay fever, and chronic bronchitis during a 15-year period. The prevalence of asthma increased slightly from 1975 (2.0% in men and 2.2% in women) to 1990 (2.9% and 3.1%). Prevalence of hay fever showed a larger increase in both genders. Compared with figures for 1976 to 1981, no significant increase in asthma incidence occurred from 1982 to 1990. The pattern of increase in asthma and hay fever prevalence with time was similar, and hay fever was a strong predictor of asthma. These diseases showed no significant increase in incidence. Today, publications from the Helsinki part of the FinEsS studies also confirm an increase in the prevalence of asthma to a level somewhat lower than in Sweden (Pallasaho et al 2002, 2005).

8. THE FINESS STUDY CO-OPERATION

8.1 BACKGROUND, IDEA

Epidemiological studies on asthma and COPD published during the 1980ies and early 1990ies led to increased interest in respiratory epidemiology. Results from the Nordic countries, and especially the model of the OLIN Studies in northern Sweden, raised several questions:

1. Does the epidemiology of respiratory diseases in Finland still differ from that of Sweden?
2. Does a north-south gradient for asthma prevalence exist also in Finland?
3. Could simultaneous collected study samples from several centres provide better possibilities for understanding risk factors for respiratory diseases in Nordic countries?

Discussions of these points during the Finnish Chest Physicians´ meeting at Oulu in 1994 between Bo Lundbäck and the author of this thesis initiated research co-operation between northern Sweden (OLIN studies) and northern Finland (Länsi-Pohja Central Hospital). At the same time, colleagues from Örebro Central Hospital in Sweden and the Pneumonology Department at the Clinical and Experimental Research Centre of Tallinn, Estonia, were about to start similar co-operation. It became obvious that broader co-operation could be of great benefit to all, and FinEsS study co-operation thus begun among these four centres.

For a north-south view in Finland, Helsinki was invited to participate. Researchers at the Stockholm unit of the former Swedish National Institute of Occupational Health were also interested, and thus Stockholm was included. The Institute of Occupational Health, Oulu, Finland, headed by Professor Juhani Hassi, participated with the Finnish centres especially in work dealing with occupational and cold-related health problems.

8.2 ORGANISATION

Participants on the steering committee of the FinEsS study were Associate Professor Bo Lundbäck (chair), Stockholm and Luleå, Professor Anssi Sovijärvi, Helsinki, Professor Lii Jannus-Pruljan (Tallinn), Professor Kjell Larsson, Stockholm, and Associate Professor Jaak Kiviloog, Örebro. In the initial phase, Professor Lauri A. Laitinen, Helsinki, Professor Markku M. Nieminen, Tampere, and Professor Per Malmberg, Stockholm, also participated. During recent years, Eva Rönmark, PhD, has participated in data management and supervision of data analyses of asthma and allergy.

The statisticians, docent Elsy Jönsson, Umeå, and Docent Matti Kataja, Tampere, have been responsible for data management for statistical analyses in the FinEsS study, assisted by the statisticians Anders Magnusson, Örebro, and Ola Bernhoff, Haparanda. Associate Professor Anders Oden, Göteborg, participated in special analyses of smoking-associated risks for COPD.

Co-ordinators were, when the study was conducted, Mai Lindström, PhD, Luleå (questionnaires), Britt-Marie Sundblad, PhD , Stockholm (lung function), and Irene Eriksson, SRN, Örebro (skin prick tests). In Estonia, Associate Professors Helle-Mai Loit and Jaak Pölluste led the study, and statistician Tanja Veidebaum the data management.

8.3 THE FINESS STUDY IN NORTHERN FINLAND

The author of this thesis has had the advantage of being included in the FinEsS study co-operation from the initial phase, the main tasks having been:

1. Responsiblity for the FinEsS study centre in Finnish Lapland
2. Participation in starting the FinEsS study centre in Helsinki
3. Participation in designing the Finnish forms of the FinEsS study questionnaire (FFQ) and interview (FFI)

The study team at Länsi-Pohja Central Hospital, Kemi, Finland, included study nurses Eila Eriksson, Minna Kiviniemi, Terttu Rantamaa, Minna Ruikka, and Sari Törrönen. They performed the fieldwork of the FinEsS study in northern Finland together with the author of this thesis. Ola Bernhoff and his team at Haparanda, Sweden, computerised the questionnaire data and the Regional Institute of Occupational Health, Oulu, the interview data.

9. AIMS OF THE FINESS STUDY IN NORTHERN FINLAND

9.1 MAIN HYPOTHESES

1. The prevalence of asthma among adults in Finland has risen to the same level observed in other Nordic countries.
2. The prevalence of chronic bronchitis and COPD among adults in Finland, if adjusted, is similar to that of the other Nordic countries.
3. The cold climate plays an important role in triggering respiratory symptoms among the adult population of northern Finland.

9.2 SPECIFIC AIMS

1. To assess the prevalence of asthma, chronic bronchitis, respiratory symptoms, and risk factors for these conditions in an adult population in northern Finland by a postal questionnaire study of a randomly chosen 8000 adults living in Finnish Lapland.

2. To investigate whether non-response bias has any significant effect on the results of a large questionnaire study on respiratory symptoms and diseases, and whether different methods used in a non-response study have any effect on the results.

3. To examine whether risks for asthma, chronic bronchitis, or respiratory symptoms are influenced by living in a cold climate, especially by outdoor work or recreational cross-country skiing.

4. To assess whether north-south differences exist in Finland in the prevalence of asthma, chronic bronchitis and respiratory symptoms, and to compare risk factors for respiratory conditions and diseases between northern and southern Finland.

5. To study the influence of smoking categories on the prevalence of respiratory symptoms and chronic bronchitis in northern Finland and northern Sweden, and to investigate whether or not differences in smoking habits and prevalence of respiratory symptoms or obstructive lung diseases between Sweden and Finland still exist.

6. To estimate the prevalence of COPD in an adult population in northern Finland by use of internationally accepted criteria, and to evaluate the association of COPD with age, gender, smoking habits, type I allergy, history of allergy, outdoor work, cross-country skiing, passive smoking during childhood, family history of allergy and asthma, and family history of chronic bronchitis or emphysema.

10. METHODS

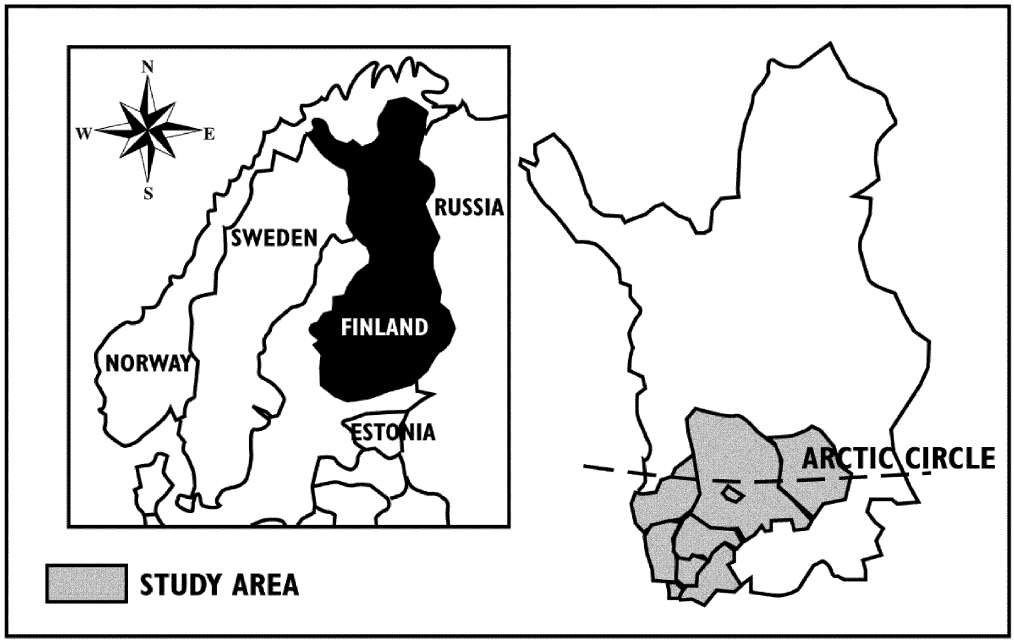
10.1 DESIGN

This is a population-based survey of an adult general population in Lapland, the northernmost province of Finland. In the first phase, a postal questionnaire study was conducted during the winter of 1995-1996 in the southwestern and central part of Finnish Lapland among a random sample of 20- to 69-year-old adults. The questionnaire included questions about heredity, respiratory symptoms, asthma, chronic bronchitis, symptoms under special circumstances, use of asthma medication, profession, and smoking habits. Data from this population-based study were analysed to assess the prevalence of respiratory symptoms and patient-reported obstructive respiratory diseases in northern Finland (Studies I to III). The results were also compared to simultaneously collected data from southern Finland, (Study IV), and northern Sweden (Study V). In the second phase, a random sample of postal study respondents was invited in 1997-1998 to a clinical study including a structured interview, skin-prick test, and pulmonary function measurements. The prevalence of COPD and its determinant were analyzed (Study VI). Further, reference values were calculated for lung function for this population (Kotaniemi and Kataja 2004). Clinical study results also served to validate questions from the questionnaire study.

10.2 STUDY AREA AND POPULATION

Lapland, the northernmost province in Finland, lies between Russia in the east, Norway in the north, and Sweden in the west. The study area is located between 65º and 67º north latitude, and 24º and 28º east longitude. The area of Lapland is 98,457 km², 29% of the area of Finland, and on December 31, 1995, it had a population of 201,411 people, comprising 4% of the population of Finland. The study area – the southwestern and central part of the Finnish Lapland (Figure 1) – consisted of 9 municipalities (Table 2), including four towns and their surroundings, lowlands, river valleys, pine and spruce forests, and fells. This study area has very little air pollution, but the climate is cold. The average temperature in July is +15°C, and in January -13°C. The yearly mean temperature in the study area is close to 0°C.

Figure 1. Study area in Finnish Lapland.



As part of the FinEsS study co-operation, similar postal questionnaire studies were conducted also in Helsinki, southern Finland, and in Norrbotten, the northernmost province in Sweden. Contrasting with Lapland's low population density, 525,031 resided in 1996 in Finland's capital, Helsinki. The main occupations in Lapland were the pulp and paper industry, steel industry, forestry, trade, farming, and social services; and in Helsinki: social services, trade, education, consumer goods manufacturing, financing and the insurance business, and administration.

In December 1995, the province of Norrbotten had 266,011 inhabitants, which comprised only 3% of the population of Sweden, but covers an area of 105,886 km^2, or 24% of Sweden's total area. The main industries include the steel, paper, and pulp industries, iron mines, and forestry, as well as commerce, trade, and administration. In northern Finland, 7% of the adult population was employed in agriculture, compared to only 3% in northern Sweden. The climate in northern Sweden is comparable to that of Lapland, but the climate in Helsinki on the southern coast of Finland is milder. The average temperature in Helsinki in January is –6°C and in July +17°C.

Table 2. Population in the study area in Lapland on 31, December, 1995, main occupations and postal questionnaire response

Name of municipality	Settlement type, mainly	Main occupations	Main industry	Area code: coastal=C inland=I	Population total	Population 20-69 y	% of Total pop.	Randomised for questionnaire	Respondents	Response rate % of pop. 20-69 y
Simo	R	industry farming and forestry		C	4,158	2,622	63.1	234	209	89.3
Kemi	T	industry, public health and social services	pulp and paper machine manufacture	C	24,696	16,416	66.5	1,456	1,188	81.6
Keminmaa	S	industry, public health and social services	mining (chromium)	C	9,411	5,824	61.9	520	436	83.8
Tervola	R	farming and forestry defense depot		C	4,079	2,528	62.0	226	200	88.5
Tornio	T	industry, public health and social services	steel manufacture beverages manufacture	C	23,156	14,445	62.4	1,287	1,097	85.2
Ylitornio	R	forestry, public health and social services		C	6,029	3,700	61.4	331	291	87.9
Rovaniemi	T	trade, public health and social services	machine manufacture	I	35,236	23,355	66.3	2,055	1,651	80.3
Rovaniemen mlk	S	social services and public health, defense		I	21,809	13,738	63.0	1,210	1,021	84.4
Kemijärvi	T	industry farming and forestry	pulp and paper electronics	I	11,775	7,711	65.5	686	540	78.7
				coastal	71,529	45,535	63.7	4,054	3,421	84.4
				inland	68,820	44,804	65.1	3,951	3,212	81.3
				study area	140,349	90,339	64.4	8,005	6,633	82.9

Settlement type: R = rural, T = town, S = suburban
pop. = population, y = year, mlk = rural community

10.3 STUDY SUBJECTS, QUESTIONNAIRE STUDY, STUDIES I-V

Studies I to III analysed data from the postal questionnaire study performed in Finnish Lapland. The population in the study area at the end of 1995 was 140,349, of whom subjects aged 20 to 69 represented 64% (Table 2). Half (51%), lived on the coast, and the majority, 57%, in urban areas. A random sample of 8,005 subjects aged 20 to 69 was taken evenly throughout the study population, i.e., the number of persons invited from the various regions correlated with the number of persons in various age cohorts residing in each respective region.

Study IV compared postal questionnaire data from Finnish Lapland with simultaneously collected questionnaire data from southern Finland, and Paper V with data from northern Sweden. Sample size in Helsinki was 8,000, and in Norrbotten, 8,333 subjects. Complete answers after two reminders were obtained from 6,633 (83%) in Lapland, 6,062 (76%) in Helsinki, and 7,104 (85%) in Norrbotten.

10.4 STUDY SUBJECTS, CLINICAL STUDY, STUDY VI

Of the respondents (n=3,420) in the southern part of the study area, a random sample of 959 subjects was invited to a clinical study; 695 participated, of whom 683 provided complete data. The clinical study included a structured interview, skin-prick test, and pulmonary function measurements. At the time of the clinical study, the participants were 21 to 70 years of age.

10.5 QUESTIONNAIRE

The Finnish version of the FinEsS questionnaire (FFQ) (Appendix) used in this study is based on the OLIN questionnaire (OQ) (Lundbäck et al 1991), which has been used in several Nordic studies (Lundbäck 1993, Larsson L 1995, Montnemery et al 1998) and was developed from a Swedish applicant of the BMRC questionnaire (Medical Research Council`s Committee 1960) with modifications from the American Thoracic Society's questionnaire (ATS) (Ferris 1978) and Tucson (Lebowitz and Burrows 1976) questionnaires. It also included two questions from the International Union Against Tuberculosis and Lung Disease (IUATLD) (Burney et al 1989) and the European Community Respiratory Health Survey (ECRHS 1996) questionnaires.

The FFQ contains 20 questions which are each divided into 1 to 9 sub-questions. The English and Finnish versions of the FFQ are Appendixes 1 and 2. The whole questionnaire has 39 different points which require either yes or no/don't know answers, and additionally four questions on

working history and main occupation, plus one question on ethnic origin. The FFQ includes questions about heredity, respiratory symptoms, asthma, chronic bronchitis, symptoms under special circumstances, use of asthma medication, smoking habits, profession, outdoor work, and skiing habits, as well as about parents´ smoking habits.
The questions (q) about heredity (q1) and respiratory history (q2), asthma attacks (q6), cough (q7), chronic productive cough (q8), recurrent wheezing (q9), symptoms under special circumstances (q13), and smoking (q14) were adopted from the OQ. Questions about wheezing with shortness of breath (q10), and chest tightness in the morning (q11) originate from the ECRHS questionnaire. Questions about physician-diagnosed asthma (q3) and physician-diagnosed chronic bronchitis or emphysema (q4), as well as the question about use of asthma medication (q5) are similar to those in the Tucson questionnaire. The question about shortness of breath when walking on the level (q12) originates from the BMRC bronchitis research questionnaire on dyspnoea. The questions about smoking (q14) and working history (q15 and q16) were modified from the OQ. Those about indoor and outdoor work (q17 and q18), as well as the questions about parental smoking history (q19) and skiing habits (q20), were developed for this questionnaire.

Questions about respiratory symptoms and diseases required either “yes” or “no/don’t know” answers. Classification of smoking habits was into either *non-smokers, ex-smokers* (those who had stopped more than 12 months prior to the study), or *current smokers*, according to the questions used, or in some analyses as *non-smokers* and *ever-smokers*, the sum of ex-smokers and current smokers. For current smokers a question was included with three alternatives about the number of cigarettes consumed; < 5, 5 - 14, or > 14 cigarettes/day.
Physician-diagnosed chronic bronchitis was based on the question "Have you been diagnosed as having chronic bronchitis or emphysema by a physician?” *Sputum production:* "Do you usually have phlegm when coughing, or do you have phlegm in your chest which is difficult to bring up?"
Chronic productive cough: "Do you bring up phlegm when coughing on most days during periods of at least 3 months during at least 2 successive years?"
Wheezing during the preceding 12 months (wheezing last 12 months): "Have you at any time during the last 12 months had wheezing or whistling in your chest?"
Dyspnoea grade 2: "Do you get short of breath or have to walk more slowly when you walk with other people of your own age on level ground at a normal pace?"
Symptoms with exercise or in cold weather were assessed by the question: “Do you get shortness of breath, wheezing or severe cough: a) with exercise b) in cold weather c) with exercise in cold weather (at a temperature below the freezing point)?”

Working history was assessed by the question: "In what profession have you been mainly working?" with a sub-question: "How many years have you been doing this work?" *Outdoor work* was assessed by the question: "Are you nowadays doing mainly a) outdoor or b) indoor work?" and "For how many years have you been doing outdoor work?", and *skiing habits* by the question "Are you or have you been a competitive skier or a regular recreational skier?"

10.6 STRUCTURED INTERVIEW QUESTIONNAIRE

The interview questionnaire used in the FinEsS studies was an expanded version of the OLIN interview questionnaire (Lundbäck 1993, Rönmark 1999). Similarly to the FinEsS postal questionnaire, it also included questions from the interview questionnaire developed for the ECRHS (1996); further, it included questions from the IUATLD questionnaire (Burney et al 1989). The questions from the ECRHS and from the IUATLD questionnaires focused on asthma. Compared to the postal questionnaire, the interview questionnaire aimed at better identifying asthma and other wheezing conditions and at obtaining a more detailed description of asthma medication. Questions aiming at quantifying dyspnoea were included and also other questions meant to differentiate between asthma and COPD; for instance, questions about variability of symptoms and symptoms following by a number of specific exposures.

10.7 LUNG FUNCTION TESTS

All tests were done according to ATS standards (ATS 1995) with a Sensor-medics VMAX 22 spirometer (the same piece of equipment for all tests), that was calibrated daily. All the four study nurses performed spirometries. Tests were done with the subject in sitting position, with noseclips and bacterial filters. The tests included flow-volume spirometry, a bronchodilatation test, slow vital capacity, and diffusing capacity by the single breath method. Diffusing capacity results have not been included in this thesis. Bronchodilatation was measured 10 minutes after inhalation of salbutamol 2 x 200mcg (Ventoline MDI 200mcg/puff with Volumatic, Glaxo Pharmaceuticals, UK), according to the current Finnish guidelines (Viljanen 1982). All data including spirometry and calibration data were stored on a separate magneto-optic disc.

10.8 SKIN PRICK TESTS

The standard duplicate method (Dreborg 1989) was used to test skin prick reactivity to 12 allergens; *Dermatophagoides pteronyssinus, Acarus siro*, cat, dog, horse, cow, birch, timothy, mugwort, *Cladosporium herbarum*, latex, and reindeer. A positive (histamine HCL, 10 mg/ml, in 50% glycerol) and a negative control (50% glycerol) were included. The reactions were read 15 minutes after application of allergens on the forearm. A reaction was considered positive if the mean wheal diameter ([d1+d2]/2) was at least 3 mm.

10.9 DEFINITIONS

10.9.1 Asthma

Patient-reported asthma was diagnosed according to question 2a: "Do you have, or have you ever had asthma?" and *physician-diagnosed asthma* according to question 3: "Have you been diagnosed by a physician as having asthma?"

10.9.2 Chronic Bronchitis and Emphysema

Patient-reported chronic bronchitis was diagnosed according to question 2c: "Do you have, or have you had chronic bronchitis or emphysema?" and *physician-diagnosed chronic bronchitis* according to question 4: "Have you been diagnosed as having *chronic bronchitis* by a physician?" A*djusted chronic bronchitis* (subjects who reported physician-diagnosed chronic bronchitis or chronic productive cough, with subjects with physician-diagnosed asthma being excluded) was diagnosed as a combination of questions 4 and 8b: "Do you usually have phlegm when coughing or do you have phlegm which is difficult to bring up…and have you had such periods of phlegm production during at least 2 successive years?" Subjects with physician-diagnosed asthma, question 3, were excluded.

10.9.3 Chronic obstructive pulmonary disease (COPD)

In this study COPD was defined according to the

1. British Thoracic Society (BTS 1997) criteria: "COPD is a chronic, slowly progressive disease characterized by airflow obstruction (reduced FEV_1 and FEV1/VC ratio) that does not change markedly over several months. Most of the lung function impairment is

fixed, although some reversibility can be produced by bronchodilator (or other) therapy." or

2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop criteria: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." (Global Initiative for Chronic Obstructive Lung Disease, updated 2004).

Airway obstruction in COPD was defined as $FEV_1/VC < 0.7$ by BTS and $FEV_1/FVC < 0.7$ by GOLD criteria. GOLD criteria refer to post-bronchodilator and BTS to pre-bronchodilator spirometry results. The BTS definition of COPD states: *"Unlike asthma, airflow limitation in COPD as measured by the FEV_1 can never be returned to normal values."* Thus only those who also had *post-bronchodilator* $FEV_1 < 80\%$ of predicted were included in BTS COPD cases. According to BTS guidelines, FEV_1 80% of predicted is the *upper limit*, whereas GOLD guidelines consider FEV_1 80% of predicted as the *lower limit* for mild COPD. In moderate COPD, FEV_1 (% of predicted) ranges from 40% to 60% by BTS criteria and from 50% to 80% by GOLD guidelines. The recently published NICE (BTS) criteria have adopted the GOLD with the exception that mild COPD according to GOLD is not included as COPD according to NICE criteria. ATS/ERS have adopted GOLD with the exception that $FEV_1/FVC \leq 0.7$ (GOLD < 0.7).

10.10 STATISTICAL METHODS AND ANALYSES

The Chi-square test was used for bi-variate analyses and one-way ANOVA to test trends. The Statistical Package for the Social Sciences (SPSS) served for multiple logistic regression analysis to calculate the influence of possible determinants in Studies I and III, and to assess the simultaneous influence of variables other than response or non-response on respiratory symptoms and diseases in Study II. In the analyses of working condition effects, those 437 subjects who reported working both in indoor and outdoor occupations were pooled with 439 subjects who reported only outdoor work in Study III.

In Study IV, odds ratios (OR) for various independent variables known to have an influence on respiratory conditions were calculated by multiple logistic regression analysis. The effects of working conditions on respiratory symptoms were assessed by stratification according to smoking and indoor or outdoor work, and those who reported both indoor and outdoor occupation were excluded from these analyses.

For analysis of clinical conditions, in addition to single symptoms and diseases, two symptom combinations were calculated:

1. *Adjusted chronic bronchitis* which comprises all those who reported physician-diagnosed chronic bronchitis *or* chronic productive cough; physician-diagnosed asthma was excluded,
2. *Wheezing with shortness of breath (SOB) without cold* which comprises all those who reported wheeze with shortness of breath apart from colds during the previous 12 months.

In Study IV, prevalence rates were presented after correction for bias caused by non-response. A separate non-response study was performed in Lapland. The prevalence rates are given assuming that the non-responders in Helsinki differed from the responders in the same way as the non-responders in Lapland by a Bayesian comparison.
Prevalence rates in Study V were standardised with the Mantel-Haenszel test for age and smoking, and Chi-square test or one-way ANOVA (analysis of variance) were used for categorical comparisons. The simultaneous effects of different independent variables on respiratory symptoms were calculated by multiple logistic regression analysis.

Although asthma and COPD have many common features, they have also many crucial differences that influence response to therapy and prognosis (Jenkins et al 2005). Optimal management of obstructive pulmonary disease should be based on firm diagnosis, and thus differentiation between asthma and COPD is important − this is especially evident in cases with specific allergies or if pulmonary obstruction is associated to occupational factors. Thus, to distinguish COPD from pure asthma in Study VI, the following adjustment was performed: *Those with both physician-diagnosed asthma and a smoking history of less than 10 pack-years were not included in the COPD group*.

The Chi-square test served for bi-variate comparisons. One-way ANOVA was used to test trends. OR for various independent variables were calculated by multiple logistic regression analysis. Interaction analysis between age, smoking, and family history of OAD was performed by an additive model with multiple logistic regression analysis.

11. RESULTS

11.1 POSTAL QUESTIONNAIRE-BASED STUDIES IN LAPLAND, STUDIES I-III

11.1.1 Response and participation

11.1.1.1 Postal questionnaire study

In November 1995, the initial questionnaire (FFQ) letter was sent to the 8,005 subjects in the study group. Those who did not answer received a reminder in December 1995 and another in February 1996. A total of 6,633 completed questionnaires were collected, and additionally 20 subjects declined to participate. The proportion of incomplete answers (no answer, or answered both yes and no) for the great majority of questions about diseases, symptoms, or smoking habits was below 2% of the study sample. Young men had the lowest participation rate, and women responded more often than men.

11.1.1.2 Non-response study

The 1,284 subjects not responding to the initial letter or the two reminders were included in a non-response study. In September 1996 the original questionnaire (FFQ) was mailed to a random sample of 382 subjects from the non-response group. An effort was made to contact by telephone those who did not respond and those who had provided insufficient information by mail.
By mail, 61subjects gave complete answers, and 78 by telephone. Additionally, 44 subjects had already answered by mail, but incompletely, and these questionnaires were completed by phone, while 47 subjects answering by phone declined to participate. In total, 183 (48%) complete questionnaires were collected. Subjects in the non-response group were younger (mean age 39 vs. 44 years, $p<0.001$), and the percentage of men was higher than among the respondents in the original study (60.1% vs. 48.5%, $p<0.01$).

11.1.2 Main findings

11.1.2.1 Smoking habits

Men were more often current smokers than women, 38.5% vs. 27.9% ($p < 0.001$). In all age groups women were more often lifetime non-smokers than men. In younger age cohorts, more men and

women were current smokers than in older cohorts**.** The proportion of current smokers was significantly higher in the non-response study than in the original study (50.3% vs. 34.0%, p<0.001). Taking into account both the results of the original postal study and the findings in the non-response study, the prevalence of current smokers would have been 36.7% in the whole study population (n=7,917).

11.1.2.2 Proportion of recreational skiers and outdoor workers

The total number of regular cross-country skiers was 1,497, proportions being 27.3% among men and 18.1% among women. A total of 876 subjects were outdoor workers; 439 of them reported only outdoor work, and another 437 did both indoor and outdoor work. The proportion of outdoor workers was 22.5% among men and 4.5% among women. Differences between the age groups in skiing habits or in the proportion of outdoor workers were small.

11.1.2.3 Asthma

The prevalence of physician-diagnosed asthma ("Have you been diagnosed by a physician as having asthma?") was 6.0% − similar in men and women. The prevalence of asthma was lower at ages 30 to 49 than in the younger or older age groups. No significant gender differences emerged. Asthma was more common in ex-smokers (7.7%) and was less common in current smokers (4.5%) than in non-smokers (6.4%), though not significantly. The prevalence of physician-diagnosed asthma was significantly (p<0.05) lower in the non-response study than in the original study, 2.2% vs. 6.0% making the prevalence of asthma in the whole population (n=7,917) an estimated 5.4% (5.3% in men, 5.5% in women). Prevalence of asthma did not differ significantly between outdoor and indoor workers or between regular skiers and non-skiers.
Significant risk factors for asthma were age, family history of allergy and family history of OAD. Neither gender, socio-economic group, area of residence, skiing habits, outdoor work, nor smoking habits were associated with significantly increased risk for asthma.

11.1.2.4 Chronic bronchitis

Prevalence of chronic bronchitis increased with increasing age and smoking. The prevalence of *adjusted chronic bronchitis* (subjects with physician-diagnosed chronic bronchitis or chronic productive cough, but subjects with physician-diagnosed asthma excluded) were in each age group

2 to 3 times as high among current smokers than among non-smokers. The prevalence of chronic bronchitis or chronic productive cough did not differ between non-respondents and respondents in the original postal study. The prevalence of physician-diagnosed chronic bronchitis among outdoor workers (4.1%) was significantly higher than among indoor workers (2.2%) ($p<0.01$), while the prevalence among skiers (3.6%), did not differ significantly from that among non-skiers (2.9%). Current smokers and ex-smokers were at significantly higher risk for chronic bronchitis than were non-smokers. Family history of obstructive airway disease or allergy was associated with significantly higher risk for chronic bronchitis. Area of domicile or cross-country skiing did not affect the odds ratios significantly, but outdoor workers were at higher risk for chronic bronchitis.

11.1.2.5 Respiratory symptoms

Prevalence of most respiratory symptoms increased significantly with increasing age and smoking. As for asthma, prevalence of wheezing during the previous 12 months and of attacks of shortness of breath was higher in young persons, lower in the middle-aged, and again higher in the elderly. Questions about wheezing yielded a slightly higher prevalence in men, and about attacks of shortness of breath in women. Wheezing, attacks of shortness of breath, or severe cough were reported by 14.1% when exposed to cold air, 18.4% during physical exertion, and by 26.3% during exercise in cold air.

Subjects with physician-diagnosed asthma frequently reported shortness of breath (SOB) during exercise, even those who were lifetime non-smokers. Risk for SOB during exercise in cold weather was significantly higher among outdoor than indoor workers, while recreational cross-country skiing did not increase this risk. Family history of OAD or allergy was associated with significantly higher OR for SOB during exercise, and in cold weather during exercise.

Non-respondents reported significantly lower prevalence rates than did respondents for shortness of breath during walking on the level, SOB during exercise, in a cold environment, and during exercise below the freezing point.

11.1.2.6 Reasons for non-response

As a reason not to respond, 103 subjects had not been sufficiently interested to answer, 40 stated that they completed the questionnaire but forgot to mail it, and 20 had the wrong address, 7 had at the time been unable to answer, 5 did not answer because they preferred to remain anonymous, and 8 gave no reason.

11.1.2.7 Effects of non-response

Some prevalence rates, particularly for asthma and use of asthma medicines, were higher in the answers collected by phone than by mail, although not significantly. The same trend appeared in the original study, where many of the differences between phone and mail answers were significant. When prevalence rates were corrected for age, gender, smoking, and socio-economic group, non-respondents had significantly lower odds ratios than did the original study respondents. This was true for symptoms related to exercise and cold weather, and odds ratios were also lower for physician-diagnosed asthma, physician-diagnosed chronic bronchitis, use of asthma medicines, longstanding cough, and wheezing, but these differences were not significant.

In order to estimate the possible effect of non-response bias for the original study, information from the 230 non-respondents was extrapolated to all those in the non-response sample who had not been contacted. With this artificial correction, the "real" prevalence of asthma, use of asthma medicines, and asthma-related symptoms for the original study population (7,937 persons) would have been 0.4% to 0.6% less than for the original study respondents. The prevalence of chronic bronchitis would have remained at the original level, but the corrected prevalence of current smoking would have been 37% instead of the 34% reported in the original study, a significant difference ($p<0.001$).

11.1.2.8 Effects of cold climate

Risk factor analysis revealed increased risks for respiratory conditions among those with a family history of OAD or allergy. Skiers did not have a significantly higher risk for asthma or respiratory symptoms. Among outdoor workers, their OR compared with that of indoor workers for SOB during exercise in cold weather was 1.23 (CI 1.03-1.47) and for chronic bronchitis 1.77 (CI 1.21-2.60).

11.2 QUESTIONNAIRE COMPARISONS: NORTHERN VS SOUTHERN FINLAND, STUDY IV, AND NORTHERN FINLAND VS NORTHERN SWEDEN, STUDY V

11.2.1 Response and participation

11.2.1.1 The Helsinki FinEsS questionnaire study

In Helsinki 8,000 subjects 20 to 69 years of age were invited to the questionnaire study during 1996. Complete answers were obtained from 6,062 (76%). Participation among men was 10% lower than in Lapland.

11.2.1.2 The Norrbotten FinEsS questionnaire study

A postal questionnaire (FQ) was sent in winter 1996 to randomly selected subjects aged 20 to 69 in Norrbotten. The size of this sample was 8,333. After the initial letter and two reminder letters containing questionnaires, complete answers came from 7,104 (85%).

11.2.2 Main findings

Comparison between Lapland and Helsinki was done with a non-response correction, but between Lapland and Norrbotten without correction for non-response.

11.2.2.1 Smoking habits

In Helsinki, 38% were current smokers, and 37% in Lapland. Smoking was more common among men in both areas. Current smoking in men was most common among those aged 20 to 29 living in Lapland, 48% for men and 40% for women. Outdoor workers were significantly ($p<0.001$) more often current smokers (47%) and ever-smokers (65%) than those working in indoor occupations (35% and 50%, respectively). The proportion of current smokers was 26% in Norrbotten, significantly lower than in Lapland or in Helsinki. Significantly more women were smokers in Norrbotten, 29% vs. 24%, with the opposite in Finland. The prevalence of those who smoked more than 14 cigarettes/day was 12% in Lapland vs. 7% in Norrbotten ($p<0.001$).

11.2.2.2 Asthma and chronic bronchitis

No significant difference existed in physician-diagnosed asthma between southern (5.6%) and northern Finland (5.5%) (results corrected for non-response). Hay fever was more common among subjects living in Helsinki, 36.0%, than among those in Lapland, 25.7%, a significant difference ($p<0.001$). Adjusted chronic bronchitis was slightly more common ($p<0.05$) in Helsinki. Prevalence of physician-diagnosed chronic bronchitis did not differ significantly between the areas in Finland, but was slightly but significantly ($p<0.001$) higher in Norrbotten.

11.2.2.3 Respiratory symptoms in different areas and working conditions

In Lapland, subjects more likely had symptoms provoked by inhaled irritants or cold weather, whereas symptoms caused by pollen or animal dander were significantly more prevalent in Helsinki. Prevalence of chronic productive cough or recurrent wheeze was higher for those working outdoors in both Helsinki and Lapland regardless of smoking category. Chronic productive cough increased by age and was more common ($p<0.05$) in Helsinki. In Finland, according to multiple logistic regression analysis, area of domicile was not a significant risk factor for developing *respiratory symptoms during exercise in cold weather,* or for the asthma-related symptom *wheezing with SOB without cold*. A slightly higher risk ($p<0.05$) appeared for chronic productive cough among those living in Helsinki than among those in Lapland.

Comparison between Lapland and Norrbotten revealed that the most common respiratory symptom in both countries was sputum production, its prevalence being 25% and 19% ($p<0.001$). Country emerged as an independent determinant for bronchitic symptoms and dyspnoea. Living in Finland was associated with a greater risk for chronic productive cough, sputum production, and dyspnoea. The influence of smoking on chronic productive cough was most pronounced among women. In both countries, manual workers in industry had a significantly increased risk for sputum production, chronic productive cough, dyspnoea, and physician-diagnosed chronic bronchitis. Socio-economic group in both countries influenced the symptoms similarly. An obvious additive effect was between smoking and family history of OAD for respiratory conditions (e.g., wheezing and chronic productive cough).

11.3 CLINICAL DATA, COPD IN NORTHERN FINLAND, STUDY VI

11.3.1 Clinical study population, response and participation

11.3.1.1 Study area and population

Of the respondents (n=3,420) in the southern part of the postal study area in Lapland, a random sample of 959 subjects were invited to a clinical study, 695 of them attended, and complete data with pulmonary function measurements of good quality was available from 683 (71% of invited subjects). This study included a structured interview, skin-prick tests, and pulmonary function measurements. At the time of the clinical study, the participants were 21 to 70 years of age.

11.3.1.2 Participation and smoking habits

Men in the youngest age group had the lowest response and participation rates. Clinical study participants were slightly older and more frequently ex-smokers than were the questionnaire respondents. Differences in respiratory diseases and symptoms between the clinical study participants and questionnaire respondents were small and not significant. Among participants, on the average, male current smokers (n=112) had a smoking history of 20.8, and ex-smokers (n=138) of 17.7 pack-years, and females, 11.7 (n=95) and 6.9 (n=75) pack-years. The mean for ever-smoking men was 19.1 pack-years, and for women 9.6.

11.3.2 Main findings

11.3.2.1 Prevalence of COPD assessed by BTS and GOLD guidelines

Overall prevalence of COPD was 5.4% by BTS and 9.4% by GOLD criteria. In men, it was 8.6% according to BTS and 15.6% according to GOLD criteria, and in women 2.5% and 3.7%. Among subjects who were lifelong non-smokers or had a smoking history of one pack-year or less, the prevalence of COPD was 1.7% according to BTS and 5.3% according to GOLD criteria, but among those with a smoking history of more than 40 pack-years the respective prevalence was 53.1% and 65.6%. COPD was associated with a smoking history of at least one pack-year in 75% of GOLD cases and in 86% of BTS cases.

11.3.2.2 Multivariate relationships and interaction analysis

According to multiple logistic regression analysis, the odds ratios for COPD increased significantly with age and amount of smoking. After adjustment for confounding factors, risk for COPD did not differ significantly between genders. Family history of obstructive airways disease was associated with a significantly higher risk for COPD, Figure 2a-d. A significant increase in risk for COPD was present with earlier start of smoking. Earlier starting age for smoking each year increased risk for COPD by 14%, with the corresponding increase per one pack-year was 7%.

11.3.2.3 COPD in relation to patient-reported previous diagnoses or symptoms

Only 15.6% of GOLD COPD cases and 21.6% of BTS COPD cases reported having physician-diagnosed chronic bronchitis or emphysema, and 31.2% and 32.4% of COPD cases, based on the postal questionnaire, had chronic productive cough.

Figure 2a. GOLD criteria
No family history of OAD

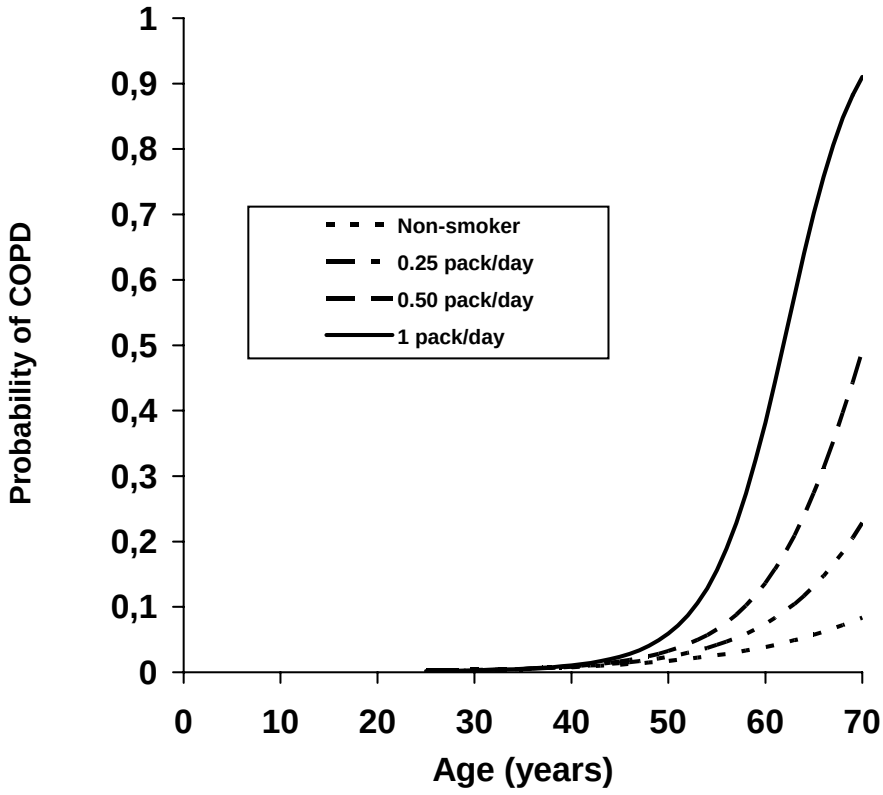


Figure 2b. GOLD criteria
Family history of OAD

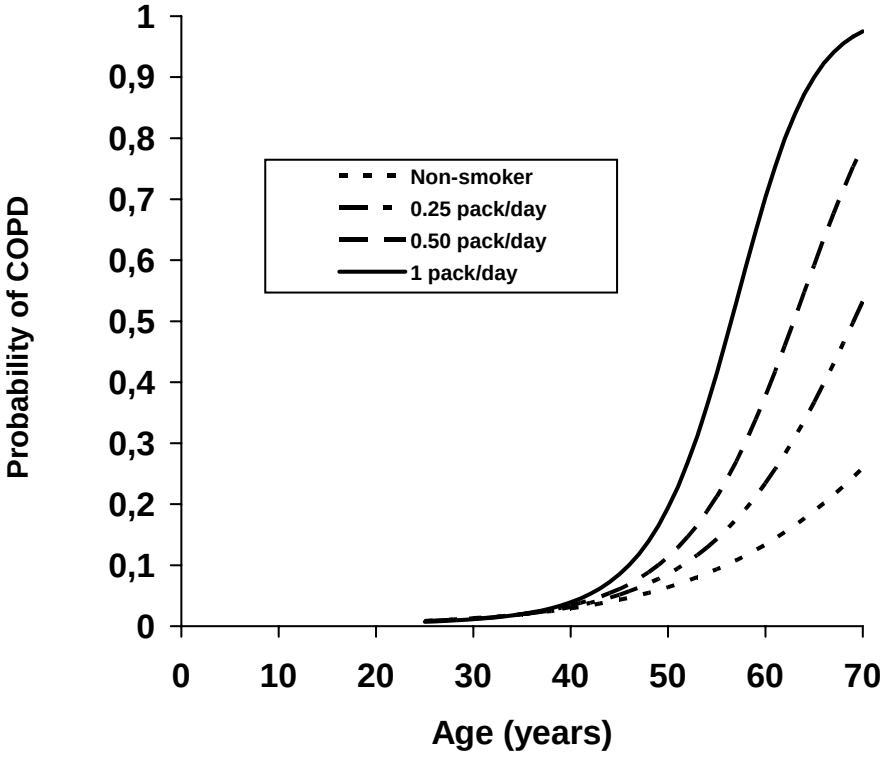


Figure 2c. BTS criteria
No family history of OAD

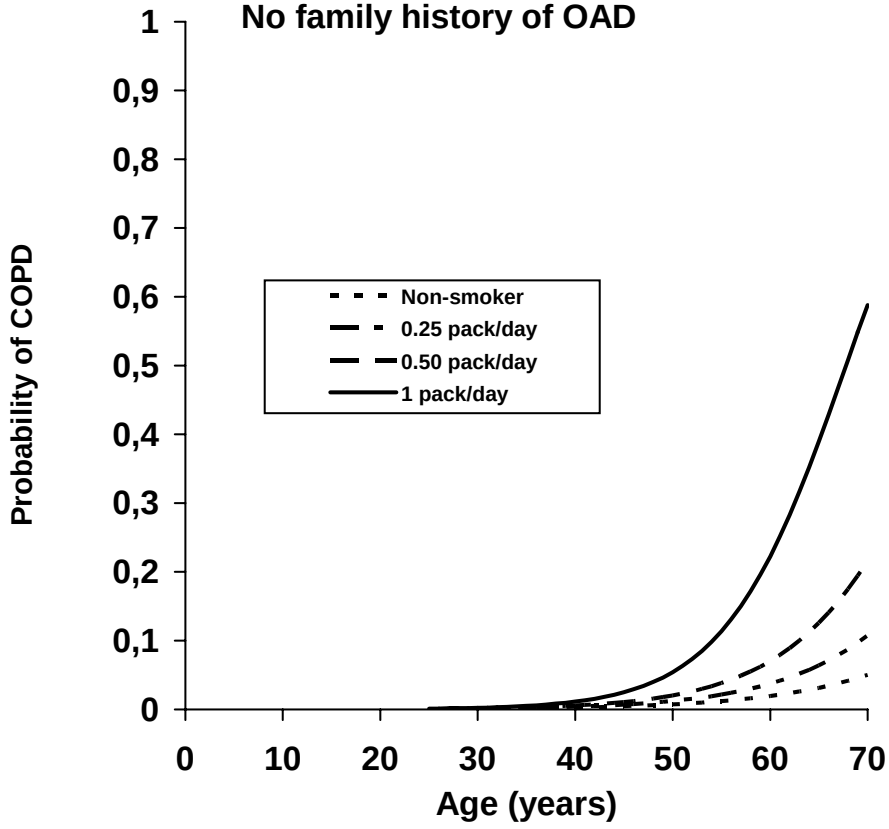


Figure 2d. BTS criteria
Family history of OAD

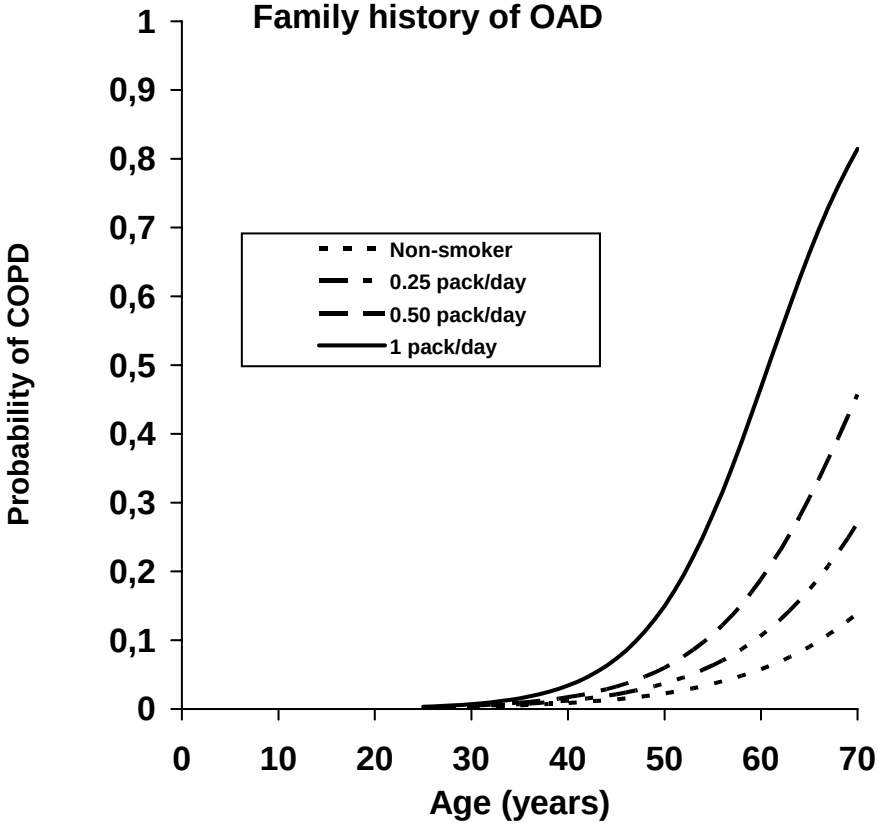


Figure 2e. GOLD criteria

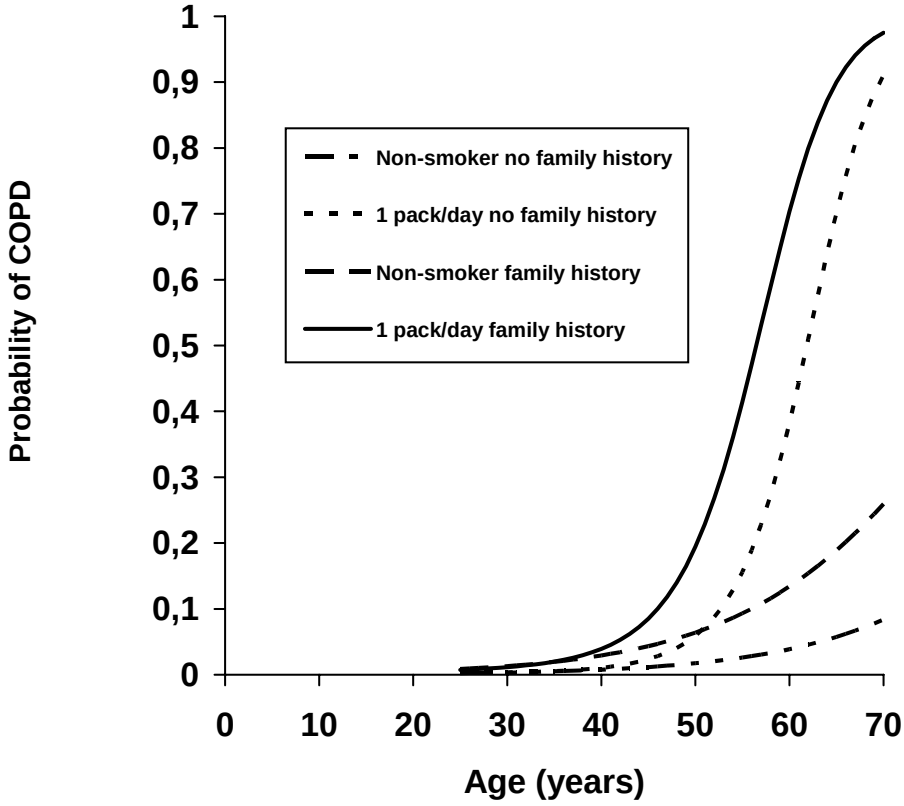
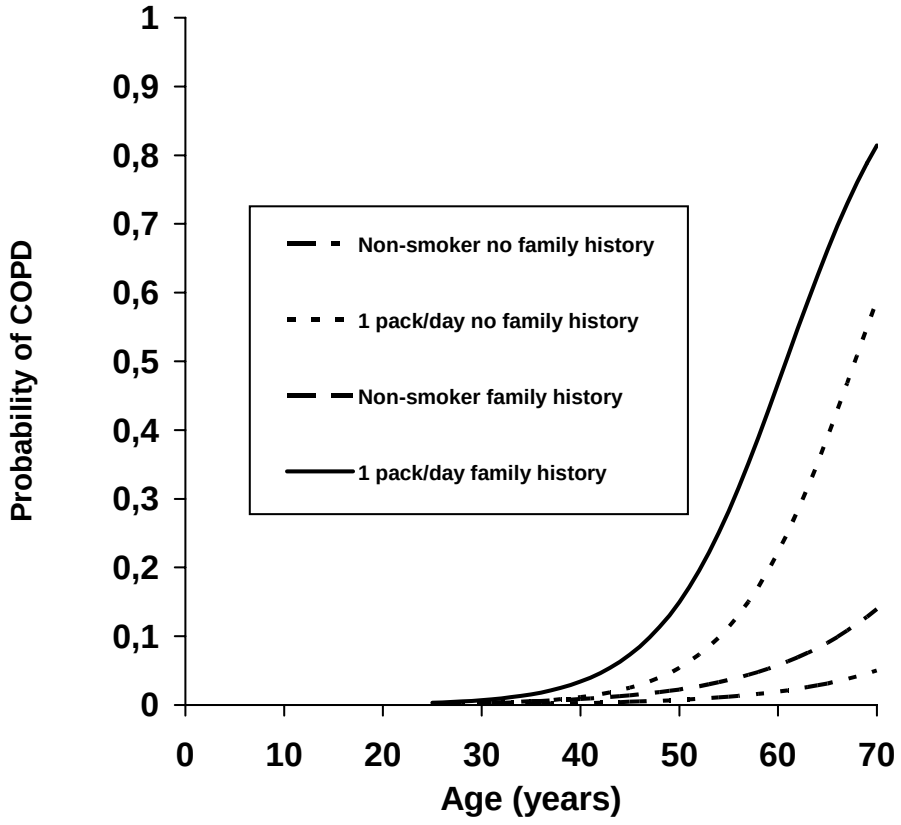


Figure 2f. BTS criteria



Footnote 2a-d: Calculations were done with the assumption that the daily smoking was 0.25, 0.50, or 1 pack per day from the age of 18 years onwards.

Footnote 2e-f: Calculations were done with the assumption that the daily smoking was pack per day from the age of 18 years onwards.

12. DISCUSSION OF METHODOLOGY

12.1 OVERVIEW

Assessment of the results in an epidemiological study requires attention to:

- relevance of the hypothesis
- clarity of the aims
- correlation between study design and aims
- validity and reliability of instruments (methods) to gather relevant data
- selection of study subjects (study sample)
- sample size
- presentation of results
- relevance of results in relation to aims
- significance and interpretation (conclusions) of results

Our hypothesis suggested that the prevalence of asthma, chronic bronchitis, and COPD among adults in Finland is on similar level to that in the other Nordic countries, and secondly, that the cold climate in northern Finland has an effect on respiratory symptoms. These are important questions considering aetiological aspects of obstructive respiratory conditions as well as arrangements for clinical work in Finland, especially in view of the Finnish national programmes for asthma (Haahtela et al 2001) and COPD (Laitinen and Koskela 1999).
Before the present study, the prevalence of respiratory conditions had never been assessed in Finland among adults in direct comparison to the findings in the other Nordic countries by internationally used methods and criteria. Previously published prevalence rates in Finland (Huhti 1965, Alanko 1970) differed markedly from those reported in the other Nordic countries (Julin and Wilhelmsen 1967, Irnell and Kiviloog 1968, Kiviloog et al 1974, Gulsvik 1979a), with Finland showing a lower prevalence of asthma and a very high prevalence of chronic bronchitis.

This study was designed to gather relevant data for assessment of obstructive respiratory conditions in northern Finland in co-operation with similar surveys in southern Finland, Estonia, and Sweden. This design and simultaneous FinEsS study co-operation offer good possibilities to compare results between study centres in these three countries. This study thus has a good opportunity to find answers to the questions presented in the aims.

A postal questionnaire study can gather information from a large proportion of a population. The questions in the Finnish FinEsS Questionnaire were developed according to international models, and have been validated in a number of studies (Lundbäck at al 1993b, 2001, Larsson L 1995). In this study, validity was further confirmed by comparison with results from the clinical study (interview and clinical measurements).

However, interpretation of the responses from the invited subjects may vary. This is especially obvious in questions dealing with asthma, which is an arbitrary diagnosis. Translation may also cause bias. In this study no bias of importance between the Finnish and Swedish translations were found except for question 9 about recurrent wheeze yielding somewhat differing results (Pallasaho et al). Another weakness may be the effect of non-response. Non-response was analysed and the results were published in the Study II. Spirometry was performed according to ATS recommendations (ATS 1995), and the method used in skin-prick test followed the EAACI standards (Dreborg 1989). Analysis of COPD prevalence followed internationally approved criteria. The validity of questionnaire data is later discussed in more detail.

The selection of study subjects in an epidemiological study is a crucial issue. The strengths of the present population-based study include a sufficiently large and representative population sample. In the postal questionnaire study a *random* sample of 8,005 subjects was taken *evenly* throughout the *whole population* 20 to 69 years of age in the study area. The study area in the clinical study was the southern part of the questionnaire study area. From the respondents (n=3,420) in the questionnaire study in this area, a *random* sample of 959 subjects was invited to participate in the clinical study. The sample size chosen, 8,000 subjects, was based on a power calculation revealing that a sample of 8000 subjects with a response rate of 75% (approximately 3,000 men and 3,000 women) had 80% power to find a difference of at least 1% between prevalence figures in the range 5% to 10%. A smaller difference was considered non-significant from both the statistical and the clinical point of view.
Results of previous large-scale epidemiological studies of asthma and respiratory symptoms in general adult populations in Finland were published more than 30 years ago. These studies had showed a lower prevalence of asthma and a higher of chronic bronchitis than in other Nordic countries. In international comparisons, however, the methods of those studies differed in many respects, for example, questionnaires were not identical, and the population samples differed. Since then, most of the epidemiological Finnish studies have been register-based or have dealt with selected populations.

Our study is the first comprehensive epidemiological respiratory study among adults in Finland, the results of which are directly comparable with those from FinEsS Estonia and FinEsS Sweden. These FinEsS studies were conducted by validated study methods and with simultaneous population samples in Finland, Estonia and Sweden. Our study population was a large random sample from the general Finnish adult population. The participation rate was high, and the quality of the answers was good. The effects of non-response were assessed. Thus, the results offer a major contribution in assessment of the epidemiology of asthma, COPD, and respiratory symptoms in Finland.

12.2 QUESTIONNAIRE

The use of internationally validated questionnaires allows direct comparisons to similar studies in the FinEsS research co-operation and further, to published studies which have used the same questions. Internal validity was further confirmed by comparing data from questionnaire and interview.

12.3 VALIDITY OF QUESTIONNAIRE DATA

The validity of questionnaire data was assessed with:

1. Correlation of the results from identical questions in the self-administered questionnaire and the interview questionnaire.
2. *Physician-diagnosed asthma* in comparison to a symptom combination, which has been validated in the OLIN Study I by a methacholine provocation test.
3. Bronchodilatation test results in subjects with *physician-diagnosed asthma* in comparison to healthy subjects, or with chronic bronchitis or COPD.

1. Correlation between results from questionnaire and interview is a measure of reliability and repeatability. Degree of agreement indicates the proportion of all responses identical in questionnaire and interview, both negative and positive. If positive responses make up only a minor proportion of the answers, the degree of agreement reflects mainly the similarity of negative responses. For example if 10% of responses are positive, and 90% negative, and all negative are in agreement, the degree of agreement should be 95%, although half of the positive answers were not in agreement.

In this kind of situation, the *Kappa coefficient* (κ) may be a better measure of correlation (Altman D 1992). Kappa is calculated as κ=(Po-Pe)/(1-Pe), where Po is observed prevalence and Pe expected prevalence, κ = +1.0 when all responses are identical, κ = -1.0 when no identical responses are observed. κ < 0.20 is considered poor, 0.21 to 0.40 fair, 0.41 to 0.60 moderately good, 0.61 to 0.80 good, and > 0.80 very good. Comparison of results from identical questions in the FinEsS questionnaire and interview shown in Table 3.

Table 3. Correlations between FinEsS questionnaire and interview (identical questions) in 683 study subjects with complete questionnaire and interview data.

Question	positive in questionnaire	positive in interview	degree of agreement (%)	Kappa
wheezing without cold	98	119	87.0	0.51
chronic productive cough	95	87	84.5	0.33
dyspnoea gr. II	96	53	88.7	0.43
ever-asthma	42	43	97.5	0.79
p-d asthma	43	44	97.5	0.79
chr. bronchitis or emphys. ever	30	23	94.3	0.24
p-d chr. bronchitis or emphys.	25	17	96.2	0.36
Longstanding cough	142	176	79.2	0.42
wheezing/ 12 months	153	161	82.1	0.50
SOB with wheezing	68	88	89.2	0.47
allergic conjunctivitis or rhinitis	195	224	81.1	0.56
SOB upon awakening	91	67	87.1	0.37

chr. = chronic

dyspnoea gr. II = dyspnoea gradus II = SOB when walking on level ground at a normal pace

emphys. = emphysema

p-d = physician-diagnosed

SOB = shortness of breath

2. *Physician-diagnosed asthma* tested against a symptom combination, Table 4.

Table 4. Correlation between question 3 (physician-diagnosed asthma) in the FinEsS questionnaire (postal study) and symptom combination in the FinEsS interview (clinical study).

Symptom combination in FinEsS interview, three of the following:

a) wheezing withouth having cold during last 12 months
b) attacks of breathlessness during last 12 months
c) attacks of breathlessness triggered by contact with furred animal or pollen
d) use of asthma medicines

Questionnaire (question3): read horizontally.
Interview, symptom combination: read vertically.

	no	yes	all
no	612	28	640
yes	16	27	43
all	628	55	683
	(91.9%)	(8.1%)	

In agreement (correct prediction) 93.6%
Kappa coefficient 0.52 (0.38-0.66) (moderate)
Predictive value for negative prognosis 95.6%
Predictive value for positive prognosis 62.8%
Sensitivity of the rule 49.1% "positivity in disease"
Specificity of the rule 97.5% "negativity in health"

3. Bronchodilatation test results in subjects with *physician-diagnosed asthma* in comparison to COPD, chronic bronchitis, and healthy subjects (asthma, chronic bronchitis, and COPD excluded), Table 5.

Table 5. Bronchodilatation test responses among those with asthma or chronic bronchitis diagnosis in questionnaire or a COPD diagnosis according to the clinical study.

		Change of FEV_1 from baseline				
		number of classified bronchodilatation responses			mean bd (%)	95% CI of bd%
	n	< 10% (n)	10-15% (n)	>15% (n)		
p-d asthma, with asthma medication	34	22	4	8	9.2	6.2 - 12.2
p-d asthma, no asthma medication	9	7	1	1	4.2	0.2 - 8.2
COPD by BTS, asthma excluded, with or without asthma medication	10	6	1	3	9.7	2.9 - 16.5
p-d chronic bronchitis, with or without asthma medication, asthma and COPD excluded	14	14	-	-	2.2	0.2 - 4.2
using asthma medication, but asthma, chronic bronchitis and COPD excluded	10	9	1	-	3.9	1.3 - 6.5
asthma, chronic bronchitis and COPD excluded, no asthma medication	606	589	14	3	3.0	2.7 - 3.3

asthma medication = medication which may be used against asthma, chronic bronchitis, COPD, or in some cases against respiratory symptoms without any specific diagnosis

bd = bronchodilatation

CI = confidence interval

COPD by BTS = COPD diagnosed according to the BTS criteria

p-d = physician-diagnosed

12.4 NON-RESPONSE ANALYSIS

The sample size of 385 persons (30% of non-respondents) was sufficiently large to allow estimation of the effects of non-response in the entire non-response population. A question was added to assess whether they had received the original study questionnaire and the reason for their non-response. Following this mailing, an attempt was made to contact by phone those who did not respond and those who had provided insufficient information by mail.
The results from non-respondents were compared to the original study results. Data from non-respondents was also compared to results calculated by the Drane method (Drane 1991). Results of the non-response study were extrapolated to the whole non-response population, allowing calculation of the "real" results for the whole study population.

12.5 ASSESSMENT OF THE EFFECT OF SMOKING

The effect of smoking habits on the main results was analysed in each study. In Papers I to IV, assessment was based on questionnaire data, mainly in smoking categories: non-smokers, ex-smokers, and current smokers. In Paper V, current smokers were classified into three groups according to daily smoking: a) less than 5 cigarettes, b) 5 to 14 cigarettes, or c) 15 cigarettes or more. Paper VI used pack-years data with results analysed also in relation to smoking habits of the parents. The analyses consider the effects of smoking in relation to reported symptoms and in relation to objective findings from clinical measurements.

Unfortunately, smoking categories do not produce the same result as pack-years. Thus, in the Studies I to V three points must be taken into account: Firstly, in Finland, many start smoking young, often in their early teens. The analysis in Study VI revealed that smoking begun at a young age had more harmful effects on the lungs than does smoking started later. Secondly, in the Studies III to IV, smoking category did not explain the difference between indoor and outdoor workers in having bronchitic symptoms. In clinically examined subjects, difference in pack-years between indoor and outdoor workers was significantly larger than difference in smoking category. The difference in pack-years could thus be the explanation for the reported differences. These two findings might also explain the difference in bronchitic symptoms between Finland and Sweden reported in Study V. Thirdly, as Study II shows, although the results of respiratory conditions reported in the Studies I to V were not significantly biased by the non-response effect, smoking was underestimated.

12.6 THE PREVALENCE OF COPD

The fixed ratio (FEV1/FVC or VC) may cause an over-diagnosis among elderly and an under-diagnosis among young subjects when defining clinically relevant COPD (Hardie et al 2002), and the clinical relevance of Stage 0 or Stage I COPD according to the GOLD criteria may be questioned (Vestbo 2004, Lindberg et al 2005a). In this thesis, over-diagnosis is not a major problem as the oldest subjects were 69-70 years and the proportion of subjects above 65 years was limited. However, it seems probable that a large proportion of the heavy smokers were in the non-response group. Thus, COPD prevalence reported in Study VI may also be underestimated.

12.7 ASSESSMENT OF THE EFFECT OF COLD CLIMATE

The effects of cold climate were assessed mainly in relation to results from outdoor work and skiing habits, Study III, and comparison of our results (FinEsS Lapland) to the results from southern Finland (FinEsS Helsinki), Study IV. This section used only questionnaire data. The FFQ includes three questions about respiratory symptoms during exercise or in cold weather.

12.8 COMPARISON WITH OTHER RESULTS

We compared data from our population to the results from the FinEsS study in southern Finland in order to find whether a similar north-south gradient as in Sweden could be demonstrated in Finland in the prevalence of asthma and respiratory symptoms, and if differences existed in the prevalence of hay fever, chronic bronchitis, and symptoms in special circumstances such as a cold environment and during exercise. Further, effects of indoor and outdoor work on respiratory symptoms were studied, and risk factors for different respiratory conditions and diseases were examined in pooled data from the two areas.

In another comparison, we studied the influence of different smoking categories on prevalence of respiratory symptoms and chronic bronchitis in northern Sweden and northern Finland. An analysis was also done to investigate whether or not the differences in smoking habits and prevalence of the symptoms and diseases between Sweden and Finland still existed. The possibility to compare the effects of smoking in northern Finland and northern Sweden by the current study was good, as the areas are similar with respect to climate, population density, degree of urbanisation, socio-economic development, type of industry, and social life. In addition these surveys used identical methods, criteria, and sample composition.

13. DISCUSSION OF MAIN RESULTS

Internationally, as well as in the Nordic countries, numerous studies have been published on asthma epidemiology, mainly about its prevalence in cross-sectional studies. The ECRHS in particular has provided new data on asthma prevalence in European and other countries (Janson et al 1997, Sunyer et al 1997, Svanes et al 1999, Strachan 2000). Among the relatively few studies assessing the incidence of asthma, Sweden is well represented with recent publications (Larsson L 1995, Rönmark et al 1997, Lundbäck et al 2001).

In comparison to asthma, the epidemiology of COPD has been studied less extensively. Recently some estimates of prevalence of COPD, based on the updated international guidelines, have been published, but very few if any data about incidence of COPD based on these guidelines exist. One vital area of focus is change in prevalence over time.

13.1. DO RESPIRATORY SYMPTOMS AMONG ADULTS IN NORTHERN FINLAND COMPARE TO SYMPTOMS REPORTED IN SOUTHERN FINLAND OR IN SWEDEN?

The prevalence of bronchitic symptoms, such as cough, sputum production, and chronic productive cough is now considerably lower than it was 30 to 50 years ago (Huhti 1965). This decrease has occurred parallel with the decrease in smoking. In contrast, questions about wheezing revealed a higher prevalence than previously found in Finnish general adult population samples. In 1966 any wheeze during the past year was reported in a commune in western Finland by only 6% (Alanko 1970), but 30 years later in the present study in northern Finland, any wheeze during the last 12 months by 20% (Paper I). In a sample in northern Finland in 1986 wheezing was reported by 10% in cold weather, and by 16% during effort (Reijula et al 1990). Similar questions in our study yielded prevalence rates of 14% and 18%. Among the socio-economic groups, manual workers, students and the military showed an increased risk for frequent wheeze. The elevated risk for students and the military probably reflects a high prevalence of asthma in young people.

Area of domicile had no major influence on symptoms or asthma within this sparsely inhabited area and seemed to have no influence even when compared with Helsinki. It might be argued that differences in reported asthma and COPD between countries or areas reflect divergent diagnostic methods and practices, not only real differences in prevalence. This argument fails, however, to explain the difference in reported symptoms, if identical questions are used. Our data show clearly that symptoms common for asthma have increased considerably during the second half of the last century, and conversely, symptoms common for bronchitis have decreased. This pattern seems to

be similar not only in northern Finland but also in Helsinki. There exist, however, some minor differences in distribution of symptoms by geographic location; in Lapland; symptoms associated with exertion and with cold weather were more common than in Helsinki, and conversely, in Helsinki, bronchitic symptoms in association with smoking and outdoor work were more common.

When comparing northern Finland with northern Sweden, most respiratory symptoms were somewhat more common in the former (Paper V). This was particularly true for bronchitic symptoms. This comparison shows that age of starting to smoke in Finland is much lower than in Sweden. The earlier start and the higher number of pack-years in Finland may thus in part explain the difference of bronchitic symptoms. Other possible reasons have been discussed extensively in Study V.

In contrast to Finland, the prevalence of chronic bronchitis and bronchitic symptoms in Sweden seem not to have changed considerably over time, with relatively low prevalence rates reported by Julin and Irnell even during the 1960ies. As the wording of the questions about wheezing has changed over time in the Swedish studies and between the older Swedish studies, the true time trend for the prevalence of wheezing in Sweden is unclear; however, according to the OLIN studies, no major increase in the prevalence of wheezing has taken place in northern Sweden since 1985 (Lundbäck et al 1991, Rönmark et al 1997, Larsson LG et al 2003).
In our studies, as also found by others, all respiratory symptoms were more prevalent among smokers. The gender differences in prevalence of asthma and respiratory symptoms were small. This is in accordance with Swedish data (Lundbäck et al 1991) but in contrast to the results from southern Europe (Viegi et al 1999).

In studies with a low participation rate, non-response may cause severe bias; in our studies, the participation rate has generally been high, usually above 80%. Though a somewhat low prevalence of symptoms appeared in our studies, the results were only slightly affected. The importance and results of studies on non-response have been discussed thoroughly in the literature section with references to the ECRHS (de Marco et al 1994), the Bergen studies (Bakke et al 1990), the OLIN studies (Rönmark et al 1999a), and a study in Finland (Hedman et al 1999).

13.2. HAS FINLAND A LOWER PREVALENCE OF ASTHMA THAN DO OTHER NORDIC COUNTRIES?

It has been suggested that, in epidemiological studies, asthma should be defined as symptomatic bronchial hyperresponsiveness (BHR) (Toelle et al 2004). Specific methods for detecting asthmatics, such as severe symptoms, diagnoses of asthma, or symptomatic BHR, may be most useful in cohort and case-control studies (Rönmark et al 2005). But, conversely, the method of choice for the first phase of prevalence comparisons is a standardised written (Torén et al 1993) or video symptom questionnaire (Pekkanen et al 1997). In order to explore reasons for the differences in asthma prevalence, and to estimate possible differential symptom reporting, questionnaires can be supplemented with tests of bronchial hyperresponsiveness and other testing for subsamples of symptomatic and nonsymptomatic subjects (Lundbäck 1993).
As the physician-diagnosed asthma seems fairly well validated (Torén et al 1993), and is also supported by our data as described in the section of discussion on methodology, the diagnosis of asthma in this thesis is based on questionnaire reporting.

According to this study, the prevalence of asthma in mid-1990ies was 6.0%, 4 to 10 times higher than the prevalence rates (0.5% - 1.6%) reported 30 years earlier in Finland (Alanko 1970, Huhti 1965). Two separate questions were used to assess the prevalence of asthma, ever-asthma, and physician-diagnosed asthma. According to these two questions, the prevalence of asthma was 6%, similar to the results of the 1986 OLIN study in northern Sweden (Lundbäck et al 1991). Further, a considerably higher proportion of adults used asthma medicines than previously. The prevalence of use of asthma medication in the present study was also 6%. The increase in prevalence of asthma-related symptoms is described above. Wheezing with breathlessness apart from colds was reported by 7%, the symptoms complex strongly overlapping clinical asthma according to the IUATLD and ECRHS questionnaires and studies (Burney et al 1989, ECRHS 1996).

At the time of the FinEsS study, the prevalence of physician-diagnosed asthma in northern Sweden was 9% (Lundbäck 1998). The difference between northern Finland and northern Sweden may reflect differences in diagnostic traditions. The results from several questions in these simultaneously performed studies confirm that a major difference between Finland and Sweden in the prevalence of asthma, as reported formerly, no longer exists. We thus found that the prevalence of asthma is on a level similar to that of most Nordic countries; however, the prevalence in Sweden may still be somewhat higher than in Finland.

13.3 IS COLD CLIMATE A RISK FACTOR FOR ASTHMA IN FINLAND?

The reported prevalence of asthma and symptoms associated with asthma were on the same level in northern as in southern Finland, i.e., with no north-south gradient. Neither was a difference in the prevalence of asthma seen among subjects working (outdoor workers) or exercising (skiers) in cold weather. In these two groups, the prevalence of asthma did not differ from that of indoor workers or non-skiers. Superficially interpreted, these results seem to be in contrast with studies in Tröndelag in Norway and in Jämtland in Sweden, in which a large proportion of skiers had asthma and respiratory symptoms (Sue-Chu et al 1996, Larsson K et al 1993) in those studies, however, skiers were elite sportsman, whereas we studied a general adult population. We had no competitive skiers in our study group; skiing was only a recreational hobby for our study subjects.

Taking into account the homogeneity of the population in Finland, this finding supports the view that the cold climate *per se* does not increase asthma prevalence. The situation seems to be different in Sweden (Larsson L et al 1994). Although the climatic difference between northern and southern Finland does not exactly compare to that between northern and southern Sweden, it seems unlikely that climate could be the only explanation for the north-south gradient found in Sweden either.

13.4 HAS THE PREVALENCE OF COPD IN FINLAND CHANGED? HAS FINLAND A HIGHER PREVALENCE OF COPD THAN OTHER NORDIC COUNTRIES?

As reviewed in the background section, COPD prevalence, based on updated guidelines, shows that age distribution, smoking habits, and criteria used all play major roles (Gulsvik 1999).
Exact comparisons with earlier Finnish studies are difficult because of differing criteria and selection of subjects (Järvinen et al 1960, Huhti 1965, Isoaho et al 1994a). Despite the fact that the prevalence of bronchitic symptoms in Finland has decreased, comparison with studies published decades ago indicates no major changes in prevalence of COPD.
When compared with Nordic figures, ranging from 4% to14% depending on age distribution and the criteria used, our prevalence of COPD conforms quite well. Prevalence of COPD according to GOLD criteria was 9.4%, and 5.4% according to BTS criteria. These estimates are very close to results reported from Norway (Bakke et al 1991a), but somewhat lower than from northern Sweden (Lundbäck et al 2003b) This Swedish study had, however, a different age distribution, with all study subjects older than 45. The fixed ratio (FEV_1/VC) in defining COPD has probably contributed to a high prevalence in very old subjects in the Swedish study (Lundbäck et al 2003a).

Another study in northern Sweden also indicates the prevalence of COPD to be similar or even somewhat higher than our results in northern Finland (Lindberg et al, 2005b). Also in this study a somewhat different age-distribution may have contributed to the results. One could have expected a higher prevalence in Finland than in Sweden, because of the difference in smoking habits. Somewhat surprisingly and in contrast with the Swedish data, we found a major difference in COPD gender distribution. That COPD was more common in men could be explained by the lifetime difference in cigarettes consumed. As in Sweden, family history of OAD was also a risk factor for development of COPD, although one much less important than smoking and increasing age. In Study VI we examined and discussed the interactions of smoking, age, and family history of OAD to development of COPD. These results are exemplified in this thesis in Figure 2a-d. Another major finding was the strong effect of early start of smoking on development of COPD.

In Finland, a national recommendation for the promotion of prevention, treatment, and rehabilitation in relation to chronic bronchitis and COPD from 1998 to 2007 has been prepared on the basis of extensive collaboration organized by the Ministry of Social Affairs and Health (Laitinen and Koskela 1999). The national Finnish COPD program estimated that over 5% of the population suffer from symptomatic forms of the disease, and that a further 5% of the population may suffer from latent COPD. According to these assumptions, a total of 400,000 Finns suffer from chronic bronchitis or COPD.

14. CONCLUSIONS

The present study reveals that in mid-1990ies the prevalence of asthma in northern Finland, and in Helsinki as well, was markedly higher than reported during the 1960ies and 1970ies, and was of similar magnitude to that found in Sweden and other Nordic countries. The increased prevalence of symptoms associated with asthma and the increased use of asthma medicines found in our study indicate a real increase in the prevalence of asthma in Finland.

The response rate of 83.6% in the original questionnaire study was sufficiently high to provide reliable and valid prevalence rates for respiratory diseases and symptoms in our study population; only the prevalence of current smoking was underestimated. Secondly, because telephone interviews yielded higher prevalence rates than did mailed answers, the method of obtaining answers may influence results. Thirdly, in assessing the effect of non-response, relevant actual data should be obtained from the non-respondents, but the statistical relevance of the results for less frequent conditions may be weakened by small sample size. Thus, calculated corrections of non-response should thus also be shown.

In a general adult population living in a cold climate, high prevalence rates for shortness of breath provoked by exercise or cold weather existed among subjects with asthma, allergic rhinitis or conjunctivitis, and chronic bronchitis. Among healthy current smokers as well, prevalence rates were significantly higher than among healthy non-smokers. Chronic bronchitis and bronchitic symptoms were slightly but significantly more prevalent among outdoor workers but not among recreational skiers, but risk for asthma was not significantly higher among those exercising by skiing or those working outdoors in cold conditions.

Hay fever, chronic bronchitis, and bronchitic symptoms were slightly more common in Helsinki than in Lapland. Symptoms provoked by inhaled irritants or cold weather were more common in Lapland. The prevalence of asthma and symptoms common in asthma were similar in the two areas. Outdoor workers reported a high prevalence of chronic productive cough, prevalence highest among current smokers working outdoors in Helsinki. Thus, climatic or environmental differences existing between northern and southern Finland may contribute to differences in prevalence of hay fever, chronic bronchitis, and bronchitis symptoms, but not of asthma and symptoms common in asthma.

Bronchitic symptoms are common in northern Sweden and northern Finland, and the prevalence of respiratory symptoms is strongly related to the number of cigarettes consumed per day. Country was an independent determinant for bronchitic symptoms. Living in Finland was associated with a greater risk, perhaps as a result of earlier start of smoking in Finland. Family history of OAD and smoking had a strong additive effect on the prevalence of respiratory symptoms.

The current study reveals a high prevalence of COPD in a general adult population in smoking men and women. The same amount of smoking resulted in a higher risk for women than for men. Among those having smoked more than 20 pack-years, the prevalence of COPD by the GOLD criteria was 38% for men and 21% for women. The prevalence among those having smoked for more than 40 pack-years was 66%. The OR for COPD was also elevated for those who had started smoking early. Although outdoor work in a cold climate may lead to increased respiratory symptoms and chronic bronchitis, it does not seem to elevate the risk for COPD.

15. PERSPECTIVES

Respiratory symptoms are very common; over 50% of our study population had experienced at least one respiratory symptom during the previous 12 months. In association with cold climate in the study area, many reported respiratory symptoms in cold weather or during exercise. The prevalence of symptoms among current smokers was double that among non-smokers. Cold climate obviously has an effect also on allergic conditions; allergic symptoms and skin-prick test positive allergy was significantly less common than in southern Finland. Moreover, asthma and COPD are prevalent diseases among the adult population in northern Finland.

Modern asthma treatment has effectively diminished the burden of asthma among patients, and also the burden on the national health care system in Finland. Nowadays, the goal of asthma treatment is to spare the patient the symptoms and limitations of this chronic disease. However, best treatment results require that diagnosis of asthma is made without delay, and that proper treatment is started early. In our study, of subjects with allergy or family history of asthma, frequent respiratory symptoms, and decreased lung function in spirometry, many had neither a respiratory diagnosis nor any relevant treatment. The Finnish National Asthma Program of 1994 to 2004 has been a success story. Our findings underline the importance of continuing effort in asthma diagnostics and treatment, both in primary care and at the specialist level.

COPD represents a major part of the health effects of tobacco. This disease continues to be a major cause of hospital treatment and mortality. Our findings revealed that after 40 pack-years a smoker has at least a 50% risk for COPD, or even higher if there is a family history of OAD, or if smoking started early in the teen years. The latter situation is unfortunately very common in Finland. In contrast with the situation with asthma, in established COPD the effects of medical treatment are modest. The best treatment for COPD is prevention, i.e., not to start smoking at all, or not to start at a young age and to quit early, at least before 20 pack-years.

As examples from California, Norway, and Ireland show, more can be done for tobacco control at workplaces and in public settings. In the health care system, at every level, more work is needed to help patients to quit smoking, especially those at risk. Although the majority of COPD cases are not diagnosed, most report symptoms if the right questions are asked. Thus, with basic clinical tools – proper history-taking and lung function measurements – most COPD could be found at an early stage.

In many studies top-level endurance athletes, especially in cross-country skiing, have been at high risk for asthma, and thus we aimed to determine whether cold climate *per se* is a risk factor for obstructive respiratory diseases. Fortunately this was not true on a population level. As our results show, respiratory symptoms were common in the cold, but the risk for asthma or COPD was not elevated among those working outdoors or exercising regularly by cross-country skiing.

The FinEsS Study co-operation between Finnish, Estonian, and Swedish researchers offers an effective model for epidemiological surveys. Working simultaneously with identical methods gives more in exchange, i.e., more accurate and more comparable results. Results presented here represent only cross-sectional data – from both the postal questionnaire and clinical study − a mostly from the FinEsS Study in northern Finland. Some papers on international FinEsS comparisons have already been published, and work on the longitudinal FinEsS study is underway.

16. ACKNOWLEDGEMENTS

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18. APPENDIX The Finnish FinEsS questionnaire

RESPIRATORY SYMPTOMS AND OBSTRUCTIVE PULMONARY DISEASES IN LAPLAND 1995

Answer crossing either "yes" or "no/don't know" in the appropriate box.
Your native language is: a) Finnish ( ) b) Lappish ( ) c) Swedish ( ) d) other ( )

	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 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 disease?	( )	( )
if "yes", which:_____		
3. Have you been diagnosed by a doctor as having asthma?	( )	( )
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 breathlessness? The symptoms may exist simultaneously with or without cough or wheezing)? If "yes":	( )	( )
a) have you had these symptoms during the last year?	( )	( )
7. Have you had longstanding cough during the last years?	( )	( )
8. Do you usually have phlegm when coughing or do you have phlegm which is difficult to bring up? If "yes":	( )	( )
a) do you bring up phlegm on most days during periods of at least three successive months?	( )	( )
b) have you had such periods during at least 2 successive years?	( )	( )
9. Do you usually have wheezing, whistling or noisy sound in your chest when breathing?	( )	( )
10. Have you had wheezing or whistling in your chest at any time during the last 12 months? If "yes":	( )	( )
a) have you been at all breathless when wheezing or whistling was present?	( )	( )
b) had you this wheezing or whistling when you did not have a cold?	( )	( )

	yes	no/don't know
11. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	( )	( )
12. Do you get short of breath when you walk with other people of your age on level ground at normal pace?	( )	( )
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, strong smelling flowers)	( )	( )
h) by pollen from grass and/or trees	( )	( )
i) at contact with furred animals (cat, dog, horse, cow)	( )	( )
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 mths)	( )	( )
If "yes": a) how many cigarettes do you smoke per day?		
i) less than 5	( )	
ii) 5-14	( )	
iii) 15 or more	( )	
If "no": b) have you been a smoker, but have stopped smoking more than one year ago?	( )	( )

15. What has been your main occupation?:_____
a) how many years have you been working in this occupation :_____ years

16. Do you have now other occupation or task (other work, unemployed, homework, retired, etc.)
If yes, which?:_____
a) how many years have you had this occupation or task?:_____ years

17. Are you now mostly working at a) outdoor occupation? ( )
or b) indoor occupation? ( )

18. How many years in all have you been working outdoors? _____ years

	yes	no/don't know
19. a) Did your mother smoke during your childhood?	( )	( )
b) Did your father smoke during your childhood?	( )	( )
20. Have you been an active skier?	( )	( )

Please, answer accurately - thank you for your co-operation!
Date: _____ **tel# :**_____
signature:

KEUHKO-OIREET JA KEUHKOPUTKIA AHTAUTTAVAT SAIRAUDET LAPISSA V. 1995

Merkitse seuraavissa kysymyksissä rasti ruutuun mielestäsi sopivien vaihtoehtojen kohdalle! (siis jokaiseen kysymysvaihtoehtoon joko **kyllä** tai **ei/en tiedä**)

Onko äidinkielesi?
a) suomi ☐ b) saame ☐
c) ruotsi ☐ d) muu ☐

	kyllä	ei/en tiedä
1. Onko jollakin **vanhemmistasi** tai **sisaruksistasi?**		
a) astmaa	☐	☐
b) allergista nuhaa (esim. heinänuhaa) tai allergista silmävaivaa	☐	☐
c) kroonista keuhkoputkentulehdusta tai keuhkonlaajentumaa	☐	☐
2. Onko **Sinulla** nyt tai onko **Sinulla** ollut aiemmin?		
a) astmaa	☐	☐
b) allergista nuhaa (esim. heinänuhaa) tai allergista silmävaivaa	☐	☐
c) kroonista keuhkoputkentulehdusta tai keuhkonlaajentumaa	☐	☐
d) muu keuhko- tai hengityselinsairaus, mikä?	☐	☐
kirjoita vastaus tähän:_____		
3. Onko lääkäri todennut Sinulla olevan astmaa?	☐	☐
4. Onko lääkäri todennut Sinulla olevan kroonista (= pitkäaikaista) keuhkoputkentulehdusta tai keuhkonlaajentumaa?	☐	☐
5. Käytätkö astmalääkkeitä (säännöllisesti tai tarvittaessa) ?	☐	☐
6. Onko Sinulla ollut astmaoireita nykyisin tai viimeisten 10 vuoden aikana? (= ajoittain hengenahdistusta tai hengenahdistuskohtauksia, samanaikaisesti voi olla yskää tai hengityksen vinkumista)	☐	☐
Jos vastasit kyllä:		
a) Onko Sinulla ollut astmaoireita viimeisten 12 kuukauden aikana ?	☐	☐
7. Onko Sinulla ollut viime vuosina pitkäaikaista yskää ?	☐	☐
8. Nouseeko yskiessä keuhkoistasi yleensä limaa tai onko keuhkoissa limaa, jota on vaikea saada irtoamaan ?	☐	☐
Jos vastasit kyllä:		
a) onko limaa noussut useimpina päivinä vähintään kolmen peräkkäisen kuukauden aikana ?	☐	☐
b) onko tällaisia vähintään kolmen kuukauden limannousujaksoja ollut vähintään kahtena peräkkäisenä vuonna ?	☐	☐
9. Onko tavallista, että keuhkoissa hengityksesi rahisee äänekkäästi tai vinkuu ?	☐	☐
10. Onko Sinulla ollut hengityksen vinkunaa kertaakaan viimeisten 12 kuukauden aikana ?	☐	☐
Jos vastasit kyllä:		
a) oliko Sinulla ollenkaan hengenahdistusta vinkunan yhteydessä ?	☐	☐
b) oliko Sinulla hengityksen vinkunaa vaikka et ollut flunssassa ?	☐	☐

	kyllä	ei/en tiedä
11. Oletko viimeisten 12 kuukauden aikana herätessäsi kertaakaan kokenut hengityksesi olevan tukossa (keuhkoissa) ?	☐	☐
12. Hengästytkö tai joudutko hengästymisen vuoksi kävelemään hitaammin kuin muut, kun kävelet ikäistesi henkilöiden kanssa tasamaalla normaalivauhdilla ?	☐	☐
13. Saatko hengenahdistusta, hengityksen vinkunaa tai vaikeita yskänpuuskia ?		
a) rasituksessa	☐	☐
b) kylmässä	☐	☐
c) pakkasessa rasituksen yhteydessä	☐	☐
d) pölyisissä olosuhteissa	☐	☐
e) tupakansavusta	☐	☐
f) autojen pakokaasuista	☐	☐
g) voimakkaista tuoksuista (esim. deodorantit, mausteet, painomuste, puhdistusaineet, kukkien tuoksut tms.)	☐	☐
h) kasvien tai puiden siitepölyistä	☐	☐
i) ollessasi tekemisissä eläinten kanssa	☐	☐
14. Tupakoitko tai poltatko piippua tai sikareita ? (vastaa **kyllä** vaikka olisitkin lopettanut viimeisten 12 kuukauden aikana)	☐	☐

Jos vastasit kyllä:

a) Kuinka monta savuketta, sätkää, sikaria tai piipullista olet polttanut ***keskimäärin vuorokaudessa ?***

a) vähemmän kuin 5 kpl	☐	vain yksi rasti
b) 5-14 kpl	☐	
c) 15 kpl tai enemmän	☐	

Jos vastasit ei:

b) Oletko aiemmin ollut tupakoitsija, mutta lopetit yli vuosi sitten? ☐ ☐

15. Missä ammatissa olet ***pääasiassa*** toiminut ?
kirjoita vastaus tähän: _____
a) montako vuotta olet yhteensä ollut tässä työssä: _____ vuotta

16. Onko Sinulla nykyisin muu työ tai tehtävä (muu ammatti, opiskelu, työtön, kotityö, eläke, sairauseläke tms.) ?
jos on niin mikä ?, kirjoita vastaus tähän: _____
a) montako vuotta olet yhteensä ollut tässä työssä, eläkkeellä, tms.: _____ vuotta

17. Onko nykyinen työsi pääasiassa
a) ulkotyötä ? ☐
b) sisätyötä ? ☐

18. Kuinka monta vuotta ***yhteensä*** olet ollut pääasiassa ulkotyössä ? _____ vuotta

19. Oliko	a) äitisi tupakoitsija lapsuutesi aikana ?	☐	☐
	b) isäsi tupakoitsija lapsuutesi aikana ?	☐	☐
20. Oletko tai oletko ollut kilpahiihtäjä tai säännöllinen kuntohiihtäjä ?		☐	☐

VASTAA TARKASTI - KIITOKSET AVUSTASI!

Päiväys: _____ **puhelinnumerosi:** _____

Allekirjoitus: